Original Article

Utility of Colour Flow Doppler Ultrasonography to Differentiate Gestational Transient Thyrotoxicosis and Graves Disease in Pregnancy

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Abstract

Introduction: Accurate diagnosis of the etiology of thyrotoxicosis in pregnancy is important to guide appropriate treatment. The role of thyroid blood flow velocities by color Doppler to differentiate between Graves' disease (GD) in pregnancy and gestational transient thyrotoxicosis (GTT) is not well explored. This study evaluated inferior thyroid artery (ITA)-peak systolic velocity (PSV) as a marker for differential diagnosis of thyrotoxicosis in pregnancy. **Methods:** Fifty-six pregnant patients with thyrotoxicosis (30 with GTT and 26 with GD) along with 30 age-matched healthy euthyroid pregnant subjects were enrolled. Thyroid ultrasound examinations and color Doppler was performed by an ultrasound scanner. The studies of the right and left ITAs were performed with Doppler, and the PSV and End diastolic velocity (EDV) values were obtained from the right and left ITA. **Results:** The mean total T4 value in GD and GTT were almost similar (25.04 ± 2.43 vs 23.25 ± 2.81, *P* value = 0.14). Beta HCG levels were significantly higher in cases of GTT as compared to GD (152946 ± 26694 vs 120608 ± 21244 mIU/ml, $P < 0.0001$). The ITA-PSV and EDV in patients with GTT were significantly lower than those of pregnant patients with GD (right: 22.5 ± 6.8 and 8.3 ± 2.3; left: 22.97 ± 6.3 and 8.13 ± 2.01; $P < 0.001$). receiver-operating-characteristic (ROC) curve demonstrated an optimal cutoff value of mean right ITA-PSV of 35 cm/sec to differentiate GTT from GD during pregnancy, with 84.6% and 93.3% sensitivity and specificity. **Conclusion:** Thyroid artery velocities can help to differentiate between GD and GTT. The cutoff point of mean ITA-PSV at 35 cm/s had an excellent value in differentiating between the two, with good sensitivity and specificity.

Keywords: GD-Graves'disease, GTT-Gestational transient thyrotoxicosis, PSV-Peak systolic velocity

Introduction

Thyrotoxicosis is seen in up to 0.1% to 0.5% of pregnancies. Graves' disease (GD) is the overwhelming autoimmune cause of thyrotoxicosis during pregnancy and if left untreated, it can lead to multiple maternal and fetal complications. Placental hCG stimulation of the thyroid gland in the first trimester exacerbates the symptoms, while immunological responses caused by changes in lymphocyte subsets could explain spontaneous improvement in the second half of pregnancy and recurrences in the postpartum period.[1,2] In contrast, gestational transient thyrotoxicosis (GTT) is a non-autoimmune transient cause of thyrotoxicosis that often resolves spontaneously by 18 weeks of gestation.[3] It is thought to be related to stimulation of the thyroid gland by human chorionic gonadotropin (hCG) or related molecular variants. In high concentrations as found in hyperemesis gravidarum (HG) (loss of 5% body weight, dehydration, and ketonuria), multiple gestation, or molar pregnancy, hCG will cause hyperthyroidism with diffuse goiter, elevated T4, and a suppressed TSH.[4,5]

Accurate diagnosis of etiology of thyrotoxicosis in pregnancy is important to guide appropriate treatment. The standard investigation such as thyroid scintigraphy, for evaluation of thyrotoxicosis, is contraindicated in pregnancy. The

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assessment of TSH-receptor antibody (TRAb) levels can be useful when investigating thyrotoxicosis of uncertain etiology, but these assays are not widely available, and cost is an important factor.[6] Thyroid ultrasonography is non-invasive, cost-effective, safe, and portable imaging modality and can be a practical alternative. The measurement of inferior thyroid artery (ITA)-peak systolic velocity (PSV), using colour-flow Doppler ultrasonography (CFDUSG) has proven to be highly sensitive and specific in cases with Graves' Disease (GD) outside pregnancy.[7,8] However, the utility of CFDUSG to differentiate GD in pregnancy and GTT) is limited by variable sensitivity and specificity among different studies, which have been carried out in different ethnic populations.[9,10] CFDUSG may be a reliable and cost-effective alternative especially in resource constraint settings. The aim of the study was to determine the utility of ITA - blood flow velocities, assessed by CFDUSG to differentiate between GTT and GD in pregnancy.

Materials and Methods

This was a hospital-based cross-sectional study, conducted at the Department of Endocrinology, during the period from September 2019 to March 2021.

Patients

Pregnant women in their first trimester of pregnancy visiting endocrine OP for evaluation of thyrotoxicosis were enrolled. All of the cases were newly diagnosed and had not received any antithyroid therapy before inclusion in the study. Patients with destructive thyroiditis, single functioning nodule, or multinodular goiter were excluded. Fifty-six pregnant patients with thyrotoxicosis (30 with GTT and 26 with GD) were found to be eligible for the study. Thirty age-matched healthy euthyroid pregnant subjects were enrolled. The cases were differentiated between Graves and GTT based on history, clinical findings, thyroid function tests, and TRAb levels. GD in pregnant patients was defined based on clinical findings, high TRAb (more than the upper limit of normal), high thyroid hormone levels (T4 >21 µg/dl), decreased TSH levels, and/or presence of a history of hyperthyroidism before pregnancy. GTT was defined as suppressed TSH and high thyroid hormone levels (T4 >21 µg/dl) in the first trimester of pregnancy and associated with HG, but self-limiting on follow-up, absence of clinical findings of GD and normal TRAb levels. HG was defined as ketosis, electrolyte disturbances, and weight loss of 5% of the nonpregnant weight.[5]

Hormone assays

Serum samples to determine T3, T4, and TSH levels for all subjects were collected after an overnight fast. On the day of the ultrasonography examination, samples for beta-HCG and TRAb levels, in cases with thyrotoxicosis, were collected. Serum T3, T4, and TSH were assessed using a direct chemiluminescence immunoassay (Siemens, ADVIA Centaur XP Immunoassay System). Beta-HCG levels were done by ELISA Kits (by DRG International, Germany), and Serum TRAb levels were done by TRAb-ELISA Kits (by Sincere Biotech, Beijing)

Doppler ultrasonography

Thyroid ultrasound examinations and color Doppler were performed by ultrasound scanner (LOGIQ V5, GE Healthcare, India) equipped with a 7–14 MHz broadband linear array transducer [Figure 1]. The volume (V) of each lobe was calculated, using the ellipsoid formula with a correction factor: V (mL) = L (cm) × A-P (cm) × W (cm) ×0.523. The studies of the right and left ITAs were performed with Doppler, and the PSV and EDV values were obtained from the right and left ITA. The limits of normal PSV values are generally accepted as 15–30 cm/s for ITA.[11]

Maternal thyroid function was monitored with T3, T4, and TSH levels at monthly intervals. All patients diagnosed with GTT were followed up expectantly until euthyroid status, without treatment with antithyroid drugs. Antithyroid therapy with propylthiouracil (PTU) was given to all pregnant patients diagnosed with GD, after the assessment of thyroid blood flows.

Statistical analysis

Data were analyzed using the SPSS software version 23.0 for Windows. Scale variables are presented as the mean ± standard deviation (mean ± 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 canonical correlation analysis was used to determine the correlation between the ITA flow velocity and the TRAb level. The most appropriate diagnostic cutoff was determined, for the right and left ITA-PSV and EDV using receiver-operating-characteristic (ROC) analysis. Sensitivity, specificity, and diagnostic accuracy were calculated for the obtained cutoff. *P* value < 0.05 was considered to be statistically significant.

Ethical aspect

Approval from the Institutional Ethics Committee (Approval number: IEC/GMC/2019/04/7; Approval date: August 23rd

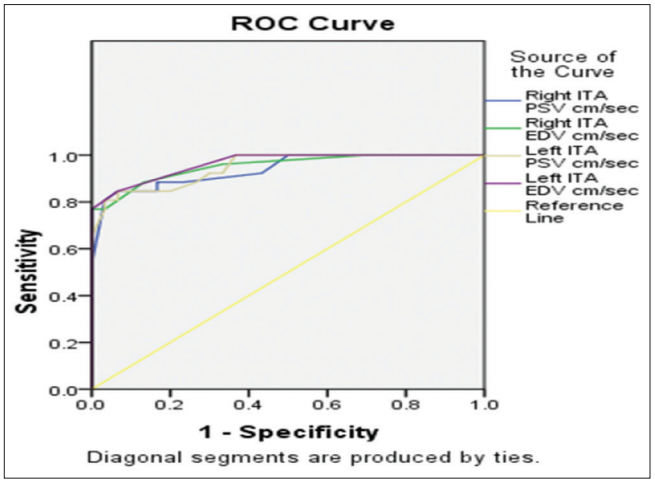

Figure 1: ROC curve of right and left ITA blood flow velocities

, 2019) was taken prior to the conduct of the study. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study procedures followed were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1964, as revised in 2013.

Results

Total of 86 subjects participated in this study. Twenty-six patients had GD in pregnancy (Group I), 30 patients had GTT (Group II), and 30 normal euthyroid pregnant women (Group III) were enrolled. The demographic and laboratory characteristics of the patients are summarized in Table 1. All the study subjects had a total T4 value >21 µg/dl and the mean total T4 value in GD and GTT were almost similar (25.04 ± 2.43 vs 23.25 ± 2.81, *P* value = 0.14). Beta HCG levels were significantly higher in cases of GTT as compared to GD (152946 ± 26694 vs 120608 ± 21244 mIU/ml, $P < 0.0001$).

Ultrasound characteristics

Patients with GD had higher thyroid volume than patients with GTT (13.33 ± 1.84 vs 10.15 ± 1.14 ml $P < .001$). The (Mean ± SD), ITA-flow velocities of all groups of study participants are shown in Tables 2 and 3. The ITA-PSV and EDV in patients with GTT were significantly lower than those of pregnant patients with GD ($P < 0.001$) [Table 2]. The ITA-PSV and EDV in patients with GTT were significantly higher than those of euthyroid pregnant subjects ($P < 0.001$) [Table 3]. The right and left ITA PSV in euthyroid pregnant subjects were 15.73 ± 3.99 and 15.43 ± 3.77 cm/sec.

Using the ROC curve, the most appropriate cutoff values for ITA velocities to differentiate between GTT from GD during pregnancy were obtained. The AUC was calculated. The optimal cutoff value of mean right ITA-PSV was 35 cm/sec to differentiate between GTT from GD during pregnancy, with 84.6% and 93.3% sensitivity and specificity [Figure 1]. Of the patients with GTT, 3 (10%) had right ITA-PSV and 3 (10%) had left ITA-PSV, above the cutoff values. Similarly, of the pregnant patients with GD, 4 (15.3%) had right ITA-PSV and 4 (15.3%) had left ITA-PSV, below the cutoff values. Hence, overlap was found among ITA blood flow velocities in a few cases of patients with GTT and pregnant patients with GD.

Table 1: The demographic and laboratory characteristics of the study subjects

Parameter	Group I *n*=26	Group II *n*=30	Group III *n*=30	*P*
Mean age (years)	27.5±1.9	24.3±3	26.7±3.4	<0.0001
Primigravida (%)	10 (38%)	17 (56%)	45	---------
Twin pregnancy (%)	-	2 (6.6%)	-	---------
Family history of thyroid disorders (%)	11 (42.3%)	4 (13.3%)	-	---------
Hyperemesis gravidarum (%)	4 (15.3%)	5 (16.6%)	4 (13.3%)	---------
Mean duration of symptoms (months)	6±2.8	2.33±0.75	-	<0.0001
Mean BMI (kg/m^2)	20.8±0.9	22±0.7	24.8±1.1	<0.0001
Mean pulse rate (beats/min)	111±10	104±9	89±7	0.005
Mean systolic blood pressure (mm Hg)	116.2±12.7	114.3±12.5	104.3±9.1	0.3
Mean diastolic blood pressure (mm Hg)	74.6±6.5	74.3±5	77±4.5	0.4
Goiter size:				
No goitre	----------	----------	9 (30%)	----------
Grade 1 (%)	17 (65.4%)	27 (90%)	20 (66.6%)	
Grade 2 (%)	9 (34.6%)	3 (10%)	1 (3.3%)	
CBC parameters:				
Mean hemoglobin (g/dl)	12.4±1.4	12±0.8	13.3±0.9	0.08
Mean WBC count (X 10^3/µL)	5.5±1.3	6.8±1.8	6.9±1.9	0.0008
Absolute neutrophil count (X 10^3/µL)	2.9±0.7	3.5±1.2	4.4±1.9	0.01
Absolute lymphocyte count (X 10^3/µL)	1.6±0.7	1.9±0.8	1.8±0.8	0.04
Mean platelet count (X 10^3/µL)	3.1±0.8	3±0.9	2.9±0.8	0.4
Liver function test:				
Mean total bilirubin (mg/dl)	0.8±0.2	0.7±0.2	0.7±0.5	0.06
Mean AST (U/L)	27.6±4.4	27.7±5	26.5±4.1	0.4
Mean ALT (U/L)	34.6±7.7	31.7±7	30.4±6.1	0.08
Total T3 (ng/ml)	3.95±0.92	3.27±0.85	1.89±0.26	0.006
Total T4 (µg/dl)	25.04±2.43	23.25±2.81	9.8±1.54	0.14
TSH (0.55-4.78 mIU/ml)	0.004±0.007	0.02±0.029	2.24±0.49	0.006
Mean thyroid volume (ml)	13.3±1.8	10.1±1.1	8.4±1	<0.0001
TRAb (<1.6 IU/L)	5.23±2.1	0.46±0.1	-	<0.0001
Beta-HCG (mIU/ml)	120608±21244	152946±26694	-	<0.0001

Comparisons (*P*) provided are between Group I and Group II

Table 2: The comparison of right and left ITA blood flow velocities in GD with pregnancy and GTT

Parameter	GD with pregnancy *n*=26	GTT *n*=30	*P*
Right ITA PSV	43.04±12.9	22.5±6.8	<0.001
Right ITA EDV	16.46±4.6	8.3±2.3	<0.001
Left ITA PSV	43.15±13.1	22.97±6.3	<0.001
Left ITA EDV	16.62±4.4	8.13±2.01	<0.001

Table 3: The comparison of right and left ITA blood flow velocities in GTT with normal pregnancy subjects

Parameter	GTT (*n*=30)	Euthyroid pregnant subjects (*n*=30)	*P*
Right ITA PSV	22.5±6.8	15.73±3.99	<0.001
Right ITA EDV	8.3±2.3	7.1±1.7	0.034
Left ITA PSV	22.97±6.3	15.43±3.77	<0.001
Left ITA EDV	8.13±2.01	6.77±1.7	0.04

The correlation coefficient r demonstrated a positive correlation of the right and left ITA-PSV with the TRAb levels (r = 0.821, $P < 0.001$ for the right ITA PSV and r = 0.822, $P < 0.001$ for the left ITA-PSV, respectively).

The most appropriate cutoff for the right and left ITA-PSV and EDV along with its sensitivity, specificity, accuracy, positive predictive value, and negative predictive value are presented in Table 4.

Discussion

Determination of the etiology of thyrotoxicosis during pregnancy is important to guide appropriate treatment. Thyroid blood flow velocities have been found to be useful for the differential diagnosis of GD from thyroiditis. Role of thyroid blood flow velocities to differentiate between GD and GTT is not well explored. This study intended to look into the utility of ITA-PSV in the differential diagnosis of thyrotoxicosis in pregnancy. We found that ITA-PSV was significantly higher in GD than GTT and can be used as an initial investigation in a resource constraint setting to differentiate between GD and GTT. The cutoff point of mean ITA-PSV at 35 cm/s had an excellent value in differentiating between the two, with good sensitivity and specificity.

In the present study, the mean right and left ITA-PSV and EDV in cases with GTT were significantly lower than in GD with pregnancy, and significantly higher than that in healthy euthyroid pregnant subjects. The increase in the mean ITA-PSV and EDV in GTT as compared to normal euthyroid pregnant females is most likely due to stimulation of the thyroid gland by hCG or its molecular variants. Pregnancy has a significant effect on the immune system to maintain the fetal-maternal allograft.[12] In GD, there is a fall in thyroid autoantibodies-TRAbs, which is seen in almost all cases as pregnancy progresses through the second and third trimesters.[3,12]

As a result of the above two findings, that is, lower TRAb levels seen in pregnant patients with GD and the stimulation of the thyroid gland by hCG or its molecular variants in patients with GTT, an overlap is expected between the ITA blood flow velocities between these two groups. Consequently, the diagnostic value of the ITA blood flow velocity measured with CFDUSG is not extensively evaluated. Zuhur *et al*.[9] attempted to address this issue in 2012 and found that ITA-PSV may be used as an auxiliary diagnostic tool, and the cutoff proposed was 29.4 cm/s, with 77.4% and 78% sensitivity and specificity, respectively, to differentiate between the two groups. Thus, they concluded that ITA-PSV in pregnancy with thyrotoxicosis does not provide sufficient sensitivity and specificity, to be recommended as an initial diagnostic test, although it can be used as a surrogate marker. The discrepancy between the results of Zuhur *et al*.[9] and our study might be due to the constitution of study participants from rural areas, different study populations, and ethnicity. Patients in rural areas seek medical attention during antenatal care, leading to the diagnosis of thyrotoxicosis first time during pregnancy, causing the delay in diagnosis and severe disease, leading to high thyroid velocities in GD.

Similar study by Xue *et al*.[10] in 2016 found a better sensitivity and specificity for STA-PSV to differentiate between GD and GTT in pregnancy. Sixty-eight cases with newly diagnosed thyrotoxicosis during pregnancy, including GTT (n = 33) and GD (n = 35) were studied. STA-PSV was used and a cutoff was drawn to differentiate between the two groups. The area under the ROC curve for STA-PSV was 0.905. The optimal cut-off points of STA-PSV was 40 cm/s, with sensitivity and specificity of 82.9% and 81.8%, respectively. In our study, we found excellent sensitivity and specificity of ITA-PSV to differentiate between GTT and GD. The optimal cut-off point of ITA-PSV was 35 cm/s, and the area under the ROC curve for ITA-PSV was 0.938 with sensitivity and specificity of 84.62% and 93.33%. The comparison of our results with previous similar studies is presented in Table 5.

GD is an autoimmune disease, and the TRAb plays a central role in the etiopathogenesis of GD. In clinical practice, TRAb levels may be helpful to differentiate between GTT and GD during pregnancy. In this study, the difficulty in initial diagnosis was avoided because all the cases with GD were confirmed with TRAb at screening. The TRAb levels were normal in all patients with GTT and higher in GD. In the current study, we found a positive correlation between ITA blood flow velocities and TRAb levels. Ueda *et al*.[13] found that the serum TRAb levels were positively correlated with ITA-PSV in patients with GD and those who had relapse of the disease. These results may suggest that increased thyroid artery velocities in GD may be related to the underlying autoimmune process.[14]

The increased blood flow in ITA in cases with GD has been also measured quantitatively in multiple studies with significant

Table 4: ROC curve, cutoff values for the right and left ITA-blood flow velocities for differentiating GTT from GD during pregnancy

Variables	Cutoff value	AUC	95% CI	Sensitivity/Specificity	Accuracy %	PPV %	NPV %
Right ITA PSV	35 cm/sec	0.938	0.877 – 0.999	84.62/93.33	89.29	91.67	87.5
Right ITA EDV	11 cm/sec	0.953	0.894 – 1	88.46/86.67	87.5	85.19	89.66
Left ITA PSV	34.5 cm/sec	0.947	0.895 – 1	84.62/93.33	89.29	91.67	87.5
Left ITA EDV	11 cm/sec	0.964	0.915 – 1	84.62/93.33	89.29	91.67	87.5

Table 5: PSV cutoff found in the previous studies conducted in pregnancy to differentiate between GD and GTT

Study	*n*	PSV in GD cm/s	PSV in GTT cm/s	Cutoff cm/s	Sensitivity (%)	Specificity (%)
Kumar *et al*., 2008[7]	4/3	92±13	20.4±2.4	-	-	-
Zuhur *et al*., 2012[9]	41/31	37.58±10.89	24.3±7.3	29.4	77	78
Xue *et al*., 2016[10]	33/35	-	-	40	82.9	81.8
Present study	30/26	43.04±12.9	22.5±6.8	35	84.6	93

sensitivity and specificity. However, quantitative doppler ultrasound needs careful adjustments of the ultrasound system so as to prevent artifacts; it can be challenging in certain cases, and yet, they have not been standardized. Therefore, quantitative techniques have been not included in national and international guidelines for the diagnosis and management of hyper thyroidism.[15,16]

We demonstrated that ITA blood flow velocities help in the etiologic diagnosis of thyrotoxicosis during pregnancy. This can be an excellent tool, especially in rural areas for this purpose. The difficulty in initial diagnosis was avoided because all the cases with GD were confirmed with TRAb at screening, adding to the strength of the study.

Our study is limited by a small number of sample size. Free T4 levels were not done in the subjects considering the fallacies in FT4 assays particularly in pregnancy.[17] Also, Beta-Hcg was measured by ELISA. All pregnant women with thyrotoxicosis were diagnosed with GTT or GD, based primarily on the TRAb results. Therefore, it was difficult to compare the ITA blood flow velocity with the TRAb level for differential diagnoses between GTT and GD. Furthermore, even though our results suggest the excellent utility of thyroid blood flow velocities, minimal overlap between the two conditions is seen; thus, studies with larger numbers of patients will further add to the diagnostic utility.

In summary, thyroid artery velocities can be considered to be one of the initial investigations that can give great help to differentiate between GD and GTT. We found that the cutoff point of mean ITA-PSV at 35 cm/s had an excellent value in differentiating between the two, with good sensitivity and specificity. ITA-PSV appears to be practical, accurate, and reliable for this purpose, especially in pregnancy when thyroid scintigraphy is contraindicated. In addition, color Doppler is cost-effective and easily available technique making it a good choice in resource constraint settings.

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Conflicts of interest
There are no conflicts of interest.

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Authors Contribution
VSRD: Study idea, protocol development, data collection, manuscript writing and will act as guarantor for the study; PL: Developing protocol, data collection, analysis and manuscript writing; SRP: Developing protocol and manuscript writing; SRD:Developing protocol, data analysis and manuscript writing;VSRD, PL, SRP: Critical appraisal and revision of manuscript. All authors approved final version of manuscript.

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