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Original article

Thyroid blood flow as a useful predictor of relapse of Graves' disease after normal delivery in patients with Graves' disease

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ABSTRACT

Objective: Measurement of the peak systolic velocity (PSV) in the inferior thyroid artery (ITA) before withdrawal of an anti-thyroid drug (ATD) is useful for predicting relapse of Graves' disease (GD). We further investigated whether the ITA-PSV can be used for prediction of GD relapse after delivery in euthyroid women with GD who stopped ATD administration during mid- to late pregnancy.

Patients and methods: ITA-PSV was monitored monthly for three months after delivery in 42 women with GD aged from 24 to 45 years old (mean \pm SE: 34.7 \pm 0.92 years old) who met the above criteria. To confirm the stability of the measurement, ITA-PSV was also measured monthly in 32 age-matched non-pregnant normal women and for three months after delivery in 10 age-matched women.

Results: ITA-PSV and thyroid volume were higher in women with GD immediately after delivery compared to normal women, but the levels of TSH receptor antibody (TRAb) and thyroid-stimulating antibody (TSAb) did not differ significantly between the two groups. Of the 42 patients, 23 had relapse of GD and the smoker/non-smoker ratio and thyroid volume in these patients immediately after delivery were significantly higher than those in the 19 patients who did not undergo relapse (10/23 vs. 0/19, $p < 0.0001$; 24280.3 \pm 2280.9 vs. 19670.0 \pm 2103.7 mm³, $p = 0.046$), while ITA-PSV, TRAb and TSAb did not differ between the two groups of patients. The ITA-PSV ratio was calculated by dividing each value in the follow-up period by that obtained immediately after delivery. A significant increase in the mean ITA-PSV ratio occurred at least one month before the time of relapse (1.00 \pm 0.00 at -3 months before relapse vs. 1.46 \pm 0.12 at -1 month, $p = 0.010$; 1.00 \pm 0.00 at -3 months vs. 1.77 \pm 0.13 at the time of relapse, $p = 0.0048$). In contrast, there were no significant changes in this ratio during the follow-up period in non-relapse patients.

Conclusion: Monthly measurement of ITA-PSV after delivery in remitted euthyroid women with GD may assist in early prediction of GD relapse.

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1. Introduction

The overall relapse rate of Graves' disease (GD) is as high as 30–50% [1], and women in the postpartum period have a particularly higher frequency of GD relapse due to the profound autoimmune modification that occurs after delivery [2]. However, there is no established method for prediction of postpartum relapse of GD, except for detection of thyroid-stimulating antibodies (TSAb) early in pregnancy [3]. The increased sophistication of ultrasonographic instruments has made it possible to measure blood flow in the inferior thyroid artery (ITA), a major feeding artery in the thyroid (Fig. 1), and this is a useful method for differentiation of various autoimmune thyroid diseases [4]. Moreover, we recently reported

that the peak systolic velocity (PSV) in the ITA might assist in the prediction of early GD relapse after anti-thyroid drug (ATD) withdrawal [5] and that the ITA-PSV in untreated hyperthyroid patients with GD may reflect GD activity and methimazole sensitivity [6]. The aim of the current study was to assess the value of monthly measurement of ITA-PSV by a pulsed Doppler method for predicting relapse of stimulatory hyperthyroidism after normal delivery in pregnant women with GD who maintained an euthyroid state without ATD administration in mid- to late pregnancy.

2. Patients and methods

2.1. Patients

Informed consent was obtained from all subjects. Pregnant women with GD aged from 24 to 45 years old (mean \pm SE:

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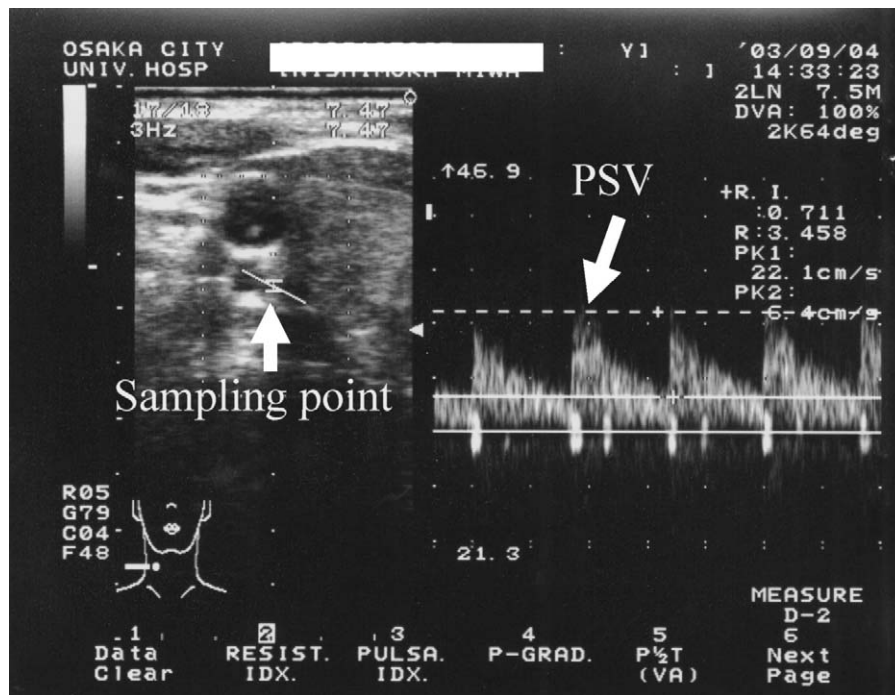


Fig. 1. Duplex Doppler recording of the right inferior thyroid artery in patients with Graves' disease. A Doppler image was used to determine the appropriate sampling point for pulsed Doppler recordings. The sample volume was positioned in the right inferior thyroid artery at the inflow point to the thyroid (arrow, left). The velocity waveform is displayed above the baseline to indicate the arterial blood flow (right).

34.7 ± 0.92 years old, $n = 42$) who had maintained an euthyroid state without ATD administration in mid- to late pregnancy were consecutively recruited into the study. ITA-PSV was measured at the time of enrolment and then every month until three months after delivery. Diagnosis of GD in these patients was based on a history of ATD administration during the first trimester of pregnancy. As controls, ITA-PSV was measured monthly for three months in 32 healthy women aged from 25 to 44 (35.7 ± 1.2) years old who were not pregnant and in 10 healthy women aged from 29 to 37 (33.0 ± 1.3) years old for three months after normal delivery. GD relapse was defined as an increase in the serum level of free thyroxine (FT₄) above the normal upper range with suppression of serum TSH below the normal lower limit. A diagnosis of hyperthyroidism due to GD relapse rather than postpartum thyroiditis was made on the basis of a positive reaction for TSH receptor antibody (TRAb) or TSAb, or a requirement for ATD therapy to normalize serum levels of FT₄ for several months.

2.2. Biochemical parameters for thyroid function and autoantibodies

Blood samples drawn just before the ultrasound study after an overnight fast were kept on ice for 1 h and then centrifuged at 1000 g for 10 min. The serum and plasma samples obtained were stored in aliquots at -20 °C until assayed. Measurements were made immediately after thawing. Commercially available high-capacity, random-access immunoassay kits were used to measure FT₄, FT₃ and TSH levels (Chiron Diagnostics, East Walpole, MA, USA) [7]. TRAb and TSAb were measured by radioreceptor assay using a commercial kit (Cosmic Corp., Tokyo, Japan) [8] and a radioimmunoassay kit (Yamasa, Chiba, Japan) [9], respectively.

2.3. Blood flow in the inferior thyroid artery and thyroid volume

Thyroid blood flow was measured in the ITA as previously reported [5,6] (Fig. 1). Ultrasound examinations were performed

using a duplex Doppler apparatus (SSD 2000, Aloka, Tokyo, Japan) with a 5 MHz convex array probe in both the color Doppler and pulsed Doppler modes. The angle correction cursor was parallel to the direction of flow. The peak systolic flow velocity (PSV) of the right ITA, which is automatically calculated by the ultrasound apparatus, was used as an index of ITA thyroid blood flow. All measurements were performed by one examiner (M. F.-U.), who was blinded to the subject characteristics. Thyroid blood flow was determined in the ITA since this artery is a major contributor to thyroid blood flow, identification and measurement are straightforward, and the procedure has a low coefficient of variation (CV) (< 5.2%). The change of blood flow in the ITA was expressed as the change in the ITA-PSV ratio, which was obtained by dividing ITA-PSV at each measurement time point by the value obtained immediately after delivery. In normal non-pregnant women, the ITA-PSV ratio was calculated by dividing ITA-PSV at each time point by the value from the first examination. Thyroid volume was measured by ultrasound and calculated using an ellipsoid model (width × length × thickness × 0.7 for each lobe) [10].

2.4. Statistical analysis

Data are shown as means ± SE unless otherwise indicated. Statistical analysis was performed with StatView v.5.0 (SAS Institute, Cary, NC). Differences in clinical factors among GD patients, normal non-pregnant women, and normal women after delivery were examined using a two-tailed multiple *t*-test with a Bonferroni correction. Differences in clinical values between GD patients with and without relapse were examined using a Mann-Whitney U test for assessment of medians. The difference in the smoker/non-smoker ratio was analyzed by Chi² test. Differences in mean monthly ITA-PSV values in each group were assessed by a two-tailed Student *t*-test for paired data. Values of $p < 0.05$ were considered to be statistically significant.

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