

# Implications of thyroid autoimmunity in infertile women with subclinical hypothyroidism in the absence of both goiter and anti-thyroid antibodies: lessons from three cases

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**Abstract.** There is a great deal of research interest regarding the underlying causes of slightly elevated TSH values in patients with subclinical hypothyroidism (SH) without abnormal findings on ultrasonography or anti-thyroid antibodies. Twelve infertile women with thyroglobulin antibody (TGAAb) and thyroid peroxidase antibody (TPOAb)-negative nongoitrous SH were referred to our department of endocrinology between September 2007 and September 2015. None had been diagnosed with autoimmune thyroid disease or had any possible causes of SH. In all cases, LT4 was prescribed to bring TSH value below 2.5 mIU/L. Among those with infertility treatments, six (50%) became pregnant and gave birth to infants. Here, we report three of these six women who successfully became pregnant with infertility treatments and were found to have thyroid autoimmunity on data obtained during the postpartum period. Two developed postpartum thyroiditis, and the remaining one woman was temporarily weakly positive for TPOAb at 9 months postpartum. We describe three infertile subclinically hypothyroid women without goiter or anti-thyroid antibodies with potential thyroid autoimmunity. Thyroid autoimmunity is one of the most important issues for management of pregnant women, and thus, our findings are noteworthy for the care of infertile women with SH. This report provides valuable insights into the presence of autoimmunity in nongoitrous thyroid-associated antibody-negative SH patients.

**Key words:** Thyroid autoimmunity, Infertility, Subclinical hypothyroidism, Negative thyroid antibody, Nongoitrous

**THE LATEST CLINICAL GUIDELINES** on management of thyroid dysfunction during pregnancy and postpartum, published by the Endocrine Society in 2012, recommend that serum TSH concentrations should be measured in women considering pregnancy and at high risk of thyroid illness, including those with infertility. Moreover, low-dose levothyroxine (LT4) treatment should be started to reach a serum TSH level <2.5 mIU/L in cases of hypothyroidism [1-4]. Some reports on assisted reproductive technology noted that LT4 supplementation, which can potentially improve pregnancy outcome, is recommended in women with subclinical hypothyroidism (SH) undergoing *in vitro* fertilization by intracyto-

plasmic sperm injection [5, 6].

On the other hand, pregnancy complications, including infertility, were reported to be related to thyroid autoimmunity. According to the 2017 guidelines of the American Thyroid Association, thyroid function and anti-thyroid peroxidase antibody (TPOAb) status must be considered in decision-making regarding LT4 treatment in pregnant women rather than serum TSH level [7]. However, other studies indicated that, regardless of the presence or absence of thyroid antibodies, appropriate LT4 treatment should be considered for pregnant individuals with TSH level >2.5 mIU/L [8-10]. The above reports suggest that thyroid autoimmunity is one of the most important issues for management of pregnant women.

Here, we report three infertile SH women without goiter or anti-thyroid antibodies who became pregnant with infertility treatments, but developed possible thyroid autoimmunity.

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**Table 1** List of infertile women of subclinical hypothyroidism negative for thyroid-antibodies, successfully getting pregnant

Pt.	Age (y)/BMI	free T4 (ng/dL)	free T3 (pg/mL)	TSH ( $\mu$ IU/mL)	Thyroid ultrasonography	The period of LT4 treatment before establishment of pregnancy (M)	Infertility treatment	Thyroid antibodies (TPOAb and TGAb) in the postpartum period	Postpartum thyroiditis
1 (Case 1)	34/18.3	1.0	1.7	4.23	Intact	7	Artificial insemination	Remained negative	(+)
2 (Case 2)	32/20.8	1.2	3.0	4.76	Intact	5	Clomiphene citrate <i>p.o.</i>	Remained negative	(+)
3 (Case 3)	38/23.6	1.0	2.4	4.60	Intact with small cysts	1–2	<i>In vitro</i> fertilization	Changed to almost positive at 9 M postpartum (TPOAb)	(–)
4	36/17.6	1.1	2.4	5.59	Intact	1–2	Naturally pregnant	Remained negative	(–)
5	38/17.6	0.9	2.1	6.12	Intact	12	Naturally pregnant	Remained negative	(–)
6	38/19.1	0.9	2.2	5.54	Intact	9	Artificial insemination	Not checked	(–)

Reference range: free T4 0.9–1.8 ng/dL; free T3 2.0–3.8 pg/mL; TSH 0.2–4.0  $\mu$ IU/mL.

BMI, body mass index; free T3, free triiodothyronine; free T4, free thyroxine; TSH, thyrotropine.

Age/BMI, free T4, free T3, TSH, Thyroid ultrasonography were data of the first visit.

## Case Report

Twelve infertile women with TGAb and TPOAb-negative nongoitrous SH were referred to our department of endocrinology by gynecologists at Shinonoi General Hospital between September 2007 and September 2015. Thyroid related data for diagnosis of SH were collected before all infertility examinations and treatments, because TSH secretion is likely to be stimulated by a series of infertility examinations and treatments [11, 12]. None of the patients had been diagnosed with autoimmune thyroid disease or had any possible causes of SH. In all cases, LT4 was prescribed to bring TSH value below 2.5 mIU/L. Among those with infertility treatments, six (50%) became pregnant and gave birth to infants (Table 1). In the three cases discussed below, possible thyroid autoimmunity was observed in the postpartum period. The courses of TGAb and TPOAb titers are shown in Fig. 1, and free T3, free T4, and TSH values in Fig. 2, in these three cases.

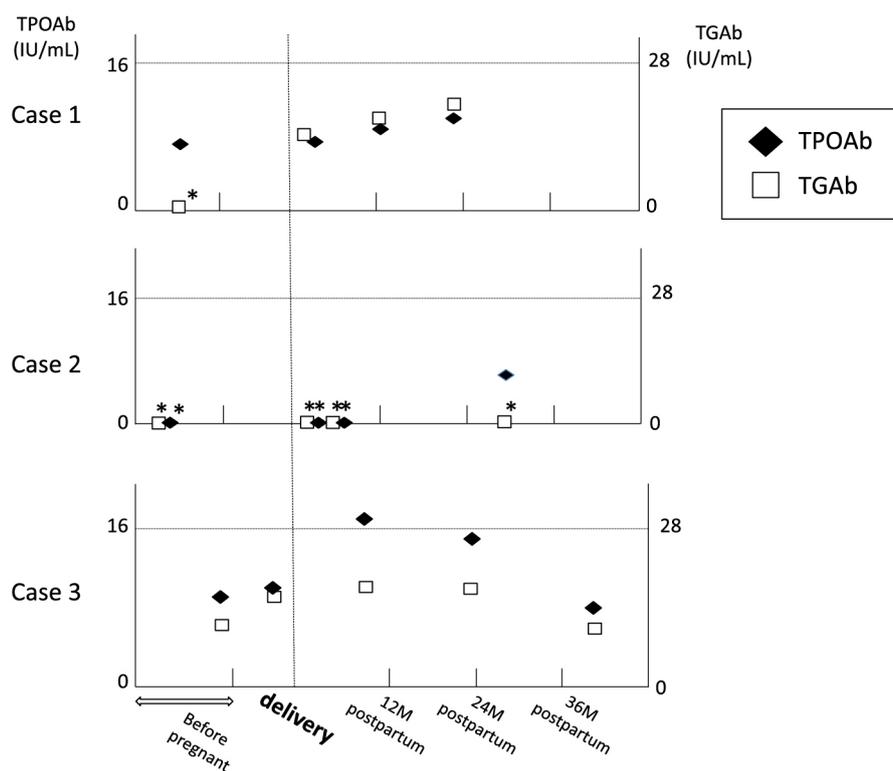
Serum TSH, free T3, and free T4 levels were measured using a chemiluminescent enzyme immunoassay (Abbott Japan Co., Ltd., Tokyo, Japan). The reference values were 0.2–4.0 mIU/L for TSH, 2.0–3.8 pg/mL for free T3, and 0.9–1.8 ng/dL for free T4. TPOAb and TgAb titers were determined using an electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). The reference ranges of TPOAb and TgAb were  $\leq 16$  IU/mL and  $\leq 28$  IU/mL, respectively. TPOAb titer >16

IU/mL and TGAb titer >28 IU/mL were considered positive.

### Case 1

A 34-year woman had been infertile for 4 years, and consulted gynecologists at Shinonoi General Hospital for infertility treatments. She had no history of particular disease or pregnancy. The patient underwent examinations related to infertility, including hysterosalpingography, transvaginal ultrasonography, and hormonal tests. Hysterosalpingography revealed no abnormalities, but slight findings of polycystic ovary were observed on transvaginal ultrasonography. In addition, thyroid function test revealed a slightly elevated TSH level (4.23  $\mu$ IU/mL) with normal ranges of serum thyroid hormones (free T3 1.7 pg/mL, free T4 1.0 ng/dL) (Table 1). Her husband's sperm motility rate was determined to be 18%, and therefore it was supposed that both partners had causes of infertility.

A diagnosis of SH was made, and she visited our department of endocrinology for treatment. Titers of both TPOAb and TGAb were negative (TPOAb 6 IU/mL, TGAb < 10 IU/mL). Ultrasonography showed that the thyroid was intact. Finally, a diagnosis of chronic thyroiditis was not made. There was no evidence of excessive iodine intake or medication, including commercial supplement intake. Although the cause of SH was not identified, LT4 was prescribed at a dose of 50  $\mu$ g per day to bring the TSH value below 2.5 mIU/L, as recommended



**Fig. 1** The courses of titers of both TPOAb and TGAb in Cases 1, 2, and 3, before and after delivery. TPOAb titer >16 IU/mL and TGAb titer >28 IU/mL were considered positive.

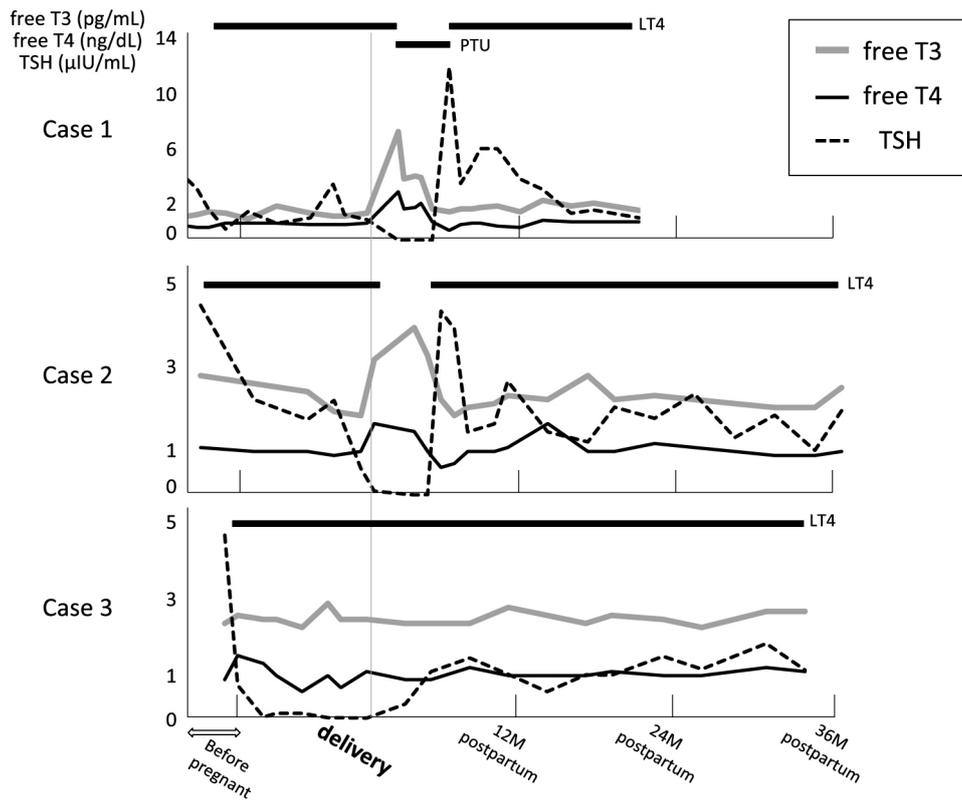
\* Below the level of detection ( $\leq 5$  IU/mL for TPOAb,  $\leq 10$  IU/mL for TGAb)

previously [1-4]. Seven months after initiation of LT4 treatment, she successfully became pregnant by artificial insemination, and finally gave birth to an infant with spontaneous cephalic delivery. However, she became evidently thyrotoxic in the first month postpartum (Fig. 2). She presented with tachycardia and finger tremor. In addition, she developed postpartum depression after childbirth. The serum concentrations of free T3, free T4, and TSH were 7.6 pg/mL, 3.4 ng/dL, and <0.01 mIU/L, respectively. TGAb, TPOAb, anti-TSH receptor antibody (TRAb) and thyroid stimulating antibody (TSAb) were all negative, and ultrasonographic analysis indicated that the thyroid status was morphologically the same as before pregnancy. Thyroidal radioactive iodide uptake was not performed because she was breast-feeding. Silent thyroiditis was more likely than Graves' disease as the initial diagnosis. However, we decided to start treatment with 150 mg of propylthiouracil per day because of the patient's strong complaints associated with thyrotoxicosis. After 1 month of treatment with propylthiouracil, serum thyroid hormone levels remained high with consistently low TSH levels. Therefore, the dose of propylthiouracil was increased to 200 mg per day. Thyrotoxicosis continued for about 2 months after commencement of treatment. Ten months after the onset of thyrotoxicosis,

she was taking only 50  $\mu$ g per day of LT4. The courses of TGAb and TPOAb titers are shown in Fig. 1.

### Case 2

A 32-year woman with no history of pregnancy and childbirth was referred to our department by a process similar to Case 1. She had no particular disease. Hysterosalpingography, transvaginal ultrasonography, and hormonal tests were performed, and no problems were found except in thyroid function test. The serum concentrations of free T3, free T4, and TSH were 3.0 pg/mL, 1.2 ng/dL, and 4.76  $\mu$ IU/mL, respectively (Table 1). A diagnosis of SH was made, but both TPOAb and TgAb were negative (below the level of detection). Ultrasonography indicated that the thyroid was intact. There was no evidence of excessive iodine intake, medication, or possible adrenal insufficiency. She was prescribed 50  $\mu$ g daily of LT4. Five months after initiation of treatment, pregnancy was established by oral administration of clomiphene citrate. After delivery, she became mildly thyrotoxic at 3 months postpartum and complained of mild palpitation. The laboratory data were 4.2 pg/mL for free T3, 1.6 ng/dL for free T4, and <0.01 mIU/L for TSH (Fig. 2). One month after first detection of the thyrotoxic state, the values of free T3, free T4, and TSH spontane-



**Fig. 2** The courses of free T3, free T4, and TSH values in Case 1, 2, and 3, before and after delivery. Reference range: free T3 2.0–3.8 pg/mL, free T4 0.9–1.8 ng/dL, TSH 0.2–4.0  $\mu$ IU/mL. LT4, levothyroxine; PTU, propylthiouracil.

ously dropped to within the normal reference ranges. A diagnosis of postpartum thyroiditis was made. TGAb and TPOAb titers remained negative during the above period (Fig. 1).

### Case 3

A 38-year woman with no history of pregnancy wished to receive infertility treatment after undergoing left ovarian cyst hysterectomy. She had no other history of disease. Hysterosalpingography and transvaginal ultrasonography revealed no abnormalities. Hormonal examination showed luteal insufficiency and SH. She visited our department for treatment of SH. Serum concentrations of free T3, free T4, TSH were 2.4 pg/mL, 1.0 ng/mL, and 4.60  $\mu$ IU/mL, respectively (Table 1), and thyroid-related antibodies were all negative (TPOAb 9 IU/mL, TGAb 11 IU/mL). Ultrasonography showed the thyroid to be almost normal with the exception of small intrathyroidal cysts. She had no history of excessive iodine intake or medication. Serum concentrations of cortisol and ACTH excluded the possibility of adrenal insufficiency. She was prescribed 50  $\mu$ g of LT4 per day. After 1–2 months of LT4 supplementation, she successfully became pregnant by *in vitro* fertilization. As shown in Fig. 1, TPOAb became weakly positive (17 IU/mL) at

9 months after delivery, but TGAb remained negative (18 IU/mL). Concentrations of free T3, free T4, and TSH were within the respective normal reference ranges with administration of the same dose of LT4 (free T3 2.4 pg/mL, free T4 1.3 ng/mL, TSH 1.54  $\mu$ IU/mL) (Fig. 2). Thereafter, TPOAb dropped to within the normal range (15 IU/mL) at 24 months after delivery. At 40 months after delivery, TPOAb titer declined further (8 IU/mL). She had no thyroid disease-associated symptoms over the clinical course.

## Discussion

We presented three patients with potential thyroid autoimmunity. In Cases 1 and 2, postpartum thyroiditis developed although TPOAb test remained negative during the postpartum period. Postpartum thyroiditis is regarded as a consequence of the immunological changes that occur during pregnancy, and is thought to be based on thyroid autoimmunity [13–16]. Thus, thyroid autoimmunity was suggested in these cases. In Case 3, the patient had a positive TPOAb test result during the postpartum period. The titer was temporarily elevated, and thereafter, dropped to within the normal range (Fig. 1). This indicated that some immunological changes could

occur during a certain period after childbirth. In these three cases, thyroid-associated antibody-negative SH patients, thyroid autoimmunity was suggested to be the underlying cause of slightly elevated TSH values before pregnancy.

TPOAb positivity in fertile women in the first trimester was reported to be a predictor of postpartum thyroiditis, whereas TPOAb-negative women have a very low incidence of postpartum thyroiditis [17-20]. However, the present report suggests that TPOAb negativity does not necessarily indicate lack of autoimmunity. That is, at least for infertile SH women, evaluation of TPOAb titer may not be indispensable for predicting the development of postpartum thyroiditis.

On the other hand, TGAb testing is considered not to be beneficial for predicting postpartum thyroiditis, because TGAb-positive but TPOAb-negative women rarely develop postpartum thyroiditis [21]. In a review article, Deroux *et al.* reported that there seemed to be some relations between female infertility and autoimmunity not only in patients with thyroid disease but also other collagen diseases, including systemic lupus erythematosus and anti-phospholipid syndrome [22]. Dahlberg

and Jansson reported that thyroid cytology revealed thyroiditis by fine needle biopsy in two women who developed postpartum thyroiditis but had no thyroid antibodies [23]. The above findings suggest that there are antibody-negative lymphocytic thyroiditis cases with unknown antibodies, and efforts should be made to detect novel autoimmune antibodies in these patients, which may be involved in infertility.

This report will be helpful for the care of infertile women with SH. The rates of subclinical hypothyroidism in infertile women were reported to be higher than fertile controls (13.9% vs. 3.9%, respectively) [24]. In such patients, even if negative for thyroid antibodies, careful observation to monitor the possible development of thyroid autoimmunity is required in the postpartum period. This case report provided valuable insights regarding the presence of autoimmunity in nongoitrous thyroid-associated antibody-negative SH patients.

## Disclosure

The authors have no potential conflicts of interest associated with this report.

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