Serum Thyroid-stimulating Hormone Receptor Antibody Levels and Thyroid Dysfunction After Hysterosalpingography: A Case-Control Study

メタデータ	言語: eng 出版者: 公開日: 2022-08-08 キーワード (Ja): キーワード (En): 作成者: So, Shuhei, Hashimoto, Koshi, Mori, Masatomo, Endo, Shigeki, Yamaguchi, Wakasa, Miyano, Naomi, Murabayashi, Nao, Tawara, Fumiko メールアドレス: 所属:
URL	http://hdl.handle.net/10271/00004167

Serum Thyroid-stimulating Hormone Receptor Antibody Levels and Thyroid Dysfunction After Hysterosalpingography: A Case-Control Study

Journal:	*Gynecological Endocrinology*
Manuscript ID	Draft
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	So, Shuhei; Hamamatsu University School of Medicine, Hashimoto, Koshi; Dokkyo Medical University Saitama Medical Center Mori, Masatomo; Metabolic and Obesity Research Institute Endo, Shigeki; Endo Naika Clinic Yamaguchi, Wakasa; Tawara IVF clinic Miyano, Naomi; Tawara IVF clinic Murabayashi, Nao; Hamamatsu University School of Medicine Tawara, Fumiko; Tawara IVF clinic
Keywords:	thyroid function, TRAb, Infertility, hysterosalpingography (HSG), thyrotoxicosis

SCHOLARONE™
Manuscripts

Serum Thyroid-stimulating Hormone Receptor Antibody Levels and Thyroid Dysfunction After Hysterosalpingography: A Case-Control Study

Short title: Thyrotoxicosis after HSG

Shuhei So,[a,b*] Koshi Hashimoto,[c] Masatomo Mori,[d] Shigeki Endo,[e] Wakasa Yamaguchi,[b] Naomi Miyano,[b] Nao Murabayashi,[a,b] Fumiko Tawara[b]

[a] *Department of Reproductive and Perinatal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka, 431-3192, Japan*

[b] *Tawara IVF Clinic, 2-20, Izumi-cho, Suruga-ku Shizuok, Shizuoka, 422-8066, Japan*

[c] *Department of Diabetes, Endocrinology and Hematology, Dokkyo Medical University Saitama Medical Center, 2-1-50, Minami-koshigaya, Koshigaya, Saitama, 343-8555, Japan*

[d] *Metabolic and Obesity Research Institute, 1155, Azami, Kasakake-cho, Midori-shi, Gunma, 379-2311, Japan*

[e] *Endo Naika Clinic, 4-4-38, Nakata, Suruga-ku, Shizuoka, Shizuoka, 422-8041, Japan*

*Corresponding Author e-mail: so@hama-med.ac.jp

For Peer Review Only

Shuhei So: so@hama-med.ac.jp

Koshi Hashimoto: k-hashi@dokkyomed.ac.jp

Masatomo Mori: mmori@gunma-u.ac.jp

Shigeki Endo: endo5115@ninus.ocn.ne.jp

Wakasa Yamaguchi: wakasa44@gmail.com

Naomi Miyano: ahirunrun0322@yahoo.co.jp

Nao Murabayashi: nm2017@hama-med.ac.jp

Fumiko Tawara: tawara@tawara-ivf.jp

Word count: 1987 words

For Peer Review Only

Abstract

Objective: Hysterosalpingography (HSG) performed with an iodine contrast media can cause thyroid dysfunction, including thyrotoxicosis and hypothyroidism. We investigated the association between the serum levels of thyroid-stimulating hormone receptor antibody (TRAb), an indicator of Graves' disease, and abnormal thyroid function after performing HSG. **Methods:** The screening of TRAb was conducted in 362 patients who first visited the Tawara IVF Clinic between April and September 2018. The association between TRAb levels and the effects of HSG examinations on thyroid function were evaluated. **Results:** Of the 362 patients, 2 (0.55%) had high levels (>2.0 IU/L) of TRAb, whereas 18 (5.0%) had intermediate TRAb levels, ranging from 0.3 to 1.9 IU/L. Of the 98 women (including 7 of the 18 women with TRAb level 0.3–1.9 IU/L, and 91 of the 342 women with TRAb level <0.3 IU/L) who had undergone HSG, two women developed overt thyrotoxicosis after HSG, and the frequency was significantly higher (p=0.0044) in the group with intermediate levels of TRAb (28.6%, 2 of 7) than that in the group with low TRAb levels (<0.3 IU/L; 0.0%, 0 of 91). **Conclusions:** These findings indicate that increased serum levels of TRAb are significantly associated with the development of thyrotoxicosis after HSG.

Key words: thyroid function, TRAb, infertility, hysterosalpingography (HSG), thyrotoxicosis

For Peer Review Only

1. Introduction

The thyroid gland utilizes dietary iodine for the secretion of two thyroid hormones, namely, triiodothyronine and thyroxine, that are essential for regulating metabolic processes throughout the body. The recommended daily iodine intake for thyroid hormone synthesis is 150 μg [1]. The thyroid gland has an intrinsic mechanism wherein excessive iodine intake acutely suppresses thyroid hormone synthesis while it inhibits iodine organization; this regulatory phenomenon is known as the Wolff-Chaikoff effect [2]. This inhibitory effect is transient, as the thyroid hormone synthesis returns to the normal level after approximately 48 hours; this is known as an escape from the Wolff–Chaikoff effect. These intrinsic regulatory mechanisms for excess iodine management are necessary to maintain normal thyroid function, and disruption in these mechanisms leads to thyroid disorders. Thyroid dysfunction, such as in Hashimoto's disease and Graves' disease (GD), is a risk factor for excess iodine-induced hypothyroidism that could possibly occur due to the failure of escape from the Wolff–Chaikoff effect [3]. However, a history of GD and the presence of thyroid nodules are known risk factors for excess iodine-induced thyrotoxicosis [3,4]. This effect is typically the converse of the Wolff–Chaikoff effect and is known as the Jod-Basedow phenomenon [5].

In fertility treatment, hysterosalpingography (HSG) has been reported to cause thyroid dysfunction [6-9]. HSG involves the use of contrast media containing several hundred milligrams of iodine per milliliter [8]. This intake is a hundred-fold higher than the recommended daily intake of iodine [8]. Therefore, the management of thyroid function after HSG examination has gained increasing importance.

For Peer Review Only

Furthermore, identifying patients who may be at risk for thyroid dysfunction due to an HSG examination is also an issue of clinical importance.

In this study, we considered the possibility that an increased serum level of the thyroid-stimulating hormone (TSH) receptor antibody (TRAb) could be a predictor of excess iodine-induced thyroid dysfunction. First, we evaluated the presence of TRAb in infertility patients. Following this, we investigated whether there exists a significant association of serum TRAb levels with the development of thyrotoxicosis after an HSG examination.

2. Materials and Methods

2.1 *Participants and study design*

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and its later amendments. This prospective study was conducted with the approval of the Institutional Review Board of the Tawara IVF Clinic. Of the 437 patients who initially visited the Tawara IVF Clinic between April and September 2018, 362 patients (age, 34.3±5.0 years) who underwent the thyroid function test at the Tawara IVF Clinic before commencing fertility treatment were prospectively enrolled and provided written informed consent before the first thyroid function test (Fig. 1). Patients with a history of thyroid dysfunction were excluded from this study. TSH levels (Elecsys TSH: Roche, Switzerland) and FT4 levels (Elecsys® FT4: Roche, Switzerland) were measured at the Tawara IVF Clinic. Levels of

For Peer Review Only

thyroglobulin (Tg) antibody (Elecsys® Anti-Tg: Roche, Switzerland), thyroid peroxidase (TPO) antibody (Elecsys® Anti-TPO: Roche, Switzerland), and TRAb (Elecsys® Anti-TRAb: Roche, Switzerland) were measured at a laboratory managed by ASKA Pharma Medical Co., Ltd.

The recommended cutoff value of TRAb is 2.0 IU/L for GD, and the detection limit for TRAb is 0.3 IU/L [10, 11]. Therefore, the reference range of TRAb used in this study was 0.3–1.9 IU/L.

During the study period, 150 women had undergone HSG. Of the 150 women, we assessed the effects of HSG on thyroid function in 98 patients by evaluating their thyroid functions before and after performing HSG (shown in Fig. 1). The thyroid function test, after HSG, was scheduled 1 month later.

In this study, less than 5 ml of water-soluble contrast medium (Isovist: Bayer Schering Pharma AG, Germany: iodine concentration: 300 mg/ml) was used in the HSG. HSG examination was conducted in a single clinical center by following a common protocol that uses a minimal contrast medium and employing methods for absorbing the contrast medium after HSG. Therefore, we considered it likely that there was almost no variation among the patient groups.

Thyroid dysfunction was defined as FT4 > 1.7 ng/dL for thyrotoxicosis, which is characterized by excess levels of thyroid hormone in the body; FT4 < 0.9 ng/dL for hypothyroidism; TSH < 0.5 mIU/L with a normal FT4 range for subclinical thyrotoxicosis; and TSH > 5.0 mIU/L with a normal FT4 range for subclinical

For Peer Review Only

hypothyroidism. Clinical evaluation of the thyroid gland was undertaken by an endocrinologist (S.E.).

2.2 *Statistical analysis*

The clinical variables were analyzed using the Student's *t*-test for intergroup comparisons and using the Fisher's exact test to compare proportions. All statistical analyses were carried out using R Packages (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria) and JMP9 software (SAS Institute, Cary, NC, USA).

3. Results

With regard to the TRAb screening test, 342 of the 362 (94.5%) women enrolled in this study had levels below the detection threshold (< 0.3 IU/L). Twenty women (5.5%) had a TRAb level of > 0.3 IU/L and among those, two (0.55%) had a TRAb level of > 2.0 IU/L, which is the diagnostic criterion for GD. The mean (±SD) age of the participants in the TRAb > 0.3 IU/L (20 patients) and TRAb < 0.3 IU/L (342 patients) groups were 34.0±5.1 and 34.3±5.0 years, respectively, with no significant intergroup differences (p=0.48). There were no significant differences in the causes of infertility between the study groups (male factor: TRAb>0.3 group 19.5% vs. TRAb<0.3 group 20.0%, oviduct factor: 10.5% vs. 5.0%, cervical factor: 12.0% vs. 15.0%, endometriosis: 13.7% vs. 5.0%, uterine factor: 36.6% vs. 25.0%, ovulatory dysfunction: 26.0% vs. 35.0%, and unexplained infertility: 26.9% vs. 40.0%).

For Peer Review Only

The median duration until thyroid function evaluation post-HSG in the overall study population was 36.5 days (25–88 days). The incidence of thyroid dysfunction was compared between 7 patients with TRAb > 0.3 IU/L and 91 patients with TRAb < 0.3 IU/L, and the median duration until thyroid function evaluation post-HSG was 46 (30–85) and 36 (25–88) days, respectively, in these two patient groups (p=0.06). The analysis showed that 2 out of 7 patients with TRAb > 0.3 IU/L developed overt thyrotoxicosis after HSG (28.6%), and were diagnosed with GD (TRAb 1.90 IU/L: the start of propylthiouracil administration) and indolent or chronic thyroiditis (TRAb 0.51 IU/L: no medication at follow-up) (shown in Table 1 and Fig. 2).

The age of the two patients with post-HSG thyrotoxicosis was 34 and 39 years, and the BMI was 19.7 and 19.6, respectively. These patients had no history of pregnancy. The duration from HSG to the re-examination of thyroid function was 30 and 80 days, respectively. One patient tested positive for the Tg antibody (392.1 IU/mL). Of the 91 patients with TRAb < 0.3 IU/L, only one patient had subclinical thyrotoxicosis (FT4 1.46 ng/dL, TSH 0.12 mIU/L, 43 days after HSG) (shown in Fig. 2). A month later, the patient had showed normal TSH levels (TSH 1.01 mIU/L); however, none of the patients had overt thyrotoxicosis. Statistical analysis showed that the frequency of overt thyrotoxicosis after HSG was significantly higher in the TRAb 0.3–1.9 IU/L group than in the TRAb < 0.3 IU/L group (p=0.0044).

For Peer Review Only

4. Discussion

In this study, the prevalence of a TRAb level > 2.0 IU/L was observed in 0.55% of patients, which is indicative of GD; in contrast, 5.5% of the patients had the TRAb level in the reference range (0.3–1.9 IU/L). Overt thyrotoxicosis developed in 2 out of 7 patients with intermediate TRAb values of 0.3–1.9 IU/L after HSG with a water-soluble iodine contrast medium. In contrast, overt thyrotoxicosis did not develop among 91 patients with serum TRAb levels < 0.3 IU/L.

It is well known that iodine overdose is a risk factor for disease pathogenesis in iodine-deficient areas [4]. Japan is one of the countries where an iodine-rich diet is consumed regularly. However, 16.1% of pregnant women have a urinary iodine concentration of < 100 μg/L, indicating that their iodine intake is insufficient [12]. Therefore, it is possible that patients who developed thyrotoxicosis after HSG had a hyperthyroid state that was masked due to iodine deficiency.

To the best of our knowledge, only one case report has been published on the development of overt thyrotoxicosis after performing HSG. Ma et al. [6] performed HSG using lipiodol, which is an oil-based contrast medium, on a 33-year-old woman with normal thyroid function. Two weeks following this, a re-examination of thyroid function revealed overt thyrotoxicosis in the woman. An ultrasonographic examination of the thyroid showed no abnormal findings, and thyroid function had normalized after 1 month. In addition, a case–control study was conducted by Rhee et al., where computed tomography (CT) was also performed with an iodine contrast medium, comparable to HSG [13]. The study reported findings related to patients with normal thyroid function after using an iodine-containing contrast medium for

URL: http://mc.manuscriptcentral.com/dgye Email: gynendo@tiscali.it

CT between 1990 and 2010. They inferred that the use of iodine contrast media was a risk factor for both thyrotoxicosis and hypothyroidism. However, the levels of TRAb were not evaluated in these studies.

Our finding suggests that the increased serum TRAb levels in euthyroid women contribute to the development of thyrotoxicosis after HSG. Therefore, serum TRAb concentration may be important in predicting the development of thyrotoxicosis after HSG.

This study had some limitations. First, this study did not assess the dietary iodine intake. The levels of dietary iodine probably varied widely among the participants and may have affected the results of this study. Second, this study had a small sample size, which may have introduced a bias and conferred a very low statistical power. Therefore, this study cannot conclusively establish that high TRAb levels contribute to the development of post-HSG thyrotoxicosis. Third, in this study, the median duration until the thyroid function test after HSG was not significantly different between patients with TRAb <0.3 IU/L and those with TRAb levels of 0.3–1.9 IU/L. However, the minimum and maximum time for re-examination was 25 and 88 days, respectively. The timing of the thyroid function test after HSG may affect the positive rate of the detection of thyrotoxicosis. Therefore, the variation in the duration between HSG to thyroid examination is another limitation of this study. Finally, this study included only Japanese participants. Future research on the effect of ethnicity-related differences is necessary to understand the implications of the results of this study in ethnically diverse study populations. Based on these

For Peer Review Only

limitations, large-scale studies with higher statistical power are necessary to confirm these preliminary findings.

Acknowledgments

The authors thank Morihiro Tomomatsu (MET-SL) for discussion.

Declaration of Interest

S. So and N. Murabayashi are employed at the laboratory of the Tawara IVF Clinic, which funded the study.

For Peer Review Only

References

[1] World Health Organization. Assessment of iodine deficiency disorders and monitoring their elimination, a guide for programme managers. 3rd ed. Geneva: World Health Organization Press; 2007.

[2] Wolff J, Chaikoff IL. The temporary nature of the inhibitory action of excess iodine on organic iodine synthesis in the normal thyroid. Endocrinology. 1949;45(5):504–513.

[3] Bürgi H. Iodine excess. Best Pract Res Clin Endocrinol Metab. 2010;24(1):107–115.

[4] Roti E, Uberti ED. Iodine excess and hyperthyroidism. Thyroid. 2001;11(5):493–500.

[5] Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014;10(3):136–142.

[6] Ma G, Mao R, Zhai H. Hyperthyroidism secondary to hysterosalpingography: an extremely rare complication: A case report. Medicine (Baltimore). 2016;95(49):e5588.

[7] Mekaru K, Kamiyama S, Masamoto H, et al. Thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium. Gynecol Endocrinol. 2008;24(9):498–501.

For Peer Review Only

[8] Kaneshige T, Arata N, Harada S, et al. Changes in serum iodine concentration, urinary iodine excretion and thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium (lipiodol). J Clin Endocrinol Metab. 2014;100(3):E469–E472.

[9] So S, Yamaguchi W, Tajima H, et al. The effect of oil and water-soluble contrast medium in hysterosalpingography on thyroid function. Gynecol Endocrinol. 2016;33(9):682–685.

[10] Noh JY, Miyazaki N, Ito K, et al. Evaluation of a new rapid and fully automated electrochemiluminescence immunoassay for thyrotropin receptor autoantibodies. Thyroid. 2008:18(11):1157–1164.

[11] Wen WB, Liu FY. Autoantibodies highly increased in patients with thyroid dysfunction. Cell Mol Immunol. 2007;4(3):233–236

[12] Fuse Y, Ohashi T, Yamaguchi S, et al. Iodine status of pregnant and postpartum Japanese women: effect of iodine intake on maternal and neonatal thyroid function in an iodine-sufficient area. J Clin Endocrinol Metab. 2011;96(12):3846–3854.

[13] Rhee CM, Bhan I, Alexander EK, et al. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med. 2012;172(2):153–159.

For Peer Review Only

Figure Legends

Figure 1: Flow diagram indicating the disposition of study participants. * Two patients with thyroid-stimulating hormone receptor antibody levels (TRAb) >2.0 did not receive hysterosalpingography (HSG) during the study period.

Figure 2: Thyroid-stimulating hormone (TSH) (A) and free thyroxine (FT4) (B) in patients before and after hysterosalpingography (HSG) with a water-soluble iodine contrast medium. The TSH value is expressed as log10. Interrupted black lines indicate patients with TSH receptor antibody levels (TRAb) >0.3 IU/L. Gray lines indicate patients with TRAb <0.3 IU/L. Chained lines indicate the lower limit of the TSH (A, TSH 0.5 mIU/L) and the upper limit of the FT4 (B, FT4 1.7 ng/dL). †Patients with subclinical hyperthyroidism after HSG. *Patients with overt hyperthyroidism after HSG.

For Peer Review Only

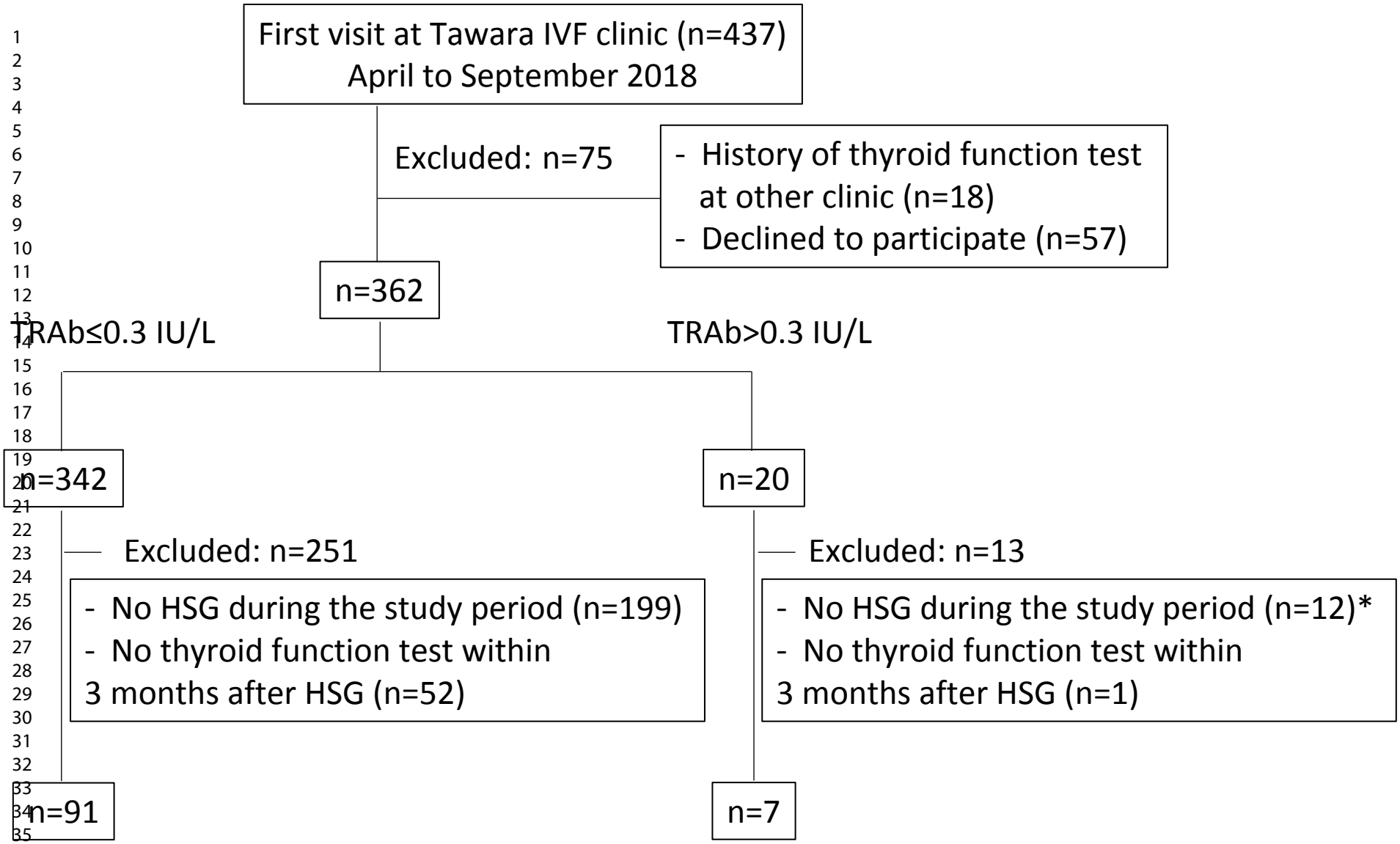
First visit at Tawara IVF clinic (n=437)
April to September 2018
Excluded: n=75
- History of thyroid function test at other clinic (n=18)
- Declined to participate (n=57)
n=362
TRAb≤0.3 IU/L
TRAb>0.3 IU/L
n=342
n=20
Excluded: n=251
- No HSG during the study period (n=199)
- No thyroid function test within 3 months after HSG (n=52)
Excluded: n=13
- No HSG during the study period (n=12)*
- No thyroid function test within 3 months after HSG (n=1)
n=91
n=7

Fig.1

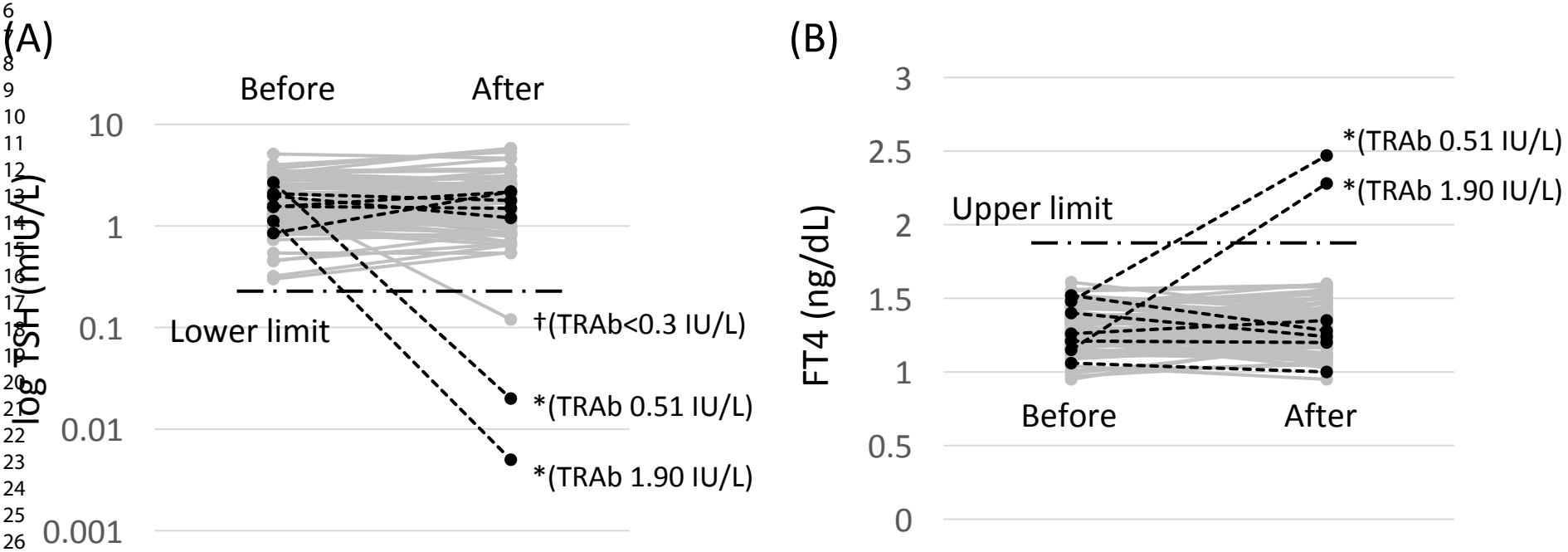
(A)
Before
After
10
1
0.1
0.01
0.001
log TSH (mIU/L)
Lower limit
†(TRAb<0.3 IU/L)
*(TRAb 0.51 IU/L)
*(TRAb 1.90 IU/L)
(B)
3
2.5
2
1.5
1
0.5
0
FT4 (ng/dL)
Upper limit
*(TRAb 0.51 IU/L)
*(TRAb 1.90 IU/L)
Before
After

Fig 2

Table 1 Clinical characteristics and thyroid function status of patients who underwent HSG and had TRAb levels ≥0.3 IU/L

No.	Age	BMI	TRAb (IU/L)	TPOAb (IU/mL)	TgAb (IU/mL)	FT4 (ng/dL)	TSH (mIU/L)	History of P/A/T/B	Possible cause of infertility	Thyroid function after HSG a. FT4; b. TSH; c. Days after HSG (Diagnosis[$])
1	34	19.7	1.90	8.83	17.41	1.15	1.12	0/0/0/0	-	a. 2.28; b. 0.005; c. 80 (Graves' disease)
2	24	23.2	1.48	372.2↑	435.3↑	1.52	0.85	0/0/0/0	PCOS	a. 1.28; b. 2.18; c. 46
3	35	25.2	1.46	11.4	10.0	1.21	1.54	0/0/0/0	-	a. 1.20; b. 2.16; c. 38
4	32	19.9	0.75	11.01	10.00	1.40	1.56	1/0/1/0	-	a. 1.24; b. 1.49; c. 49
5	30	17.2	0.66	7.53	46.96↑	1.26	2.08	0/0/0/0	-	a. 1.35; b. 1.78; c. 34
6	29	22.8	0.54	16.88↑	10.31	1.06	1.97	0/0/0/0	PCOS	a. 1.00; b. 1.20; c. 85
7	39	19.6	0.51	9.14	392.1↑	1.48	2.68	0/0/0/0	Leiomyoma	a. 2.47; b. 0.02; c. 30 (indolent thyroiditis/ chronic thyroiditis)

Abbreviations: FT4: free T4; TSH: thyroid-stimulating hormone; TRAb: thyroid-stimulating hormone receptor antibody; TD: thyroid disease; TPOAb: thyroid peroxidase antibody; TgAb: thyroglobulin antibody; ST: subclinical thyrotoxicosis; PCOS: polycystic ovary syndrome; nt: no treatment. ↑: Above the upper limit. ↓: Below the lower limit; P/A/T/B, history of pregnancy/abortion/artificial termination/birth before recruitment into this study.

None of the patients had a history of thyroid disease. [$]Diagnosis by a specialist (S.E.) when the FT4 exceeded the standard value or the patient tested TRAb positive (≥2.0 IU/L). *History of laparoscopic surgery in 2014.

For Peer Review Only