## CLINICAL SCIENCE

# Is the measurement of inferior thyroid artery blood flow velocity by color-flow Doppler ultrasonography useful for differential diagnosis between gestational transient thyrotoxicosis and Graves' disease? A prospective study

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**OBJECTIVE:** To determine the role of peak systolic velocity, end-diastolic velocity and resistance indices of both the right and left inferior thyroid arteries measured by color-flow Doppler ultrasonography for a differential diagnosis between gestational transient thyrotoxicosis and Graves' disease during pregnancy.

**METHODS:** The right and left inferior thyroid artery-peak systolic velocity, end-diastolic velocity and resistance indices of 96 patients with thyrotoxicosis (41 with gestational transient thyrotoxicosis, 31 age-matched pregnant patients with Graves' disease and 24 age- and sex-matched non-pregnant patients with Graves' disease) and 25 age- and sex-matched healthy euthyroid subjects were assessed with color-flow Doppler ultrasonography.

**RESULTS:** The right and left inferior thyroid artery-peak systolic and end-diastolic velocities in patients with gestational transient thyrotoxicosis were found to be significantly lower than those of pregnant patients with Graves' disease and higher than those of healthy euthyroid subjects. However, the right and left inferior thyroid artery peak systolic and end-diastolic velocities in pregnant patients with Graves' disease were significantly lower than those of non-pregnant patients with Graves' disease. The right and left inferior thyroid artery peak systolic and end-diastolic velocities were positively correlated with TSH-receptor antibody levels. We found an overlap between the inferior thyroid artery-blood flow velocities in a considerable number of patients with gestational transient thyrotoxicosis and pregnant patients with Graves' disease.

**CONCLUSIONS:** This study suggests that the measurement of inferior thyroid artery-blood flow velocities with color-flow Doppler ultrasonography does not have sufficient sensitivity and specificity to be recommended as an initial diagnostic test for a differential diagnosis between gestational transient thyrotoxicosis and Graves' disease during pregnancy.

**KEYWORDS:** Gestational transient thyrotoxicosis; Graves' disease; Inferior thyroid artery; Color-flow Doppler ultrasonography; Pregnancy.

## INTRODUCTION

Thyrotoxicosis affects up to 0.1% to 0.4% of pregnancies. Graves' disease (GD) is the overwhelming autoimmune cause of thyrotoxicosis during pregnancy. Unless it is treated, thyrotoxicosis may result in maternal and fetal complications (1-3). In contrast, gestational transient thyrotoxicosis (GTT) is a non-autoimmune cause of thyrotoxicosis of variable severity that is often associated with hyperemesis gravidarum (HG) (2-4). GTT is defined as transient thyrotoxicosis during early pregnancy with a lack of clinical features of GD, no evidence of hyperthyroidism before pregnancy and an absence of thyroid autoantibodies (2). The etiology of GTT is thought to be related to stimulation of the thyroid gland by human chorionic gonadotropin (hCG) or related molecular variants (2-6). Apart from rare cases in which persistent and severe clinical

symptoms might require treatment with low doses of anti-thyroid drugs, usually for a short period of time, GTT often resolves spontaneously before 18 weeks of gestation (1-7). Other causes of thyrotoxicosis such as toxic multinodular goiter, single toxic adenoma and different forms of destructive thyroiditis are rare during pregnancy. Because nonspecific symptoms of hyperthyroidism may occur normally in pregnancy, the evaluation of thyrotoxicosis in a pregnant woman is difficult. In the presence of thyrotoxicosis with clinical features of GD, the diagnosis is straightforward. However, the differential diagnosis between GD and GTT is difficult in the absence of clinical features of GD. The assessment of TSH-receptor antibody (TRAb) levels is generally useful when investigating thyrotoxicosis of uncertain etiology, including thyrotoxicosis associated with HG (8). Although the new generation of TSH-receptor antibody (TRAb) assays is highly sensitive and specific for discriminating GD from various causes of thyrotoxicosis (9), these assays are not widely available, and cost remains an important factor when considering their use in routine clinical practice. Recently, the measurement of the peak systolic velocity (PSV) of the inferior thyroid artery (ITA) with color-flow Doppler ultrasonography (CFDUSG) was suggested as a sensitive diagnostic tool for the differential diagnosis of thyrotoxicosis (10,11). Previously, Kumar et al. indicated the utility of CFDUSG for the differential diagnosis of thyrotoxicosis during pregnancy (12). However, because of the small number of patients included, Kumar et al. were not able to determine the exact role of CFDUSG for a differential diagnosis between GTT and GD. Therefore, we conducted the present study to evaluate the role of PSV, end-diastolic velocity (EDV) and resistance indices (RIs) of the right and left ITA, measured with CFDUSG, for a differential diagnosis between GTT and GD during pregnancy.

## PATIENTS AND METHODS

### Patients

Seventy-eight pregnant women in their first trimester of pregnancy (between 8-12 weeks gestation) who were referred to our center for evaluation of thyrotoxicosis, 24 age-matched non-pregnant patients with GD and 25 age- and sex-matched healthy euthyroid subjects were enrolled in this study. All of the cases were newly diagnosed and had not received antithyroid therapy before inclusion in the study. A detailed history was taken, and all patients with thyrotoxicosis were examined physically for clinical features of GD (ophthalmopathy, a significant goiter, pretibial myxedema and nail changes). Patients with a history of previous thyroid surgery, radioactive iodine ablation therapy and radiation exposure to the neck; patients with single or multinodular goiter on gray-scale ultrasonography (USG); patients with destructive thyroiditis; and patients under treatment with thionamides or L-thyroxine were excluded from the study. Accordingly, six pregnant patients with thyrotoxicosis (two with multiple nodules and one with a single nodule on USG, one with factitious thyrotoxicosis, one with painless thyroiditis and one with a previous history of radiation therapy to the neck for the treatment of childhood lymphoma) were excluded from the study. Eventually, 72 pregnant patients with thyrotoxicosis (41 with GTT and 31 with GD) were found to be eligible for the study. GTT was defined as suppressed TSH and high free

thyroid hormone levels presenting within the first trimester of pregnancy and associated with HG, but self-limiting on follow-up; absence of clinical findings of GD; a normal TRAb level; and absence of a history of hyperthyroidism before pregnancy (13). GD in pregnant patients was defined based on clinical findings, high TRAb and free thyroid hormone levels, decreased TSH levels and presence of a history of hyperthyroidism before pregnancy. GD in non-pregnant patients was defined based on the clinical findings, decreased TSH level, high free thyroid hormone and TRAb levels and high uptake values for $^{99m}$Tc-pertechnetate. Destructive thyroiditis in pregnant women was defined as the presence of thyrotoxicosis lasting for fewer than three months and/or later development of transient hypothyroidism associated with a positive result for thyroid peroxidase and/or thyroglobulin antibodies, normal TRAb levels, decreased echogenicity and hetero-geneous appearance of the thyroid parenchyma on USG and low uptake values for $^{99m}$Tc-pertechnetate in non-pregnant patients with thyrotoxicosis. HG was defined as electrolyte disturbances, ketosis and weight loss of >%5 of the non-pregnant weight (13).

### Hormone assays

Serum samples to determine TSH, fT3 and fT4 levels for all subjects; TRAb level in all patients with thyrotoxicosis; and β hCG level in all pregnant patients were collected after an overnight fast and sent immediately for laboratory assessment on the day of ultrasonography examination. Serum TSH, fT3, fT4 and β HCG levels were assessed using a direct chemiluminescence immunoassay (Siemens, ADVIA Centaur XP Immunoassay System, Tarrytown, NY, USA). Serum TRAb levels were assessed with TRAb-Fast-ELISA (Euroimmun AG Seekamp 31, D-23560 Lübeck. Germany) (14).

### Doppler ultrasonography

All thyroid ultrasound examinations were performed by the same radiologist (A.O.), who was blinded to the clinical status of the subjects. A color Doppler ultrasound scanner (Toshiba, Aplio XV, Tokyo, Japan) equipped with a 7-14 MHz broadband linear array transducer was used. The studies of the right and left ITAs were performed with transverse scanning, in which the vessels crossed the common carotid arteries posteriorly, or with longitudinal scanning of the ascending parts of the arteries, in which the vessels lay parallel to the common carotid arteries. The angle correction cursor was parallel to the direction of flow, and the Doppler angle was kept at or below 60˚. The PSV, EDV and RI values were obtained from the right and left ITA.

Maternal thyroid function was monitored with respect to fT3, fT4 and TSH levels at monthly intervals. All pregnant patients diagnosed with GTT were followed up until the normalization of the TSH level without treatment with antithyroid drugs. Antithyroid therapy with propiltiouracil (PTU) was administered after the assessment of thyroid blood flows to all pregnant patients diagnosed with GD, and the patients were followed up until delivery. The aim of the treatment was to maintain the FT3/FT4 in the upper quartile of the normal, non-pregnant range. Non-pregnant patients with GD were treated appropriately. Informed consent was obtained from all participants, and the study was approved by the local ethics committee.

## Statistical analysis

Data were analyzed using SPSS version 12.0.0 for Windows (SPSS Inc., Chicago, IL). Scale variables are presented as the mean $\pm$ standard deviation (mean $\pm$ SD). Categorical data were evaluated using Chi-square analysis or with Pearson's correlation and Fisher's exact tests as appropriate. Student's t-test was used for a comparison of parametric quantitative data. A one-way analysis of variance (ANOVA) was performed to compare quantitative variables within different groups followed by post-hoc analyses for multiple comparisons (Tamhane's test). A canonical correlation analysis was used to determine the correlation between the ITA flow velocity and the TRAb level. Patients with GTT were tested to determine a diagnostic cutoff for the right and left ITA-PSV and EDV using receiver-operating-characteristic (ROC) analysis. $p < 0.05$ was considered to be statistically significant.

## RESULTS

The demographic and laboratory features of the study participants are summarized in Table 1. In the present study, the right and left ITA-PSV and EDV in patients with GTT were lower than those of pregnant patients with GD ($p < 0.001$) and higher than those of euthyroid subjects ($p < 0.001$). However, the right and left ITA-PSV and EDV in pregnant patients with GD were lower than those of non-pregnant patients with GD ($p < 0.001$). The right and left ITA-RI were not different among the four groups of study participants ($p > 0.05$). The mean, minimum and maximum ITA-flow velocities of all groups of study participants are shown in Table 2.

In the current study, 30 (97%) of 31 pregnant patients with GD and 23 (96%) of 24 non-pregnant patients with GD had high TRAb levels. The TRAb levels were also significantly different among the three groups of patients with thyrotoxicosis ($p < 0.001$ for all groups with thyrotoxicosis). The canonical r coefficient of the correlation demonstrated a positive correlation of the right and left ITA-PSV and EDV with the TRAb levels (r = 0.515, $p = 0.440$ for the right ITA PSV, r = 0.463, $p = 0.461$ for the left ITA-PSV, r = 0.615, $p = 0.356$ for the right ITA-EDV and r = 0.526, $p = 0.382$ for the left ITA-EDV, respectively). However, of the patients with GTT, nine (22%) had right ITA-PSV, 13 (31.7%) had left ITA-PSV, 12 (29.3%) had right ITA-EDV, and 13 (31.7%) had left ITA-EDV above the cutoff values. Similarly, of the pregnant patients with GD, seven (22.6%) had right ITA-PSV, eight (25.8%) had left ITA-PSV, eight (25.8%) had right ITA-EDV, and eight (25.8%) had left ITA-EDV below the cutoff values. Hence, an overlap was found among ITA blood flow velocities in a considerable number of patients with GTT and pregnant patients with GD. The most appropriate cutoff values for the right and left ITA-PSV and EDV for differentiating GTT from GD during pregnancy are presented in Table 3.

The TSH, fT3 and fT4 levels returned to normal pre-pregnancy levels before the 20th week of pregnancy in patients with GTT. However, despite treatment with different doses of PTU, the TSH levels in the 20th week of pregnancy were significantly lower in pregnant patients with GD than in those with GTT ($p < 0.001$). The fT3 and fT4 levels in the 20th week of pregnancy were not different between patients with GTT and pregnant patients with GD ($p > 0.05$) (Table 1). Because the thyroid function returned to normal before the 20th week of pregnancy in patients with GTT, the thyroid function was only followed in pregnant patients with GD beyond the 20th week of pregnancy. The TSH levels also remained reduced after the 30th week of pregnancy in the majority of pregnant patients with GD, irrespective of treatment with PTU.

**Table 1 -** Demographic information and laboratory values of the study participants.

| | patients with GTT | pregnant patients with GD | non-pregnant patients with GD | healthy euthyroid subjects | *p*-value |
|---|---|---|---|---|---|
| | (n = 41) | (n = 31) | (n = 24) | (n = 25) | |
| Age (years) | 29.1 $\pm$ 4.8 | 29.1 $\pm$ 5.12 | 29.1 $\pm$ 3.5 | 30.8 $\pm$ 7.1 | 0.29 |
| Hyperemesis gravidarum (%) | 73.2 | 19.4 | - | - | <0.001 |
| Multiple pregnancy (%) | 7.3 | 9.7 | - | - | 0.52 |
| TSH (0.55-4.78 μIU/ml)[d,e] | 0.03 $\pm$ 0.03 | 0.03 $\pm$ 0.07 | 0.007 $\pm$ 0.005 | 1.62 $\pm$ 0.85 | - |
| fT3 (2.3-4.2 pg/ml)[b,c] | 3.94 $\pm$ 0.95 | 5.57 $\pm$ 2.21 | 25.86 $\pm$ 40.97 | 3.05 $\pm$ 0.388 | - |
| fT4 (0.76-1.4 ng/dl)[f] | 1.73 $\pm$ 0.36 | 2.11 $\pm$ 1.25 | 5.86 $\pm$ 12.7 | 1.03 $\pm$ 0.13 | - |
| TRAb (<1 IU/L)[a] | 0.28 $\pm$ 0.22 | 3.47 $\pm$ 1.43 | 14.09 $\pm$ 11.71 | - | - |
| βhCG (mIU/ml) | 111965 $\pm$ 52688 | 103043 $\pm$ 65998 | - | - | 0.79 |
| 20 weeks TSH level | 1.05 $\pm$ 0.5 | 0.34 $\pm$ 0.43 | - | - | <0.001 |
| 20 weeks fT3 level | 2.73 $\pm$ 0.29 | 2.95 $\pm$ 0.45 | - | - | 0.71 |
| 20 weeks fT4 level | 0.92 $\pm$ 0.09 | 0.95 $\pm$ 0.13 | - | - | 0.058 |
| 34 weeks TSH level | - | 0.38 $\pm$ 0.45 | - | - | |
| 34 weeks fT3 level | - | 2.91 $\pm$ 0.44 | - | - | |
| 34 weeks fT4 level | - | 0.99 $\pm$ 0.15 | - | - | |

[a]$p < 0.001$ when GTT was compared with pregnant patients with GD, when pregnant patients with GD were compared with non-pregnant patients with GD and when GTT was compared with non-pregnant patients with GD.
[b]$p = 0.003$ when GTT was compared with pregnant patients with GD.
[c]$p > 0.05$ when GTT and pregnant patients with GD were compared with non-pregnant patients with GD.
[d]$p < 0.001$ when GTT was compared with non-pregnant patients with GD.
[e]$p > 0.05$ when GTT was compared with pregnant patients with GD and when pregnant patients were compared with non-pregnant patients with GD.
[f]$p > 0.05$ when GTT was compared with pregnant patients with GD, when pregnant patients were compared with non-pregnant patients with GD and when GTT was compared with non-pregnant patients with GD.

**GTT**: gestational transient thyrotoxicosis, **GD**: Graves' disease, **TSH**: thyroid-stimulating hormone, **fT3**: free triiodothyronine, **fT4**: free thyroxine, **TRAb**: TSH-receptor antibody, **β hCG**: β human chorionic gonadotropin; values in parentheses indicate normal laboratory reference ranges.

**Table 2 -** The right and left ITA blood flow velocities of the study participants.

| | patients with GTT | pregnant patients with GD | non-pregnant patients with GD | healthy euthyroid subjects |
|---|---|---|---|---|
| | (n = 41) | (n = 31) | (n = 24) | (n = 25) |
| Right ITA PSV cm/sec[a] | 24.3 ± 7.3 (10.6-42) | 37.58 ± 10.89 (20.9-58.1) | 57.03 ± 25.7 (11.6-129.8) | 17.08 ± 4.83 (9.4-30) |
| Right ITA EDV cm/sec[a] | 10.39 ± 3.7 (3.1-20) | 15.9 ± 6.2 (7-33.6) | 24.03 ± 11.87 (3.9-53.8) | 7.78 ± 3.07 (4.1-14.4) |
| Right ITA RI[b] | 0.57 ± 0.07 (0.45-0.71) | 0.57 ± 0.08 (0.37-0.72) | 0.58 ± 0.07 (0.48-0.79) | 0.55 ± 0.08 (0.43-0.73) |
| Left ITA PSV cm/sec[a] | 24.75 ± 6.15 (11.4-36.6) | 35.19 ± 11.19 (21-69.7) | 59.4 ± 22.77 (22.4-112.5) | 17.37 ± 4.81 (9-27) |
| Left ITA EDV cm/sec[a] | 11.43 ± 3.93 (4.7-21.49) | 15.8 ± 5.05 (6.9-26.6) | 25.97 ± 11.80 (7.6-58.2) | 8.16 ± 2.73 (4.4-13.7) |
| Left ITA RI[b] | 0.54 ± 0.074 (0.4-0.8) | 0.54 ± 0.08 (0.4-0.7) | 0.56 ± 0.07 (0.4-0.7) | 0.53 ± 0.06 (0.4-0.7) |

[a]$p < 0.001$ when GTT was compared with healthy euthyroid subjects as well as pregnant and non-pregnant patients with GD, when pregnant patients with GD were compared with non-pregnant patients with GD and when pregnant and non-pregnant patients with GD were compared with healthy euthyroid subjects.

[b]$p > 0.05$ when GTT was compared with healthy euthyroid subjects as well as pregnant and non-pregnant patients with GD, when pregnant patients with GD were compared with non-pregnant patients with GD and when pregnant and non-pregnant patients with GD were compared with healthy euthyroid subjects.

**GTT**: gestational transient thyrotoxicosis, **ITA**: inferior thyroid artery, **PSV**: peak systolic velocity, **EDV**: end-diastolic velocity, **RI**: resistance index, R results are presented as mean ± SD; values in parentheses indicate the minimum and maximum ranges.

## DISCUSSION

Determination of the etiology of thyrotoxicosis during pregnancy is crucial for providing the patient with an appropriate treatment plan. The measurement of ITA-PSV using CFDUSG has proven to be highly sensitive and specific in identifying patients with GD (11), but its capability to discriminate GTT from GD during pregnancy is not well known. According to our findings, the mean right and left ITA-PSV and EDV in patients with GTT was significantly lower than that in pregnant and non-pregnant patients with GD and significantly higher than that in healthy euthyroid subjects, which is a result that has not been found before. This increase in the mean ITA-PSV and EDV in GTT is most likely a result of the stimulation of the thyroid gland by hCG or molecular variants of hCG with higher thyrotrophic activity.

In the present study, the right and left ITA-PSV and EDV were found to be significantly lower in pregnant than in non-pregnant patients with GD. GD is an autoimmune disease, and the TRAb level plays a central role in the pathogenesis of GD (15). In clinical practice, GD can be diagnosed based upon the clinical presentation of the patients; however, TRAb level is useful for establishing a diagnosis in uncertain clinical situations, including the differential diagnosis between GTT and GD during pregnancy (16). In this study, the TRAb level was normal in all patients with GTT, and it was higher than normal in 97% and 96% of pregnant and non-pregnant patients with GD, respectively. This result was consistent with previous reports (17,18). However, similar to ITA-PSV and EDV, the TRAb level among GD patients was significantly lower in pregnant patients than in non-pregnant patients.

Pregnancy has a profound effect on the immune system and, as in other autoimmune diseases, the autoantibody titers decrease in autoimmune thyroid diseases during pregnancy (19,20). Although still not fully understood, it is thought that these changes in the immune system occur to protect the fetal allograft during pregnancy (19,20). Although no other studies have compared TRAb levels between pregnant and non-pregnant patients with newly diagnosed GD, the lower serum TRAb levels observed in pregnant compared with non-pregnant patients in this study are most likely related to the immunosuppressive effect of pregnancy.

In the current study, we also found a positive correlation between ITA blood flow velocities and TRAb levels. Ueda et al. previously found that the serum TRAb level was significantly and positively correlated with ITA PSV in patients whose GD had relapsed (21). Baldini et al. also found an association of increased ITA-PSV and high levels of TRAb in the relapsing form of GD and suggested that thyroid hypervascularization was most likely related to the activity of the underlying autoimmune processes (22). As demonstrated in our study, among GD patients, the lower ITA blood flow velocities in pregnant compared with non-pregnant patients may be related to the lower TRAb levels seen in pregnant patients with GD. Presumably, as a result of the lower TRAb levels seen in pregnant patients with GD as well as the stimulation of the thyroid gland stimulation by hCG or its molecular variants in patients with GTT, an overlap occurred between the ITA blood flow velocities measured with CFDUSG. Consequently, the diagnostic value of the ITA blood flow velocity measured with CFDUSG was not high during pregnancy. These results also suggest that high ITA blood flow velocities are neither pathognomonic nor specific for GD and can be seen in GTT.

**Table 3 -** The most appropriate cutoff values for the right and left ITA-blood flow velocities for differentiating GTT from GD during pregnancy.

| | Cutoff value | AUC | Sensitivity/Specificity (%) | PPV (%) | NPV (%) | CI (95%) | Diagnostic accuracy (%) |
|---|---|---|---|---|---|---|---|
| Right ITA PSV | 29.4 cm/sn | 0.844 | 77.4/78 | 82.1 | 72.7 | 0.756-0.932 | 77 |
| Right ITA EDV | 11.95 cm/sn | 0.789 | 74.2/70.7 | 78.4 | 65.7 | 0.685-0.893 | 72 |
| Left ITA PSV | 26.65 cm/sn | 0.778 | 74.2/68.3 | 77.8 | 63.9 | 0.668-0.887 | 70 |
| Left ITA EDV | 12.7 cm/sn | 0.750 | 74.2/68.3 | 77.8 | 63.9 | 0.637-0.864 | 70 |

**ITA**: inferior thyroid artery, **PSV**: peak systolic velocity, **EDV**: end-diastolic velocity, **AUC**: area under the curve, **PPV**: positive predictive value, **NPV**: negative predictive value, **CI**: confidence interval.

The main limitation of this study is that all pregnant patients with thyrotoxicosis were diagnosed with GTT and GD based mainly on the TRAb level results. Therefore, it was difficult to compare the ITA blood flow velocity with TRAb level for differential diagnoses between GTT and GD. However, the follow-up data from our study demonstrate that the TRAb level is better than Doppler ultrasonography for the differential diagnosis of these two distinct diseases during pregnancy.

In summary, this study suggests that the measurement of ITA blood flow velocities with CFDUSG does not provide sufficient sensitivity and specificity to be recommended as an initial diagnostic test for differential diagnoses between GTT and GD during pregnancy. CFDUSG may be used as an auxiliary diagnostic tool, but the results should be interpreted with caution and in the context of additional clinical and laboratory findings.

**Conflict of interest**: The authors of this study declare that they have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Zuhur SS contributed to the study design, implementation, data analysis and preparation of the manuscript. Özel A performed the ultrasonographic examinations and contributed to the study design. Velet S, Çil E recruited and screened the patients. Buğdaci MS, Altuntas Y contributed to the data analysis and preparation of the manuscript.

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