Effect of thyroxine treatment on pregnancy outcomes in infertile Japanese women with TSH levels between 2.5 μIU/mL and the upper reference limit: a retrospective study

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Abstract. Recent randomized controlled studies have revealed that levothyroxine (LT4) treatment improves pregnancy outcomes only in infertile women with subclinical hypothyroidism who have thyroid autoantibodies (TAs), but not for those with high TSH levels within the normal range who have TAs. Here, we retrospectively investigated pregnancy outcomes in infertile Japanese women with 2.5 μIU/mL ≤ TSH < upper reference limit (URL). Between 2012 and 2018, 286 patients diagnosed with infertility were followed for more than 1 year at our institution. Among them, we included 106 patients with 2.5 μIU/mL ≤ TSH < URL. We divided these patients into four groups based on the combination of TA positivity and LT4 treatment status to assess the effects of LT4 treatment considering TA positivity on the incidence of pregnancy or miscarriage. In this study, we did not find any significant differences in the rates of pregnancy or miscarriage among the four groups (p = 0.81 and 0.52, respectively). In addition, logistic regression analysis showed that age and history of miscarriage were associated with the incidence of pregnancy, but presence of TAs and LT4 treatment status were not and that no variables examined were associated with the incidence of miscarriage. In summary, we were not able to demonstrate the benefit of LT4 treatment for pregnancy outcomes in Japanese euthyroid infertile women with 2.5 μIU/mL ≤ TSH < URL regardless of TA status in this study.

Key words: Infertility, Euthyroid, Miscarriage, Thyroid autoantibodies, Levothyroxine
with normal thyroid function. In this study, we retrospectively investigated the effect of LT4 treatment on pregnancy outcomes among Japanese euthyroid (2.5 μIU/mL ≤ TSH < URL) infertile women divided by TA status.

**Subjects and Methods**

**Patients**

In this study, infertility was defined as the failure to achieve clinical pregnancy over 12 months. Between February 1, 2012, and August 31, 2018, there were 345 Japanese infertile women referred by reproductive clinics to the Diabetes and Endocrine Clinics of Juntendo University Hospital because they showed that TSH was higher than 2.5 μIU/mL and/or positive TA (thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb)). Among these 345 patients, 59 who were lost to follow-up at 1 year were excluded from the study. Among 286 patients, 106 infertile women with 2.5 μIU/mL ≤ TSH < URL were divided into four groups based on the combination of TA positivity and LT4 treatment status as follows: TA–LT4–, TA–LT4+, TA+LT4–, and TA+LT4+. Initiation of LT4 treatment for each infertile woman was based on the clinical judgment of the treating physician. All infertile women in the LT4+ groups were started on LT4 with the dose titrated to maintain TSH <2.5 μIU/mL. Mean LT4 dose was calculated as the cumulative LT4 dose divided by the number of days of LT4 treatment. Reproductive specialists classified causes of infertility based on the results of infertility testing, including serum hormonal level testing, semen analysis, and hysterosalpingography. The study protocol was approved by the ethics committee of Juntendo University.

**Measurement of serological markers**

Blood samples were collected from all patients during clinic visits. Free thyroxine (FT4), free triiodothyronine (FT3), and TSH were measured using commercially available electrochemiluminescence immunoassays (Roche Diagnostics) with the following normal ranges: FT4, 1.00–1.70 ng/dL; FT3, 2.40–4.50 pg/mL; and TSH, 0.56–4.30 μIU/mL. Serum TPOAb and TgAb values were measured using an enzyme-linked immunosorbent assay (Roche Diagnostics) with a normal range of <16.0 IU/mL and <28.0 IU/mL, respectively. Serum anti-Müllarian hormone (AMH) values were measured using the AMH GenII enzyme-linked immunosorbent assay kit (Medical & Biological Laboratories) with the limit of quantification of 0.16 ng/mL.

**Definition of pregnancy outcomes**

Pregnancy was defined as the presence of a fetal sac with an increase in serum human chorionic gonadotropin (hCG) values. Miscarriage was defined as clinical miscarriage occurring after pregnancy as defined above. Chemical pregnancy only with an increase in serum hCG levels was excluded.

**Statistical analysis**

Results are presented as frequencies (%) or means ± standard deviation (SD). After verification of the interaction between TA status and LT4 treatment, baseline clinical features and outcomes of patients in the four groups were compared using the χ² test for categorical data and two-way analysis of variance for continuous data. To elucidate factors affecting outcomes, independent variables were included in a logistic regression model. The presence of a significant difference was defined as p < 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL).

**Results**

Table 1 shows characteristics of the study subjects. Mean age was 36.5 ± 4.5 years, mean TSH was 3.33 ± 0.55 μIU/mL, and mean FT4 was 1.2 ± 0.3 ng/dL. TPOAb, TgAb, or both were present in 36 patients (34.0%). Mean TSH values during the observation period in the groups without LT4 (TA–LT4–, TA–LT4+) was 3.19 ± 0.79 μIU/mL. On the other hand, that in the LT4 treatment groups (TA–LT4+, TA+LT4+) was 1.70 ± 0.81 μIU/mL and the mean LT4 dose used was 41.5 ± 19.3 μg/day. Mean duration of infertility was 2.2 ± 2.4 years. Mean AMH concentration was 3.3 ± 3.6 ng/mL. There were 56 (52.8%) patients treated with artificial reproductive technology (ART). Except for TA positivity and TA levels, there were no statistically significant differences among the four groups in characteristics including age, basal TSH value, duration of infertility, AMH concentration, and proportion of patients who underwent ART, which is closely related to infertility. Mean LT4 dose and mean TSH value during LT4 treatment were similar between the TA–LT4+ and TA+LT4+ groups.

Table 2 shows pregnancy outcomes among the four groups. First, the interaction between TA positivity and LT4 therapy status did not have a significant effect on pregnancy or miscarriage rates (p = 0.907 and 0.484, respectively). The number of infertile women who became pregnant during observation period in the TA–LT4–, TA–LT4+, TA+LT4–, and TA+LT4+ groups was 15 (42.9%), 15 (42.9%), 6 (54.5%), and 13 (52.0%), respectively (p = 0.81). Likewise, the number of pregnant women who experienced miscarriage during observation period in each group was 3 (20.0%), 4 (26.7%), 1
(16.7%), and 3 (21.4%), respectively (p = 0.52).

Table 3 shows characteristics among infertile women divided by the incidence of pregnancy or miscarriage. Infertile women who became pregnant were younger (p = 0.02), more likely to have prior pregnancies (p = 0.03) or a history of miscarriage (p = 0.02), and had higher AMH values (p = 0.04) than with those who did not become pregnant. Infertile women who had a miscarriage were more likely to have prior pregnancies than those who did not experience a miscarriage (p = 0.05).

The proportion of patients treated with LT4, mean dose of LT4, and TSH level during the observation period were similar for each pregnancy outcome.

Next, logistic regression was used to investigate variables related to pregnancy outcomes. First, univariate logistic regression analysis showed that age (p = 0.021; odds ratio (OR), 0.90), gravidity (p = 0.046; OR, 1.81) and history of miscarriage (p = 0.030; OR, 2.16) were associated with pregnancy (Supplemental Table 1). No variables including TSH value during the observation period were significantly associated with pregnancy outcomes.
period were associated with miscarriage. The multivariate logistic regression analysis was performed using significant variables in the univariate logistic regression analysis and presence of TAs, LT4 treatment, and ART, which are reportedly related to pregnancy outcomes. Except age ($p = 0.03$; OR, 0.90 [95% confidence interval (CI), 0.82–0.98]) and history of miscarriage ($p = 0.04$; OR, 2.15 [95% CI, 1.04–4.45]), no other variables were associated with pregnancy and no variables were associated with miscarriage.

**Discussion**

In this study, we retrospectively investigated pregnancy outcomes among Japanese euthyroid (2.5 μIU/mL ≤ TSH < URL) infertile women categorized by the combination of TA positivity and LT4 treatment status. We found no difference in pregnancy outcomes across groups. Neither the presence of TAs nor LT4 treatment was associated with pregnancy outcomes.

Previous studies have reported the obstetric characteristics and outcomes of infertile women with 2.5 ≤ TSH < 4.5 μIU/mL compared with those with TSH <2.5 μIU/mL [9, 10, 13-15]. Infertile women with TSH ≥2.5 μIU/mL had similar embryo quality as those with TSH <2.5 μIU/mL [14]. In addition, the rates of pregnancy, miscarriage, and live births in infertile women with TSH ≥2.5 μIU/mL were similar to those with TSH <2.5 μIU/mL [9, 10, 13, 15]. Although a few studies have reported that infertile women with TSH ≥2.5 μIU/mL have a lower pregnancy rate [16] and lower ovarian reserve [17] than those with TSH <2.5 μIU/mL, the present study was not able to show the difference mentioned before, similar to most previous studies [9, 10, 13, 15].

Regarding LT4 treatment as an intervention to improve obstetric prognosis in infertile women, previous retrospective studies reported that LT4 treatment in infertile women with TSH >2.5 μIU/mL including subclinical hypothyroidism who underwent ART was associated with better obstetric outcomes compared to no intervention [18, 19]. Two RCTs [7, 8] have reported that LT4 treatment in infertile women with subclinical hypothyroidism (TSH ≥4.5 μIU/mL) and TAs who underwent in vitro fertilization (IVF) had better rates of pregnancy, miscarriage, and live birth than those who did not receive LT4 treatment. On the other hand, a RCT in Italy [11] reported that LT4 treatment in infertile women with TSH <2.5 μIU/mL and TAs who underwent IVF is not associated with better rates of pregnancy, miscarriage, or live birth when compared with rates in those without LT4 treatment. Another recent RCT [12] reported that LT4 treatment in 567 euthyroid infertile women with TAs who underwent IVF is not associated with better rates of pregnancy, miscarriage, or live birth when compared with those who did not receive LT4 treatment. Based on the results of these RCTs, infertile women with normal thyroid function do not have better obstetric outcomes with LT4 treatment. Our results with Japanese patients are consistent with these previous reports. In addition, our study supports that LT4 treatment is dispensable for euthyroid infertile women without TAs as with those with TAs.

Logistic regression analysis showed that ART is not significantly associated with pregnancy, which indicates that infertile women who underwent ART do not have a better pregnancy rate. These results could be due to the different characteristics between infertile women who underwent ART and those who did not. Indeed, infertile women who underwent ART were older (38.8 vs. 35.0 years; $p < 0.01$) and had lower serum AMH concentrations (1.5 vs. 3.3 ng/mL; $p < 0.01$) than those who did not. As the interactions between ART and age or AMH were not significantly associated with pregnancy rate ($p = 0.486$ and 0.751, respectively), age was the most influential variable on pregnancy rate in the present study. Therefore, the effects of ART may be statistically underestimated in the present study.

According to the guidelines of the ATA and European Thyroid Association [4, 20], when infertile women with 2.5 μIU/mL ≤ TSH < URL become pregnant, strict management of thyroid function should be considered only in

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**Table 2** Pregnancy outcomes of 106 infertile patients by presence of thyroid autoantibodies and levothyroxine treatment status

| Outcome       | TA–LT4– (n = 35) | TA–LT4+ (n = 35) | TA+LT4– (n = 11) | TA+LT4+ (n = 25) | p    |
|---------------|-----------------|-----------------|-----------------|-----------------|------|
| Pregnancy     | 15 (42.9%)†     | 15 (42.9%)      | 6 (54.5%)       | 13 (52.0%)      | 0.81 |
| Miscarriage   | 3 (20.0%††)     | 4 (26.7%)       | 1 (16.7%)       | 3 (23.1%)       | 0.52 |

† Calculated by dividing the number of women who became pregnant by the total number of infertile women during observational period in each group.

†† Calculated by dividing the number of women who experienced a miscarriage by the number of women who became pregnant during observational period in each group.
those with TAs. However, many studies of euthyroid infertile women with $2.5 \leq \text{TSH} < \text{URL}$, including this study, do not support this recommendation. Indeed, another large-scale retrospective study in 2017 that investigated the effects of LT4 treatment in 5,405 infertile women with $2.5 \leq \text{TSH} \leq 10.0$ μIU/mL until mid-pregnancy on obstetric prognosis found a lower rate of pregnancy loss only in infertile women with $\text{TSH} \geq 4.1$ μIU/mL [21]. The TABLET study [5] was a recent RCT involving 952 pregnant women with normal TSH

| Characteristic                  | Pregnancy (+) (n = 49) | Pregnancy (-) (n = 57) | p   | Miscarriage (+) (n = 11) | Miscarriage (-) (n = 38) | p   |
|--------------------------------|------------------------|------------------------|-----|-------------------------|--------------------------|-----|
| Age (years)                    | 35.4 ± 4.4             | 37.4 ± 4.3             | 0.02| 36.7 ± 5.2              | 35.1 ± 4.2               | 0.31|
| Smoker                         | 3                      | 4                      | 0.58| 2                       | 1                        | 0.08|
| BMI (kg/m²)                    | 21.1 ± 3.0             | 21.4 ± 3.9             | 0.98| 22.1 ± 2.7              | 20.8 ± 3.1               | 0.15|

**Thyroid function at first visit**

|                      | Pregnancy (+) | Pregnancy (-) | p  | Miscarriage (+) | Miscarriage (-) | p  |
|----------------------|---------------|---------------|----|-----------------|-----------------|----|
| TSH (μIU/mL)         | 3.31 ± 0.60   | 3.34 ± 0.52   | 0.79| 3.42 ± 0.50     | 3.29 ± 0.62     | 0.68|
| FT4 (pg/mL)          | 2.8 ± 0.4     | 2.8 ± 0.4     | 0.99| 2.8 ± 0.4       | 2.9 ± 0.3       | 0.85|
| FT4 (ng/dL)          | 1.3 ± 0.5     | 1.2 ± 0.2     | 0.69| 1.6 ± 1.0       | 1.2 ± 0.2       | 0.52|
| TPOAb (IU/mL)        | 26 ± 56       | 27 ± 55       | 0.93| 39 ± 52         | 23 ± 58         | 0.11|
| TPOAb positive       | 10            | 12            | 0.56| 3               | 7               | 0.26|
| TgAb (IU/mL)         | 88 ± 150      | 80 ± 96       | 0.74| 96 ± 133        | 88 ± 154        | 0.81|
| TgAb positive        | 15            | 11            | 0.23| 4               | 11              | 0.27|
| TA positive          | 19            | 17            | 0.22| 4               | 15              | 0.49|
| TRAb (IU/L)          | 0.4 ± 0.2     | 0.4 ± 0.2     | 0.96| 0.5 ± 0.2       | 0.4 ± 0.2       | 0.77|
| Mean TSH value during observation (μU/mL) | 1.81 ± 1.02   | 1.90 ± 0.84   | 0.33| 1.74 ± 0.93     | 1.84 ± 1.05     | 0.55|
| No. of patients treated with LT4 | 28             | 32            | 0.53| 7               | 21              | 0.44|
| Mean LT4 dose (μg/day) | 42.0 ± 23.8   | 41.0 ± 14.6   | 0.61| 47.2 ± 18.4     | 40.2 ± 25.5     | 0.30|

**Infertility**

|                      | Pregnancy (+) | Pregnancy (-) | p  | Miscarriage (+) | Miscarriage (-) | p  |
|----------------------|---------------|---------------|----|-----------------|-----------------|----|
| Duration of infertility (years) | 1.8 ± 1.7     | 2.6 ± 2.8     | 0.18| 2.2 ± 1.7       | 1.7 ± 1.8       | 0.28|
| Gravida              | 0.6 ± 0.8     | 0.3 ± 0.6     | 0.03| 1.3 ± 0.7       | 1.7 ± 0.9       | 0.05|
| Para                 | 0.1 ± 0.3     | 0.1 ± 0.3     | 0.78| 1.0 ± 0.7       | 0.5 ± 0.8       | 0.58|
| H/O miscarriages (n) | 0.5 ± 0.7     | 0.2 ± 0.5     | 0.02| 0.2 ± 0.4       | 0.1 ± 0.3       | 0.10|
| Cause of infertility | 1.6 ± 0.9     | 1.8 ± 0.9     | 0.24| 0.7 ± 0.7       | 0.4 ± 0.7       | 0.55|
| Ovarian factor       | 14            | 23            | 0.14| 3               | 11              | 0.51|
| Uterine factor       | 17            | 21            | 0.47| 4               | 13              | 0.23|
| Tubal factor         | 9             | 6             | 0.49| 1               | 8               | 0.47|
| Endometriosis        | 9             | 14            | 0.19| 0               | 9               | 0.13|
| Unexplained          | 10            | 12            | 0.56| 1               | 9               | 0.40|
| AMH (ng/mL)          | 3.7 ± 3.5     | 2.9 ± 3.7     | 0.04| 2.8 ± 1.5       | 3.9 ± 3.7       | 0.41|

**ART**

|                      | Pregnancy (+) | Pregnancy (-) | p  | Miscarriage (+) | Miscarriage (-) | p  |
|----------------------|---------------|---------------|----|-----------------|-----------------|----|
| ART (–)              | 24            | 26            | 0.44| 6               | 18              | 0.74|
| LT4 treatment        | 13            | 16            | 0.77| 3               | 10              | 1.00|
| ART (+)              | 25            | 31            | 0.6 | 5               | 20              | 0.74|
| LT4 treatment        | 15            | 16            | 0.79| 4               | 11              | 0.12|

Results are presented as frequencies or means ± SD.

H/O, History of
values (0.44–3.63 μIU/mL), TPO positivity, and a history of recurrent miscarriages. It investigated the effect of LT4 (50 μg per day) on the live birth rate and found that LT4 treatment does not improve the live birth rate in these patients. These data also support our finding.

The present study has several limitations. First, this was a small, retrospective study. We cannot deny the possibility that a negative finding may be due to inadequate sample size. However, this is the first report involving Japanese subjects; there are no clear guidelines regarding LT4 treatment in Japanese euthyroid infertile women with 2.5 μIU/mL ≤ TSH < URL and obstetric outcomes, thus, this study provide useful information for the treatment of such women. Second, initiation of LT4 treatment was based on the clinical judgment of each treating physician. However, interactions between LT4 therapy status and other clinical variables examined did not have significant effects on pregnancy or miscarriage rates (data not shown). Thus, LT4 treatment initiation might not be biased. Third, we could not confirm serum TSH levels frequently in patients without LT4 treatment in one year. Finally, we only evaluated whether pregnancy occurred after infertility treatment within one-year observation period.

In conclusion, regardless of TA status, we were not able to demonstrate the benefits of LT4 treatment in Japanese euthyroid infertile women with 2.5 μIU/mL ≤ TSH < URL. Our data suggest that LT4 treatment may be dispensable for such subjects.

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Disclosure

The authors have no multiplicities of interest to disclose.

Supplemental Table 1 Results of univariate logistic regression analysis for pregnancy outcomes

| Characteristic          | Pregnancy | Miscarriage |
|-------------------------|-----------|-------------|
|                         | p         | OR          | p         | OR          |
| Age                     | 0.021     | 0.90        | 0.335     |             |
| Smoker                  | 0.853     |             | 0.062     |             |
| BMI                     | 0.615     | 0.269       |           |             |
| Thyroid function        |           |             |           |             |
| TSH                     | 0.810     | 0.573       |           |             |
| FT3                     | 0.795     | 0.693       |           |             |
| FT4                     | 0.279     | 0.183       |           |             |
| TPOAb value             | 0.996     | 0.325       |           |             |
| TPOAb positive          | 0.935     | 0.296       |           |             |
| TgAb value              | 0.113     | 0.884       |           |             |
| TgAb positive           | 0.180     | 0.325       |           |             |
| TA positive             | 0.333     | 0.700       |           |             |
| TRAb value              | 0.177     | 0.574       |           |             |
| LT4 treatment           | 0.917     | 0.181       |           |             |
| TSH during observation  | 0.328     | 0.546       |           |             |
| Infertility             |           |             |           |             |
| Duration of infertility | 0.104     | 0.413       |           |             |
| Gravida                 | 0.046     | 1.81        | 0.130     |             |
| Para                    | 0.781     | 0.325       |           |             |
| H/O miscarriages        | 0.030     | 2.16        | 0.178     |             |
| Cause of infertility    | 0.269     | 0.335       |           |             |
| Ovarian factor          | 0.206     | 0.727       |           |             |
| Uterine factor          | 0.818     | 0.499       |           |             |
| Tubal factor            | 0.253     | 0.540       |           |             |
| Endometriosis           | 0.442     | 0.999       |           |             |
| Unexplained             | 0.935     | 0.454       |           |             |
| AMH                     | 0.314     | 0.372       |           |             |
| ART                     |           |             |           |             |
| ART (+)                 | 0.729     | 0.663       |           |             |
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