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CLINICAL ARTICLE

Evaluation of thyrotoxicosis during pregnancy with color flow Doppler sonography

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Abstract

Objective: To determine whether color flow Doppler sonography (CFDS) is useful in differentiating Graves vs non-Graves thyrotoxicosis during pregnancy, when nuclear imaging is contraindicated. *Methods:* Ten pregnant women with thyrotoxicosis were divided into Graves and non-Graves disease groups following CFDS evaluation of thyroid volume, thyroid vascularity, and inferior thyroid artery (ITA) flow velocity. Each patient was matched with a euthyroid woman of the same pregnancy duration. *Results:* Of the 10 patients, 3 were diagnosed with Graves disease, 4 with gestational toxicosis, and 3 with destructive thyroiditis. Those in the Graves disease group had a greater thyroid gland volume (18.9±1.5 cm^3 vs 12.1±2.4 cm^3; $P<0.05$), greater thyroid vascularity, and greater ITA flow velocity than those in the non-Graves disease group (92±13 cm/s vs 20.4±2.4 cm/s; $P<0.05$). There was no significant difference in the corresponding values between the patients with gestational toxicosis and those with destructive thyroiditis or between them and their healthy controls. *Conclusion:* Thyroid evaluation by CFDS is useful for the differential diagnosis of thyrotoxicosis in pregnant women.

1. Introduction

Thyrotoxicosis, or hyperthyroidism, occurs in Graves disease (GD), destructive thyroiditis in its thyrotoxic phase, and gestational thyrotoxicosis, and is seen in about 0.1% to 0.4% of pregnant women [1]. The evaluation of pregnant women with thyrotoxicosis is doubly difficult. Hyperthyroidism mimics common physiologic changes of pregnancy such as the enlargement of the thyroid gland, tachycardia, wide pulse pressure, and thyroid hormone alterations, and established investigations such as nuclear imaging are contraindicated. In the presence of ophthalmopathy or of skin and/or nail changes, the diagnosis of GD is not difficult

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Table 1 Clinical, biochemical, and color flow Doppler sonography data of patients with thyrotoxicosis

Patient no.	Age, years	Symptoms	Pregnancy duration, week	Eye signs	T3, ng/dL	T4, ng/dL	T3/T4 ratio	TSH, μIU/mL	TPO	Thyroid gland volume, cm^3	Vascularity, grade	ITA velocity, cm/s	Diagnosis	3-month follow-up
1	24	Weight loss Palpitations Congestive ophthalmopathy	16	Yes	390	23.4	16.7	<0.01	Negative	20.5	4	96	GD	Euthyroid on treatment [a]
2	23	Palpitations Vomiting	12	No	261	18.2	14.3	0.18	-	10.9	1	13	GT	Euthyroid
3	27	Poor weight gain Heat intolerance	30	No	360	19.2	18.8	<0.01	Positive	12.9	1	18	DT	Hypothyroidism [b]
4	25	Tremors Palpitations Congestive ophthalmopathy	22	Yes	800	27.9	28.7	<0.01	Positive	17.5	4	103	GD	Euthyroid, on treatment [a]
5	24	Palpitations Vomiting	18	No	250	21.5	11.6	<0.01	Positive	15.9	1	23	DT	Euthyroid
6	27	Weight loss Palpitations	19	No	406	18	22.5	0.13	Negative	14.4	2	25	DT	Hypothyroidism [b]
7	28	Weight loss Palpitations	10	No	180	18.6	9.7	0.18	-	9.5	1	21	GT	Euthyroid
8	21	Weight loss Palpitations Hyperemesis	14	No	426	21.0	20.3	<0.01	-	10.9	1	23	GT	Euthyroid
9	31	Palpitations	16	No	248	19.4	12.8	0.08	Negative	10.0	1	20	GT	Euthyroid
10	22	Palpitations Goiter No weight gain	30	Yes	530	18.6	28.5	<0.01	Positive	18.9	3	78	GD	Hyperthyroidism [a]

Abbreviations: DT, destructive thyroiditis; GD, Graves disease; GT, gestational thyrotoxicosis; ITA. inferior thyroid artery; ST, destructive thyroiditis T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

[a] The patient was taking antithyroid drugs.

[b] The patient was taking levothyroxine.

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to reach. It is difficult to differentiate between the Graves and non-Graves forms of thyrotoxicosis in their absence, however, and yet the differentiation is essential because their treatments differ. Antithyroid drugs are indicated only in GD as the other forms are self-limiting.

Although color flow Doppler sonography (CFDS) of the thyroid gland has been established as a reliable tool in the differential diagnosis of thyrotoxicosis, it has been underutilized [2,3]. Although studies exist on the role of CFDS in the diagnosis of thyrotoxicosis in the non-pregnant state, its role during pregnancy has not been established. We conducted this study with 10 pregnant women with thyrotoxicosis to characterize CFDS findings based on the underlying thyroid disease and to report on the use of CFDS in the differential diagnosis of this clinically challenging condition, especially during pregnancy.

2. Materials and methods

We conducted the study with 10 consecutive pregnant women referred for thyrotoxicosis in the last 6 months. Their mean ± SD age was 25.2 ± 3.04 years and mean pregnancy duration at presentation was 18.7 ± 6.8 weeks. All had a high free triiodothyronine (FT_3) to free thyroxine (FT_4) ratio or a total serum T_4 level greater than 1.5 times the upper limit of normal, with thyroid-stimulating hormone levels of 0.1 mIU/L or less. A detailed history was taken with emphasis on pregnancy duration, hyperemesis, palpitations, weight loss, visual complaints, a similar condition during a past pregnancy, or a family history of thyroid disease. Radial pulse, blood pressure, pulse pressure, ophthalmopathy, skin and nail changes related to hyperthyroidism, thyroid volume, and thyroid bruit were evaluated. A test for thyroid peroxidase (TPO) antibody was requested when autoimmune thyroiditis was suspected.

The patients were divided into 3 groups for analysis: a GD group ($n=3$); a non-GD group ($n=7$) comprising patients with destructive thyroiditis ($n=3$) and patients with gestational thyrotoxicosis ($n=4$); and a control group ($n=10$). Graves disease was defined as hyperthyroidism associated with clinical features such as weight loss or poor weight gain, palpitations, goiter, ophthalmopathy (NOSPECS class 3 or higher), and/or a T3/T4 ratio greater than 20 [4]. Destructive thyroiditis was defined as hyperthyroidism associated with any 2 of following: (A) a T3/T4 ratio less than 20; (B) a positive result to the TPO antibody test; and (3) self-limiting hyperthyroidism, with documented hypothyroidism or euthyroidism on follow-up. Gestational thyrotoxicosis was defined as hyperthyroidism presenting within the first 3 months of pregnancy and associated with hyperemesis gravidarum, but no longer present on follow-up. A T3/T4 ratio greater than 20 was seen in 2 of the 3 patients in the GD group and 2 of the 7 patients in the non-GD group. The results of the thyroid peroxidase antibody test were positive in 2 of 3 the patients in the GD group and 2 of the 7 patients in the non-GD group.

A CFDS evaluation of the thyroid gland was performed for all patients by the same radiologist to avoid interobserver variability. The scans were done using a real-time scanner (Envisor; Philips Medical Systems, Andover, MA, USA) with a 7.5-MHz linear probe. Various parameters were assessed, such as echogenecity, thyroid volume and vascularity, and flow velocity of inferior thyroid arteries (ITAs). Thyroid volume was calculated in cubic centimeters using the following equation: (Wr × Tr × Lr + Wl × Tl × Ll) × 0.7, with *W* as the maximum width, *T* as the thickness, and *L* as the length of the right (r) or left (l) lobe, all in centimeters [5]. Thyroid gland vascularity was graded from 1 (low vascularity) to 4 ("inferno pattern") [6,7]. Blood flow in the right and left ITAs was reported as peak systolic velocity (PSV) in centimeters per second from Doppler spectrum time-averaged mean velocity and vessel diameter, with the Doppler angle corrected to 60° or less; ITA diameter was calculated by positioning calipers on the internal walls on the gray-scale image; and flow velocity was calculated by measuring twice on each side, with the arithmetic mean taken to minimize intrarater variability. As there was no significant difference between right and left ITA flow (data not shown), the mean from both sides combined was used. All tests were performed in a thyrotoxic phase before treatment was initiated.

Summary data are expressed as mean ± SD and comparisons between means were done using one-way analysis of variance. $P<0.05$ was considered significant.

3. Results

The patients' clinical, biochemical, and CFDS data are summarized in Table 1. The mean thyroid gland volume was greater in the GD than in the non-GD or in the controls group (18.9 ± 1.5 cm^3 vs 12.1 ± 2.4 cm^3 vs 10.9 ± 2 cm^3; $P<0.05$). The mean ITA flow velocity was also greater in the GD than in the non-GD or in the control group (92 ± 13 cm/s vs 20.4 ± 2.4 cm/s vs 16.6 ± 4.3 cm/s; $P<0.05$). The intraparenchymal vascularity pattern was significantly increased in all patients with GD. The Doppler parameters did not differ significantly between patients with destructive thyroiditis, those with gestational toxicosis, and the matched controls. Two patients in the non-GD group had hypothyroidism on follow-up and levothyroxine treatment was initiated.

4. Discussion

This study highlights the utility of CFDS in the differential diagnosis of thyrotoxicosis during pregnancy. The clinical characteristics of patients with GD were not significantly different from those with non-Graves thyrotoxicosis, and features such as goiter and hyperdynamic circulation can be seen in normal pregnancies. Antithyroid drugs are indicated only in GD and are not indicated in the management of other forms of thyrotoxicosis. Hence, the etiologic differentiation of thyrotoxicosis is essential for proper drug therapy.

Technetium 99 m-labeled pertechnate thyroid uptake scans differentiate between GD (increased uptake) and destructive thyroiditis (decreased uptake), but the scans are contraindicated during pregnancy. The other measures proposed in this differentiation are a T3/T4 ratio greater than 20 and a third-generation, highly sensitive thyroid-stimulating hormone (TSH) assay [8,9]. In our study a T3/T4 ratio greater than 20 was seen in 2 of 3 patients with GD and 2 of 7 patients with non-GD thyrotoxicosis. This indicates a marked overlap of this ratio between the 2 types of thyrotoxicosis, as reported earlier [10]. A TSH receptor antibody measurement is useful for the diagnosis of GD, and is positive in 99% to 100% of the patients affected with this condition [11]. However, the TSH receptor antibody assay is not widely available in our country, and a reliable, quick, non-isotopic method of establishing the correct diagnosis of thyrotoxicosis in pregnancy is therefore desirable.

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Doppler ultrasonography has previously been found to be useful in the differential diagnosis of thyrotoxicosis [6,12,13]. Increased parenchymal vascularity and a peak systolic velocity greater than 50 cm/s indicates GD as the cause of thyrotoxicosis [14,15]. In our study, thyroid vascularity and peak systolic velocity were significantly greater in the GD than in the non-GD group, as was also found in earlier studies [6,13]. With a technique such as power Doppler sonography, CFDS of the thyroid gland is projected to overtake nuclear imaging in the etiologic diagnosis of thyrotoxicosis [2,3,16,17].

Our study is limited by its small sample size and lack of TSH receptor antibody confirmation of GD. Interoperator variability of the Doppler study was avoided because a single radiologist performed ultrasonography in all patients. Even though our results indicated no overlap between the 2 conditions, further studies with larger numbers of patients may strengthen our conclusion.

We demonstrated that ITA blood flow assessment by CFDS helps in the etiologic diagnosis of thyrotoxicosis during pregnancy, and suggest that CFDS be included in the thyrotoxicosis workup during pregnancy.

References

[1] Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynecol 2006;108:1283–92.
[2] Kurita S, Sakurai M, Kita Y, Ota T, Ando H, Kaneko S, et al. Measurement of thyroid blood flow area is useful for diagnosing the cause of thyrotoxicosis. Thyroid 2005;15(11):1249–52.
[3] Erdogan MF, Anil C, Cesur M, Baskal N, Erdogan G. Color flow Doppler sonography for the etiologic diagnosis of hyperthyroidism. Thyroid 2007;17(3):223–8.
[4] Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab 1977;44:203–4.
[5] Murakami Y, Takamatsu J, Sakane S, Kuma K, Ohsawa N. Changes in thyroid volume in response to radioactive iodine for Graves' hyperthyroidism correlated with activity of thyroid-stimulating antibody and treatment outcome. J Clin Endocrinol Metab 1996;81:3257–60.
[6] Bogazzi F, Bartalena L, Brogioni S, Burelli A, Manetti L, Tanda ML, et al. Thyroid vascularity and blood flow are not dependent on serum thyroid hormone levels: studies in vivo by color flow doppler sonography. Eur J Endocrinol 1999;140:452–6.
[7] Ralls PW, Mayekawa DS, Lee KP, Colletti PM, Radin DR, Boswell WD, et al. Color-flow Doppler sonography in Graves' disease: "thyroid inferno.". Am J Roentgenol 1988;150:781–4.
[8] Amino N, Yabu Y, Miyai K, Fujie K, Azukizawa M, Onishi T, et al. Differentiation of thyrotoxicosis induced by thyroid destruction from Graves' disease. Lancet 1978;2:344–6.
[9] Kasagi K, Kousaka T, Misaki T, Iwata M, Alam MS, Konishi J. Comparison of serum thyrotropin concentration determined by a third generation assay in patients with various types of overt and subclinical thyrotoxicosis. Clin Endocrinol (Oxf) 1999;50:185–9.
[10] Izumi Y, Hidaka Y, Tada H, Takano T, Kashiwai T, Tatsumi KI, et al. Simple and practical parameters for differentiation between destruction induced thyrotoxicosis and Graves' thyrotoxicosis. Clin Endocrinol (Oxf) 2002;57:51–8.
[11] Costagliola S, Morgenthaler NG, Hoermann R, Badenhoop K, Struck J, Fritag D, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab 1999;84:90–7.
[12] Vitti P, Rago T, Mazzeo S, Brogioni S, Lampis M, De Liperi A, et al. Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. J Endocrinol Invest 1995;18:857–61.
[13] Ota H, Amino N, Morita S, Kobayashi K, Kubota S, Fukata S, et al. Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. Clin Endocrinol (Oxf) 2007;67:41–5.
[14] Summaria V, Salvatori M, Rufini V, Mirk P, Garganese MC, Romani M. Diagnostic imaging in thyrotoxicosis. Rays 1999;24(2):273–300.
[15] Saleh A, Cohnen M, Furst G, Godehardt E, Modder U, Feldkamp J. Differential diagnosis of hyperthyroidism: Doppler sonographic quantification of thyroid blood flow distinguishes between Graves' disease and diffuse toxic goiter. Exp Clin Endocrinol Diabetes 2002;110(1):32–6.
[16] Arslan H, Unal O, Algun E, Harman M, Sakarya ME. Power Doppler sonography in the diagnosis of Graves' disease. Eur J Ultrasound 2000;11(2):117–22.
[17] Bogazzi F, Vitti P. Could improved ultrasound and power Doppler replace thyroidal radioiodine uptake to assess thyroid disease? Nat Clin Pract Endocrinol Metab 2008;4(2):70–1.

Please cite this article as: Kumar KVSH, et al, Evaluation of thyrotoxicosis during pregnancy with color flow Doppler sonography, Int J Gynecol Obstet (2008), doi:10.1016/j.ijgo.2008.03.014