Gestational transient thyrotoxicosis (GTT) is defined as transient thyrotoxicosis caused by the stimulating effect of human chorionic gonadotropin (hCG) on the TSH receptor in the first trimester of gestation. We attempted to identify the serum hCG level that causes GTT, and we compared the serum hCG levels and thyroid hormone levels of GTT patients according to whether they had a background of thyroid disease. We also evaluated serum hCG as a parameter for differentiating between active Graves’ disease (GD) and GTT. We reviewed the 135 cases of pregnant women who came to our hospital to be evaluated for thyrotoxicosis during their 7th to 14th week of pregnancy, and their serum hCG level was measured at that time. Among the 135 pregnant women with thyrotoxicosis; 103 of the women had GTT, and the other 32 women had active GD. There were no correlations between their serum hCG levels and free thyroid hormone levels. There were no significant differences in thyroid hormone levels or hCG levels among the GTT groups with different thyroid disease backgrounds; i.e., the GTT group without thyroid disease, GTT group with chronic thyroiditis, GTT group with non-functioning thyroid nodules, and GTT group with GD in remission. The serum hCG level of the GTT group was significantly higher than in the active GD group, but it was not a good parameter for differentiating between the two groups. The FT3/FT4 ratio of the active GD was significantly higher than in GTT group, and was a better parameter for differentiation.

Key words: Human chorionic gonadotropin, Gestational transient thyrotoxicosis, Graves’ disease
subjects of this study. Thyroid ultrasonography and serum tests for the presence of thyroid-related antibodies (anti-TSH receptor antibody [TRAb], thyroglobulin antibody [TgAb], and anti-thyroid peroxidase antibody [TPOAb]) were performed, and underlying thyroid disorders were diagnosed.

We diagnosed GTT when the results of the TRAb test remained negative throughout the hyperthyroid state and the hyperthyroid state spontaneously improved in the absence of treatment. Active GD was diagnosed when the serum TRAb test was positive and antithyroid drugs were required to suppress the thyroid hormone level. Chronic thyroiditis was diagnosed when the serum TgAb test and/or TPOAb test was positive. A diagnosis of non-functioning thyroid nodule was made when ultrasonography showed one or more thyroid nodules and the hyperthyroid state spontaneously improved to a normal thyroid state in the absence of treatment. GTT without thyroid disease was diagnosed when serum TRAb, TgAb, and TPOAb tests were all negative and thyroid ultrasonography showed normal findings. This study received approval by the local ethics committee. All participants gave informed consent.

**Laboratory methods**

Free triiodothyronine (FT$_3$) and free thyroxine (FT$_4$) levels were measured by an electrochemiluminescence immunoassay (ECLI) (ECLusys FT$_4$, Roche Diagnostics GmbH, Mannheim, Germany; manufacturer’s reference limits: 2.2-4.3 pg/mL, 0.8-1.6 ng/dL respectively). The TSH level was measured by an ECLI (ECLusys TSH; Roche Diagnostics GmbH, Mannheim, Germany; manufacturer’s reference limits: 0.2-4.5 mIU/L). Based on the results of our previous study of a large population, the reference intervals for FT$_3$ and FT$_4$ and TSH at 4-12 weeks of gestation were 2.01-4.9 pg/mL, 0.77-1.91 ng/dL, and 0.01-3.35 mIU/L, respectively.

TPOAb and TgAb were determined by an ECLI performed with Roche ECLusys Anti-Tg and Anti-TPO (Roche Diagnostics GmbH, Mannheim, Germany; reference values were: TPOAb, <28 IU/mL; TgAb, <40 IU/mL). Until September 30, 2008, TRAb levels were determined with a solid-phase immunoradioreceptor assay kit (RSR, Cardiff, UK; TRAb-CT; reference values <10%), but since October 1, 2008, they have been determined with an electrochemiluminescence immunoassay kit (ECLusys TRAb; Roche Diagnostics GmbH, Mannheim, Germany; reference values <2.0 IU/L). HCG was determined with an enzyme immunoassay kit (Fujirebio Inc., Tokyo, Japan).

**Statistical analysis**

The statistical analysis was performed with JMP software, version 11.0.0, (SAS Institute Inc., Cary, NC). The data were analyzed by the Wilcoxon/Kruskal-Wallis test for differences between two groups. Correlations between two parameters were evaluated by calculating Spearman’s rank correlation coefficient. Tukey-Kramer’s test and ANOVA were used to compare the hCG levels and thyroid hormone levels among different groups. A $p$-value <0.05 was considered significant. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of serum hCG levels and FT$_3$/FT$_4$ ratios of patients for differentiating between active GD and GTT.

**Results**

The 135 hyperthyroid women consisted of 103 women with GTT and 32 women with active GD. Of the 32 active GD patients, 11 patients had been newly diagnosed with GD, and the other 21 patients had a recurrence of GD. The 103 GTT patients consisted of 30 women with no underlying thyroid disease, 19 women with chronic thyroiditis, 24 women with non-functioning thyroid nodule, and 30 women with GD in remission. None of the women had a hydatidiform mole or choriocarcinoma. The characteristics of the GTT group and active GD group are shown in Table 1.

The serum hCG level of the active GD group was significantly lower than in the GTT group ($p$ = 0.0009). The median serum hCG of the GTT group was 71,000 mIU/mL (range 20,000–220,000 mIU/mL) and 51,500 mIU/mL (range 8,900–150,000 mIU/mL) in the active GD group. There were no significant differences between the serum hCG levels among the GTT group according to thyroid disease background (no thyroid disease, chronic thyroiditis, non-functioning thyroid nodule, and women with GD in remission). There were no significant differences between the serum hCG levels among the GTT group according to thyroid disease background (no thyroid disease, chronic thyroiditis, non-functioning thyroid nodules, GD in remission). There were no correlations between the serum hCG levels and free thyroid hormone levels (either FT$_3$ or FT$_4$) in either the GTT group or active GD group. The serum FT$_3$ level and FT$_4$ levels of the active GD group were significantly higher than in the GTT group ($p < 0.0001$), and the FT$_3$/FT$_4$ ratios were also significantly higher in the active GD group than in the GTT group ($p < 0.0001$). Also, the serum FT$_3$ level and FT$_4$ levels of the active
We attempted to identify the serum hCG level that causes GTT, and we compared the serum hCG levels and thyroid hormone levels of GTT in patients according to whether they had a background of thyroid disease. HCG shares a common α-subunit with TSH and possesses thyroid stimulating activity [3]. The prevalence of GTT among pregnant women in Europe has been estimated to be 2-3% [4], and a higher prevalence is estimated in Asia [1, 2]. Lockwood et al. reported that hCG concentrations higher than 400,000 IU/L suppresses TSH level and most patients with hCG higher than 200,000 IU/L lack overt hyperthyroid symptoms [5].

Furthermore, a hydatidiform mole or choriocarcinoma, GD group were significantly higher than in the GTT with GD in remission group (FT$_3$, $p < 0.0001$; FT$_4$, $p = 0.0004$), and the FT$_3$/FT$_4$ ratios were also significantly higher in the active GD group than in the GTT with GD in remission group ($p < 0.0001$). There were no significant differences in thyroid hormone levels among the GTT groups (Table 1). The ROC curve analysis revealed that the cut-off hCG level for differentiating between active GD and GTT was 70,000 mIU/mL. The area under the ROC curve for differentiating between active GD and GTT was 0.7, and sensitivity was 84%, and specificity 51%. In addition, the cut-off FT$_3$/FT$_4$ ratio for differentiating between active GD and GTT was 2.7. The area under the ROC curve was 0.87; sensitivity was 77%, and specificity was 88%.

### Discussion

We attempted to identify the serum hCG level that causes GTT, and we compared the serum hCG levels and thyroid hormone levels of GTT in patients according to whether they had a background of thyroid disease. HCG shares a common α-subunit with TSH and possesses thyroid stimulating activity [3]. The prevalence of GTT among pregnant women in Europe has been estimated to be 2-3% [4], and a higher prevalence is estimated in Asia [1, 2]. Lockwood et al. reported that hCG concentrations higher than 400,000 IU/L suppresses TSH level and most patients with hCG higher than 200,000 IU/L lack overt hyperthyroid symptoms [5]. Furthermore, a hydatidiform mole or choriocarcinoma,
and twin pregnancies are also known to cause GTT [6, 7]. The hCG levels in the GTT group in this study ranged from 20,000 to 220,000 mIU/mL, and there were no correlations between the serum hCG levels and thyroid hormone levels. In addition, there were no significant differences between the thyroid hormone levels or hCG levels of the GTT group without thyroid disease, GTT group with chronic thyroiditis, GTT group with non-functioning thyroid nodules, and GTT group with GD in remission. This result suggests that the characteristics of GTT do not vary with thyroid disease background.

The exact molecular variants of hCG responsible for thyrotrophic effects are still unknown. There is one report of a change in the thyroid stimulating activity of hCG as a result of a modification of the carbohydrate chain [8].

We also evaluated serum hCG levels as a parameter for differentiating between active GD and GTT. The thyroid function of most untreated GTT patients becomes normal by the second trimester, and it is important to differentiate GTT from GD in order to prevent patients from undergoing unnecessary ATD treatment.

Tagami et al. evaluated the serum hCG values and FT3/FT4 ratios of pregnant GD patients and found that the hCG values were higher and FT3/FT4 ratios were lower in the GTT group than in the non-GTT group [9]. Our results in the present study were consistent with the findings in that report. We attempted to identify hCG and FT3/FT4 ratio cut-off levels for differentiating between active GD and GTT by performing an ROC curve analysis. The hCG cut-off level for differentiating between active GD and GTT was 70000 mIU/mL and the area under ROC curve for differentiating active GD between GTT was 0.7. Since the FT3/FT4 ratio cut-off level for differentiating between active GD and GTT was 2.7, and the area under the ROC curve was 0.87, we concluded that the FT3/FT4 ratio is a better parameter than the serum hCG level for differentiating between active GD and GTT, including GTT with GD in remission. Our study had the limitations of being retrospective and the numbers of patients in each group being small. Also, since hCG was measured only once in every subject, and the weeks of gestation when the measurements were made differed from subject to subject, we did not follow the hCG levels throughout the pregnancy of any of the subjects. However, the diagnosis of GTT in each subject was confirmed by reviewing the subjects’ clinical course.

In conclusion, there was no correlation between the serum hCG levels and thyroid hormone levels of the GTT patients, and there were no significant differences between the thyroid hormone levels or hCG levels of the GTT groups. The FT3/FT4 ratio was a better parameter than the hCG level for differentiating between GTT and active GD.

**Disclosure Statement**

The authors declare that they have no competing financial interests.

**References**