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Changes in TSH levels after pregnancy in women undergoing fertility treatment taking thyroid hormones

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ABSTRACT

When women who are taking thyroid hormones become pregnant, they are often requested to take double doses twice a week. However, it remains unclear whether this treatment also applies to women with subclinical hypothyroidism (TSH >4.0 mU/L) or high normal TSH (TSH 2.5–4.0 mU/L). Therefore, the present study compared TSH levels before and after pregnancy (4–10 weeks gestation, mean 6.7 weeks) in 89 women undergoing fertility treatment who were taking levothyroxine (LT4). TSH levels before pregnancy ranged between 0.5 and 2.5 mU/L and the LT4 dose was not changed at the time of pregnancy. TSH levels decreased after pregnancy in 49 women and increased in 40 women. No significant differences were observed in TSH levels between before and early pregnancy (1.48 ± 0.54 and 1.67 ± 1.59 mU/L, respectively, $p = 0.263$). In conclusion, when women with subclinical hypothyroidism or high normal TSH who are taking LT4 for fertility treatment become pregnant, it is preferable to adjust the dosage based on TSH levels in early pregnancy rather than immediately increasing the dosage without testing.

Introduction

Subclinical hypothyroidism, defined by elevated TSH levels and normal thyroid hormone levels, has been associated with multiple adverse maternal and neonatal outcomes, including pregnancy loss [1]. Women with subclinical hypothyroidism (TSH > 4.0 mU/L) and high normal TSH (TSH 2.5–4.0 mU/L) undergoing fertility treatment are frequently treated with levothyroxine (LT4) [2]. The American Thyroid Association state that when hypothyroid patients receiving LT4 become pregnant, the administration of two additional tablets weekly of the patient's current daily LT4 dosage is recommended [3]. However, the studies on which these guidelines are based involved patients with overt hypothyroidism [4,5]. On the other hand, FT4 is increased and TSH is decreased by human chorionic gonadotropin (hCG), the level of which is high in early pregnancy [6]. In contrast to the thyroid tissue of patients with overt hypothyroidism, that of patients with subclinical hypothyroidism and high normal TSH is often nearly normal and, thus, is considered to respond to hCG. It currently remains unclear whether an increase in the dose of LT4 immediately upon conception may be applied to patients with subclinical hypothyroidism and high normal TSH. Therefore, the present study compared TSH levels before and after pregnancy in patients with subclinical hypothyroidism and high normal TSH who did not have their LT4 dose changed at the time of pregnancy.

Methods

Eighty-nine infertile women who started LT4 at our clinic due to subclinical hypothyroidism (TSH >4.0 mU/L) or high normal TSH (TSH 2.5–4.0 mU/L) were included. Their TSH levels before pregnancy ranged between 0.5 and 2.5 mU/L, and their thyroid hormone doses were not changed at the time of pregnancy. LT4 doses before pregnancy ranged between 25 and 100 μg/day with an average of 55.7 μg/day. TSH levels before and after pregnancy (4–10 weeks gestation, mean 6.7 weeks) were compared. TSH and thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase antibodies) were measured by AIA-CL2400 (Tosoh, Tokyo, Japan). Using StatFlex Ver.7 (Osaka, Japan), a paired *t*-test was used to compare between two related groups, and a one-factor analysis of variance (ANOVA) or a Kruskal-Wallis test was employed for comparisons among independent groups. The present study was approved by the Ethics Committee of Okamoto Thyroid Clinic.

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Results

As shown in Fig. 1, TSH levels decreased after pregnancy in 49 women and increased in 40 women. No significant differences were observed in TSH levels between before and early pregnancy (1.48 ± 0.54 and 1.67 ± 1.59 mU/L, respectively, p = 0.263).

TSH levels in early pregnancy remained between 0.5 and 2.5 mU/L in 61 patients, but were lower than 0.5 mU/L in 12 and higher than 2.5 mU/L in 16. Since a TSH level of between 0.5 and 2.5 mU/L is desirable in early pregnancy, we investigated the characteristics of women with TSH levels lower than 0.5 mU/L or higher than 2.5 mU/L in early pregnancy. The presence of thyroid autoantibodies, the thyroid volume, the TSH level before treatment, the TSH level before pregnancy, and the LT4 dosage before pregnancy were compared among the three groups (Table 1). No significant differences were observed.

Table 1
Relationships between TSH levels in early pregnancy and the presence of thyroid autoantibodies, the thyroid volume, the TSH level before treatment, the TSH level before pregnancy, and the LT4 dosage before pregnancy (mean ± SD).

	TSH level in early pregnancy (mU/L)			significance test
	< 0.5	0.5–2.5	2.5 <	
thyroid autoantibodies (positive/negative)	6 / 6	30 / 31	3 / 13	p = 0.083
thyroid volume (mL)	12.57 ± 3.93	13.45 ± 5.64	11.04 ± 4.45	p = 0.263
TSH level before treatment (mU/L)	4.68 ± 1.48	4.92 ± 2.82	4.94 ± 2.26	p = 0.956
TSH level before pregnancy (mU/L)	1.35 ± 0.66	1.45 ± 0.52	1.65 ± 0.50	p = 0.297
LT4 dosage before pregnancy (μg/day)	60.4 ± 20.5	57.0 ± 17.3	47.1 ± 17.6	p = 0.092

Discussion

In patients with subclinical hypothyroidism and high normal TSH, if the dosage of thyroid hormone was not changed at the time of pregnancy, the number of patients whose TSH levels decreased and those whose levels increased in early pregnancy were similar. Furthermore, serum FT4 levels did not significantly differ before and after pregnancy (1.37 ± 0.22 ng/dL before pregnancy and 1.39 ± 0.26 ng/dL in early pregnancy, p = 0.473).

The woman with the highest TSH level of 12.02 mU/L in early pregnancy was positive for thyroid autoantibodies and had a diffusely enlarged thyroid gland with a thyroid volume of 22.7 mL, which was diagnosed as Hashimoto's disease. She also had subclinical hypothyroidism based on her pre-treatment TSH level of 5.56 mU/L. The two other women with TSH levels higher than 4.0 mU/L in early pregnancy were negative for thyroid autoantibodies, had thyroid volumes of 8.4 and 11.9 mL, and had no evidence of thyroid enlargement or atrophy. One woman had subclinical hypothyroidism based on a pre-treatment TSH value of 6.03 mU/L.

The woman with the lowest TSH level in early pregnancy had transiently high FT4 levels, even though the LT4 dose was not changed. A previous study reported that overtreatment with LT4 may have a negative impact on pregnancy outcomes [7]. Therefore, it was considered inappropriate to increase the dosage of LT4 immediately upon conception in these patients.

In 88 patients, excluding one who self-interrupted the administration of LT4 during pregnancy, the LT4 dosage adjusted according to TSH levels was lower before delivery than in early pregnancy (56.8 ± 19.5 μg/day in early pregnancy and 54.4 ± 20.9 μg/day before delivery, p = 0.044). Although serum hCG levels are known to peak in early pregnancy, the results obtained showed that serum TSH levels did not increase even though serum hCG levels decreased in late pregnancy.

Although there was no significant difference, women with TSH levels higher than 2.5 mU/L in early pregnancy had higher TSH levels before pregnancy. Of the 20 women with a TSH level before pregnancy of 2.0–2.5 mU/L, 6 had a TSH level higher than 2.5 mU/L in early pregnancy, while 3 had a TSH level lower than 0.5 mU/L. Even among the 18 women with a TSH level before pregnancy of 0.5–1.0 mU/L, one had a TSH level higher than 2.5 mU/L in early pregnancy. Therefore, it was considered difficult to determine who would have TSH levels higher than 2.5 mU/L in early pregnancy based on their TSH levels before pregnancy.

Women with TSH levels higher than 2.5 mU/L in early pregnancy had lower dosages of LT4, although there was no significant difference. Seven of the 18 patients who took less than 50 μg/day of LT4 before pregnancy had a TSH level higher than 2.5 mU/L in early pregnancy, whereas one had a TSH level lower than 0.5 mU/L. In addition, 4 of the 36 patients whose LT4 dosage before pregnancy was higher than 50 μg/day had TSH levels higher than 2.5 mU/L in early pregnancy. Therefore, it was not possible to determine women with TSH levels higher than 2.5 mU/L in early pregnancy based on the dosage of LT4 taken before

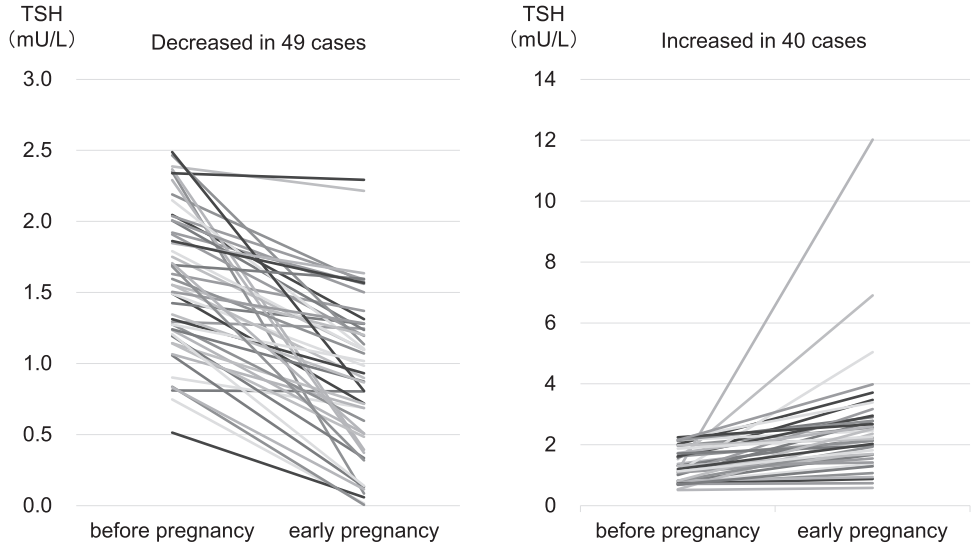

Fig. 1. Changes in TSH levels with pregnancy.

pregnancy.

In the present study, only patients who were followed up until after delivery were analyzed. Of the patients with pre-pregnancy TSH values between 0.5 and 2.5 mU/L during the same time period as the present study and who did not change their LT4 dosage when they became pregnant, 13 had miscarriages. In 12 of these patients, TSH levels in early pregnancy remained between 0.5 and 2.5 mU/L, and only one had a TSH level higher than 2.5 mU/L (4.13 mU/L). Therefore, in the present study, a relationship was not observed between early pregnancy TSH levels and miscarriage.

In conclusion, if a woman with subclinical hypothyroidism or high normal TSH who is taking thyroid hormones for fertility treatment becomes pregnant, it is preferable to adjust the dosage based on the TSH level in early pregnancy rather than immediately increasing the dosage without testing.

CRediT authorship contribution statement

Yoh Hidaka: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yoshiko Fukuda:** Resources. **Yuka Tsukamoto:** Resources. **Yuko Wada:** Resources. **Kazuyo Okamoto:** Resources. **Yasuyuki Okamoto:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid 2016;26(4):580–90. https://doi.org/10.1089/thy.2015.0418.

[2] Sankoda A, Suzuki H, Imaizumi M, et al. Effects of levothyroxine treatment on fertility and pregnancy outcomes in subclinical hypothyroidism: a systematic review and meta-analysis of randomized controlled trials. Thyroid 2024;34(4):519–30. https://doi.org/10.1089/thy.2023.0546.

[3] Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27(3):315–89. https://doi.org/10.1089/thy.2016.0457.

[4] Yassa L, Marqusee E, Fawcett R, et al. Thyroid hormone early adjustment in pregnancy (The THERAPY) trial. J Clin Endocrinol Metab 2010;95(7):3234–41. https://doi.org/10.1210/jc.2010-0013.

[5] Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;351(3):241–9. https://doi.org/10.1056/NEJMoa040079.

[6] Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994;331(16):1072–8. https://doi.org/10.1056/NEJM199410203311608.

[7] Hales C, Taylor PN, Channon S, et al. Controlled antenatal thyroid screening II: effect of treating maternal suboptimal thyroid function on child behavior. J Clin Endocrinol Metab 2020;105(3). https://doi.org/10.1210/clinem/dgz098. dgz098.