CHAPTER

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Practical Approaches to a Person with Abnormal TSH

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INTRODUCTION

The thyroid is distinctive amid the endocrine glands owing to the large store of hormone it contains. The metabolic homeostasis in an adult is maintained by the thyroid gland which is achieved through secretion of two hormones, thyroxine (T4) and triiodothyronine (T3); regulated by thyroid stimulating hormone (TSH), secreted by the anterior pituitary.Thyroxine is obtained from thyroid and triiodothyronine is formed by the conversion of fT4 to fT3. The thyroid produces only 20% of tri-iodothyronine hormone (T3). The other 80% is produced by the conversion of fT4 to fT3 in the liver, kidney and pituitary gland.[1]

The hypothalamo-pituitary-thyroid (HPT) axis regulates the level of thyroid hormones in the blood by feedback mechanisms. When the thyroid is stimulated by thyrotropin hormone, it leads to increased levels of thyroid hormones (free T4 and free T3). Increased levels of these hormones sendsignals to the pituitary to stop the production of thyrotropin hormone. On the contrary, the pituitary gland is stimulated if there are low levels of free hormones in the blood, thus producing fT3 and fT4 from the thyroid until it reaches the normal level. This is called as the negative feedback mechanism (Figure 1).[1, 2]

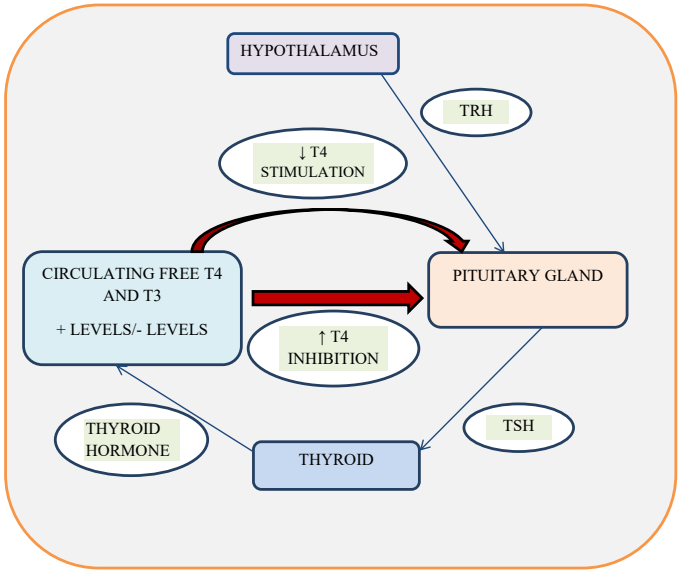

Fig. 1: Thyroid hormone regulation cycle, TRH- Thyrotropin releasing hormone

THYROID STIMULATING HORMONE

TSH is the major regulator for the growth and functions of the thyroid (Figure 2). In a healthy adult, the rate of production of TSH is within 100 and 200 mU/day. In normal serum, TSH is present at concentrations between 0.4 and 4.2 mIU/L. TRH released from the hypothalamus triggers the pituitary to secrete TSH which in turn stimulates the thyroid to release fT3 and fT4. The level is increased in primary hypothyroidism and decreased in primary hyperthyroidism. Serum TSH concentration is used as the first line in the diagnosis of primary hypothyroidism and hyperthyroidism (Table 1). Serum total T4, T3 and fT4, fT3 increases in case of hyperthyroidism and decreases in hypothyroidism. Serum thyrotropin is the most sensitive assay to diagnose thyroid diseases but overtreatment can lead to increased liver function test, exaggerated bone demineralization, changes in the electrocardiogram and atrial fibrillation

HYPOTHYROIDISM

Hypothyroidism is caused by insufficient secretion of thyroid hormones which results from a defect anywhere in the HPT axis. In majority of the cases, hypothyroidism is caused by thyroid and autoimmune thyroid diseases. It is the first manifestation for pituitary or thyroid disease.[2]

Table 1: Concentration of thyroid hormones

	TSH	Free T4	Free T3
1° Hypothyroidism	↑	↓	or normal
Subclinical Hypothyroidism	↑	Normal	Normal
2° Hypothyroidism	↓ or normal	↓	↓ or normal
1° Hyperthyroidism	↓	↑↑	↑
T3 Toxicosis	-	Normal	↑↑
Subclinical Hyperthyroidism	↓	Normal	Normal
2° Hyperthyroidism	↑ or normal	↑	↑
Thyroidhormone resistance	↑ or normal	↑	↑

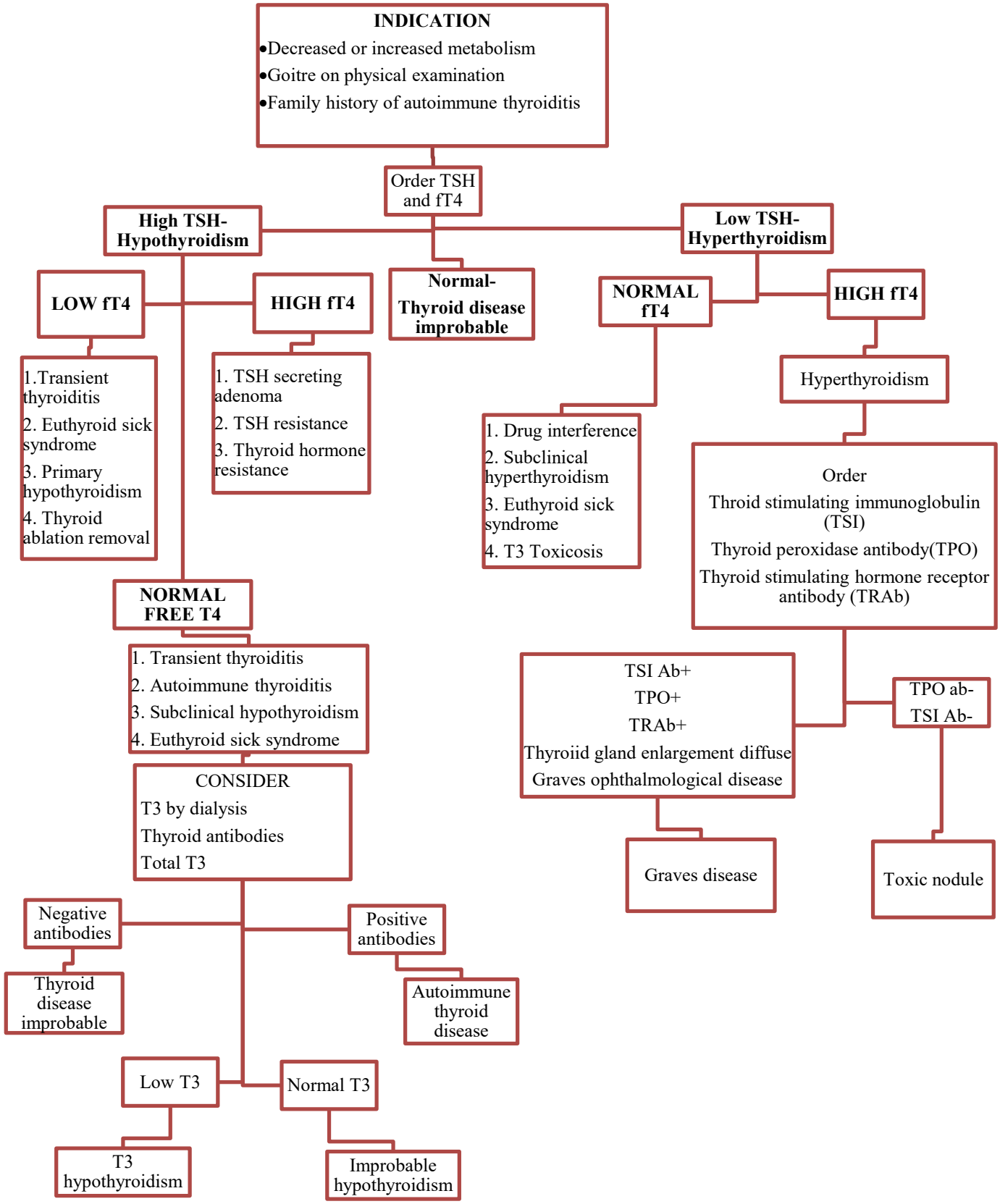

Fig. 2: Algorithm for abnormal TSH levels

In patients with primary hypothyroidism there is a decreased secretion of fT4 and fT3 which leads to a reduction in the serum concentrations of the two hormones eventually resulting in an increased thyrotropin secretion. The causes of primary hypothyroidism include chronic autoimmune thyroiditis, iodine deficiency or excess, iatrogenic causes, transient thyroiditis, congenital thyroid agenesis, subtotal thyroidectomy, subacute granulomatous thyroiditis and drugs like amiodarone and thionamide.[2,3]

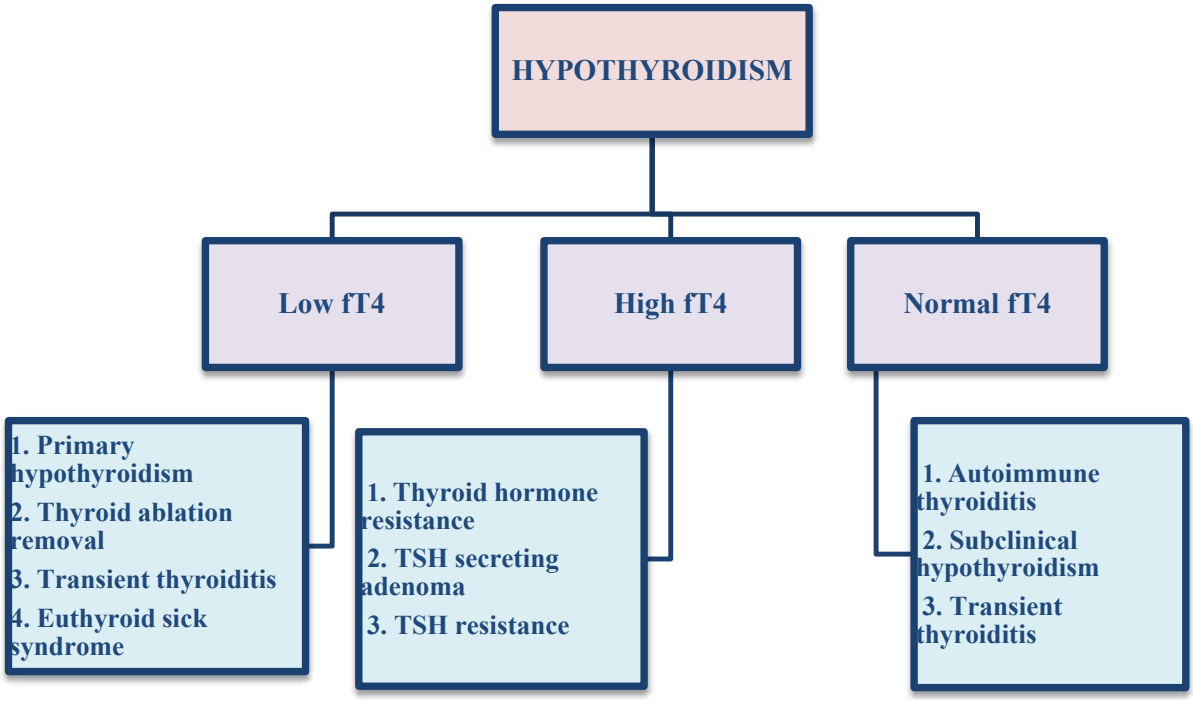

Fig. 3: Disease conditions associated with increased serum TSH levels

Hypothyroidism can be either subclinical or overt. Subclinical hypothyroidism is characterized by high TSH concentration and normal fT4 and fT3 concentration in the serum. Such patients will be asymptomatic. In overt hypothyroidism, the TSH levels will be high and fT4 levels will be low. Patients with a high serum TSH concentration and a low serum fT4 confirm the diagnosis of hypothyroidism. Treatment of primary hypothyroidism in adults should be based on their disease condition (cardiac and pregnant patients) (Figure 3).[3,4]

Secondary hypothyroidism can be due to pituitary disorder, Sheehan's syndrome, trauma and hypophysitis. Patients with macroadenoma are hypothyroid after surgery or radiation. These patients have other types of pituitary hormone deficiency. Tertiary hypothyroidism is attributed to deficiency in TRH to stimulate the pituitary. Most patients with central hypothyroidism have low or normal serum TSH concentrations.[3]Secondary and tertiary hypothyroidism can be suspected in the following situations such as:

- Known pituitary or hypothalamic disease
- Mass lesion in the pituitary
- When symptoms are related to other hormonal deficiencies.

Resistance to thyroid hormone (RTH), a rare syndrome is characterized by diminished response to increased circulating levels of fT4 and fT3 and non suppressed serum TSH. These patients present with short stature, hyperactivity, goiter, learning disability and attention deficit. No treatment is required for most of the patients but if required β-adrenergic blockers can be given.Myxedema coma occurs in patients with severe hypothyroidism and is mainly due to predisposing factors such as cold exposure, infection and trauma. It is characterized by hypothermia, hypoxia, hypoventilation, hypercapnia, hypotension and hyponatremia. These patients can be treated with levothyroxine 300-500mcg IV bolus followed by 50-100 mcg orally daily. If there is no improvement after 48 hours, 10 mcg IV of T3 every 8 hours must be given along with T4.[2, 3, 4]

Table 2: Manifestations of Hypothyroidism[4]

Symptoms	Signs
Fatigue, weakness	Slow movement, slow speech
Cold intolerance	Delayed relaxation of tendon reflexes
Dyspnea on exertion	Bradycardia
Weight gain	Carotenemia
Depression, cognitive dysfunction	Coarse skin
Edema	Puffy facies, loss of eyebrows
Constipation	Periorbital edema
Growth failure	Enlargement of the tongue
Hoarseness, Dry skin	Diastolic hypertension
Menorrhagia	Pleural, pericardial effusions
Myalgia and paresthesia	Ascites
Decreased hearing	Galactorrhea
Arthralgia	

CLINICAL MANIFESTATION

Hypothyroidism varies according to the degree, severity, promptness with which it occurs and psychological characteristics of the patient (Table 2).

HASHIMOTOS THYROIDITIS

Hashimotos thyroiditis is a chronic autoimmune thyroiditis which is the most common cause of hypothyroidism. The patient may present with normal thyroid function or overt or subclinical hypothyroidism. Autoimmune thyroid diseases (AITD) occur more in females than in males and increases with age. People with other autoimmune diseases are more prone to develop autoimmune thyroid disease. Patients presenting with chronic thyroiditis are mostly euthyroid. Few patients present with goiter. In such patients, anti-thyroid peroxidase antibodies (TPOAb) are tested.

Few studies have shown that women with autoimmune thyroiditis are more prone to increased risk of miscarriage. In such patients thyroxine can be given if TSH is within the range of 2.5-5 mIU//L.[4]

INVESTIGATION

As per the ATA/AACE guidelines, patients with autoimmune thyroiditis can be diagnosed by the following tests.

- Thyroid antibodies-

i. Anti-thyroglobulin antibodies (TgAb)- positive in 20-25% patients

ii. Anti-microsomal / anti-thyroid peroxidase antibodies (TPOAb)

iii. TSH receptor antibodies (TSHRAb)

- Total tri-iodothyronine
- Equilibrium dialysis

TREATMENT

These patients can be treated with levothyroxine based on the TSH value. Appropriate dosage among patients may vary but the mean replacement dosage of levothyroxineis 1.6-1.8mcg/kg of body weight per day. The appropriatemethod of treatment depends on the duration,severity and the presence of other associated disorders. The starting dose in patients who are above 50 years of age or who have cardiac diseases is 25mcg/day. The dose has to be titrated to obtain a euthyroid state. In younger patients, levothyroxine can be started at a dose of 50-100mcg.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is a common disorder characterized by increased serum TSH levels, normal fT4 andfT3 and may occur in the presence or absence of symptoms. The prevalence is high in females, advanced age and also in those with dietary iodine intake.

Subclinical hypothyroidism is usually asymptomatic and can be identified by routine screening of TSH. Regardless of patients being asymptomatic, the risks associated with the condition include cardiovascular effects, progression to overthypothyroidism, hyperlipidemia, and neuropsychiatric effects. Few studies have shown that treatment of subclinical hypothyroidism can reduce these risks in patients with TSH > 10 μIU/ML.Two samples must be taken within a period of 2-3 months to differentiate from non-thyroidal illness.

MANAGEMENT

Treatment in subclinical hypothyroid patients are based on the TSH levels

- TSH>10mU/L- give levothyroxine
- If TSH is slightly increased (4-10 mU/L) with positive TPO antibodies, check TSH yearly.
- If the patient is TPO negative, check TSH every 3-5 years
- If the patient has symptoms of hypothyroidism and persistent TSH with a serum TSH between 4-10 mU/L, the patient has to be initiated with levothyroxine for 3-6 months.
- If the patient's condition improves, treatment can be continued.
- If the patient presents with positive TPO antibodies and without symptoms, the patient may progress to overt hypothyroidism. Therefore the patient has to undergo a yearly TSH examination.
- If TPO antibodies are negative, the risk of progression to overt hypothyroidism is lesser. The patient has to go for TSH investigation every 3 years.[4]

HYPOTHYROIDISM IN PREGNANCY

Thyroxine (T4) and tri-iodothyronine (T3) increases in a pregnant woman leading to hypothyroidism. Thyrotropin hormone decreases due to the effect of placental human chorionic gonadotropin (hCG) in the first trimester of pregnancy. Thyroid antibodies develop in most of the pregnant women which is a major risk factor for spontaneous abortion independent of thyroid hormone and TSH levels. Untreated overt hypothyroidism during pregnancy can lead to increased risk of preeclampsia, maternal hypertension, postpartum hemorrhage, cardiac ventricular dysfunction, low birth weight and spontaneous abortion. Slight increase in serum TSH levels may increase the risk of fetal death. TSH measurement should be routinebefore pregnancy or during 1st trimester.

Thyroid hormone replacement therapy is the most suitable treatment during pregnancy. Levothyroxine is considered to be the safest drug in pregnancy. These patients should check their TSH every 6 weeks to make sure if the same dosage has to be continued.[4, 5]

HYPERTHYROIDISM

Hyperthyroidism occurs as a result of excess action of the thyroid hormone. Thyrotoxicosis occurs when the tissues are exposed to high concentration of thyroid hormone. This can occur during Graves' disease, pituitary thyrotroph adenoma, pituitary thyroid hormone resistance syndrome, and multinodular goitre. In patients with thyrotoxicosis, TSH will be suppressed and fT4 levels will be elevated. TSH receptor antibodies are useful for assessing risk of thyrotoxicosis of the fetus. If

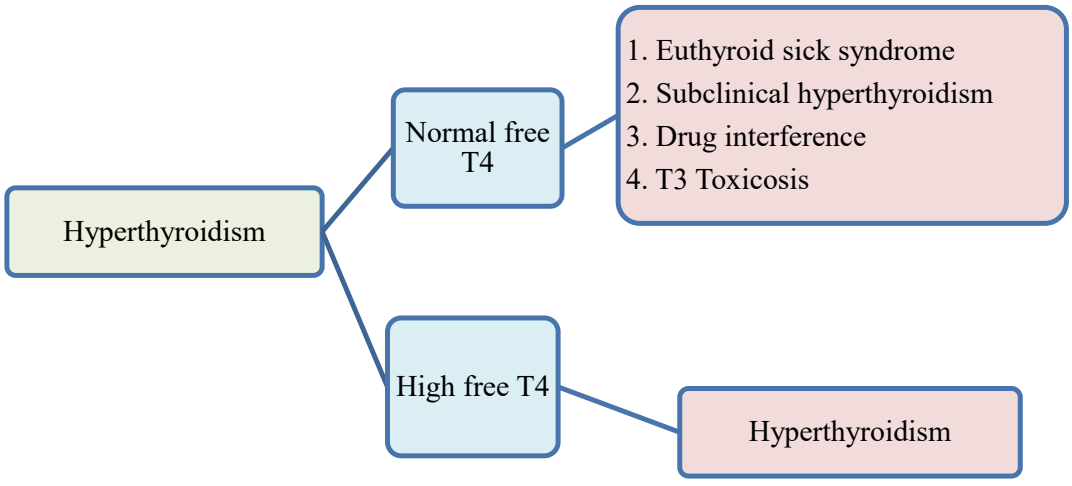

Fig. 4: Conditions associated with decreased TSH levels

Table 3: Manifestation of Hyperthyroidism

Symptoms	Signs
Nervousness , irritability, anxiety, insomnia	Sinus tachycardia
Palpitation, tachycardia	Fine tremor, hyperkinesia, hyperreflexia
Heat intolerance, increased sweating	Warm, moist skin
Thirst, polyuria	Palmar erythema
Weight loss or gain	Hair loss
Changes in appetite	Muscle weakness, wasting
Oligomenorrhoea, loss of libido, erectile dysfunction	Congestive heart failure, chorea, periodic paralysis
Diarrhoea	

the diagnosis is still uncertain radionucleotide thyroid scan has to be done. Causes of hyperthyroidism are excess iodine mostly due to trophoblastic disease, toxic adenoma, Plummer's disease, subacute thyroiditis and toxic adenoma. The complications of hyperthyroidism include hypothyroidism and thyroid storm.[5]

CLINICAL MANIFESTATION

Signs and symptoms are shown due to excess circulating thyroid hormone in the blood. The severity depends on the magnitude and duration of the thyroid hormone and age of the patient (Table 3).

DIAGNOSIS

A detailed history must be taken, physical examination must be done and laboratory investigation must be conducted to diagnose hyperthyroidism (Figures 4 and 5).

Physical examination includes eye examination, weight, blood pressure, dermatologic examination, pulse rate, cardiac rhythm, thyroid palpation and auscultation.

Laboratory investigations include:

- TSH assay
- Triiodothyronine and thyroxine
- Free T3
- Thyroid autoantibodies-TSH receptor antibodies (TRAb) / thyroid-stimulating immunoglobulins (TSI)
- Radioactive iodine uptake

TREATMENT

- Carbimazole 10-20 mg every 8-12 hours and once daily dose every 6-8 weeks after achieving the euthyroid status.
- If the patient experience sweating, tachycardia and tremor, propranolol 40 mg initially has to be given and then slowly titrate the dose to 120 mg/day
- Other treatment option- surgery in younger patients and radioactive iodine in patients with recurrent thyrotoxicosis.[5, 6, 7]

GRAVES' DISEASE

Graves is the most common form of hyperthyroidism. The conditions associated with Graves disease are type 1 diabetes mellitus, Addison's disease, vitiligo, pernicious anemia, myasthenia gravis and coeliac disease.

MANAGEMENT (FIGURE 6)

1. Drug of choice- carbimazole 5mg
2. Propylthiouracil (PTU)- initial dose is 300-450mg/day and maintenance dose is 100-150mg/day.

After achieving euthyroid, combine carbimazole with T4 of 100mcg. Antithyroid drugs must be stopped 3-7 days

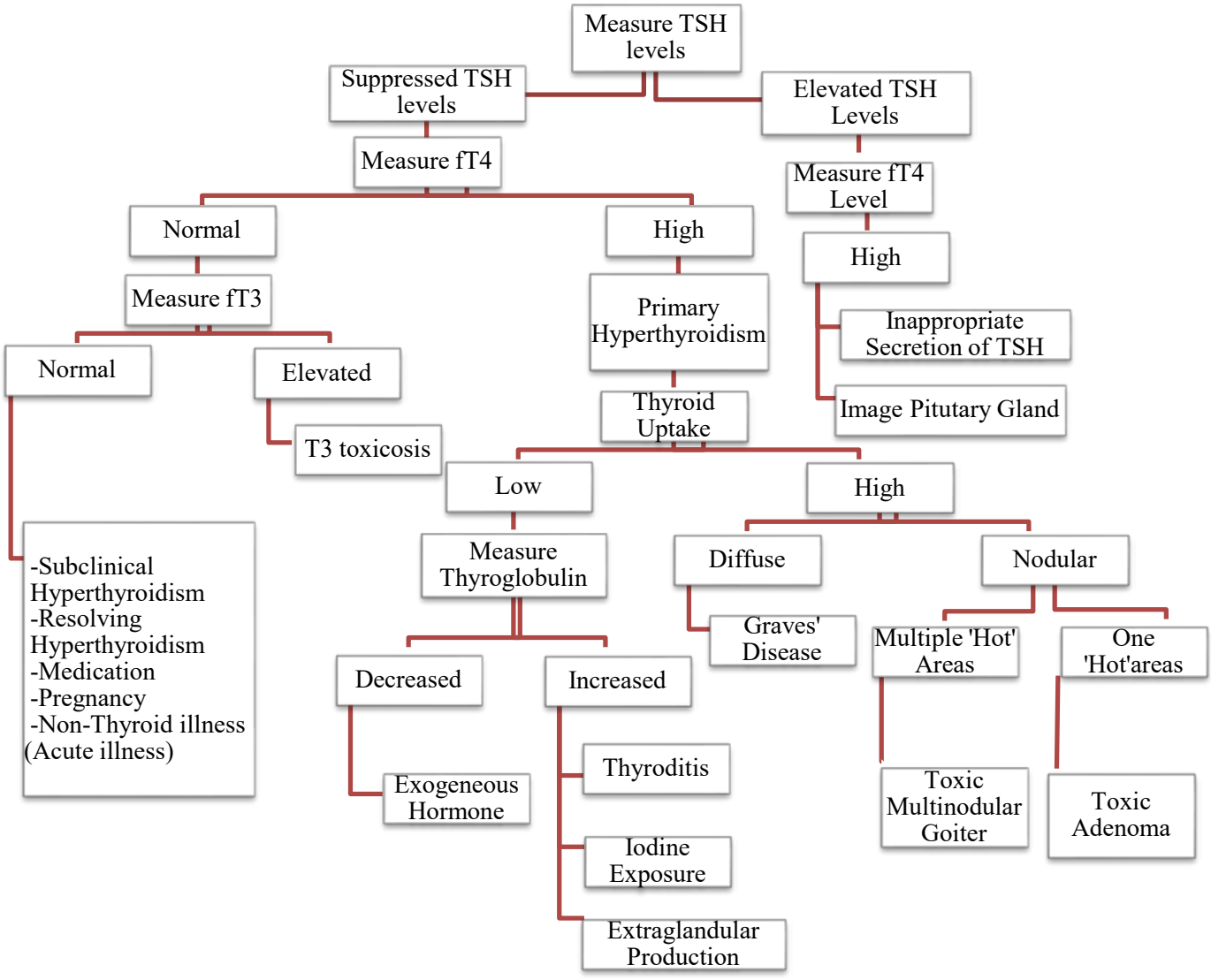

Fig. 5: Diagnostic Approach- Hyperthyroidism

prior to RAI therapy and should be given only after 3-7 days of RAI treatment.

3. Radioactive iodine (RAI) is given at a dose of 4-10 mCi orally. Larger doses are used in patients with toxic nodular goitre. They destroy the cells that concentrate iodine and decrease the thyroid hormone production.
4. Propranolol is usually prescribed at a dose of 20-40mg four times a day which reduces symptoms of thyrotoxicosis. They are the adjunctive therapy to RAI.
5. Thyroidectomy is done if all other therapy fails. It is a difficult procedure but the success rate is high and the cure is rapid in such patients. [7]

SUBCLINICAL HYPERTHYROIDISM (FIGURE 7)

It is a condition in which the serum thyrotropin concentration is low in patients with normal fT4 and fT3. Inorder to treat subclinical hyperthyroidism, the following has to be considered:

- TSH<0.1
- Atrial fibrillation
- Osteoporosis.

The risk of fracture is high in female patients. Thyroid function test must be performed in these patients every 6 months. In elderly patients with atrial fibrillation or osteoporosis, low dose of antithyroid drug therapy or ablation therapy must be initiated.

HYPERTHYROIDISM IN PREGNANCY

Thyrotoxicosis mainly occurs in pregnancy due to Graves disease, gestational hyperthyroidism and trophoblastic neoplasia. In these patients fT3 and fT4 increases and TSH decreases. Symptoms in these patients include hyperemesis gravidarum which is more commonly seen. Other symptoms include tiredness, palpitation, muscle weakness, shortness of breath, heat intolerance and irritability. Inability to gain weight, persistent tachycardia at rest is the sign shown in these patients.

Diagnosis in pregnant patients is usually difficult and can be identified if the patient has pregnancy induced hypertension or congestive heart failure.Pregnant patient

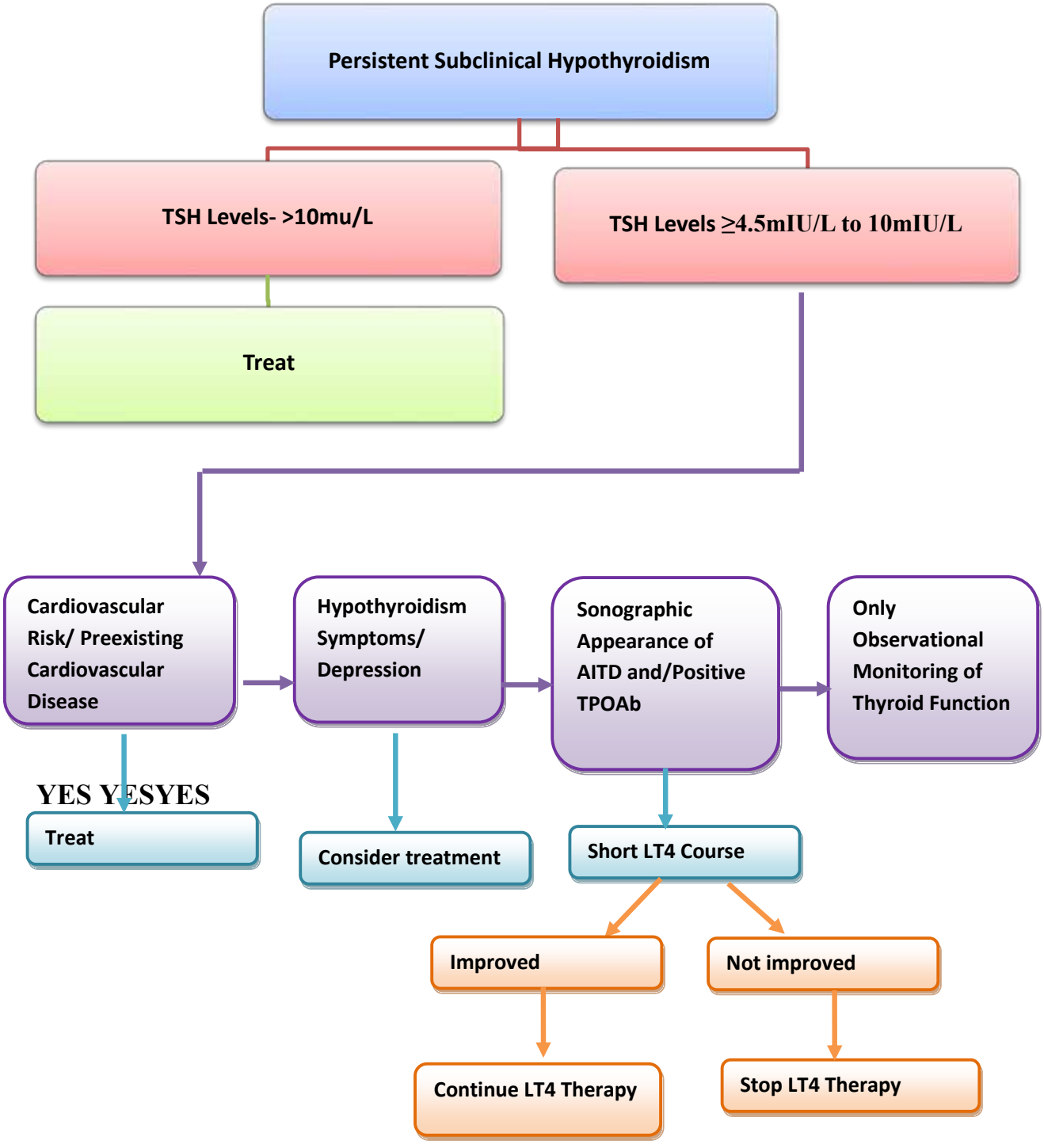

Fig. 7: Algorithm for persistent hypothyroidism, AITD: Autoimmune thyroid disease

with Graves disease present with aggravating symptoms in the first half, amelioration of symptoms in the second and recurrent symptoms in the post partum period.

Gestational trophoblastic disease (GTD) is a very rare complication of pregnancy which occurs due to molecular mimicry between TSH and human chorionic gonadotropin (HCG). Free T3 and free T4 are found to be in the normal range and the patientis asymptomatic most of the time. This occurs due to high levels of HCG hormone and it resolves as the hormone levels fall.[4,5,7]

TREATMENT

Propylthiouracil can be given at a dose of 100-150mg every 8 hours andcarbimazole at a dose of 10-20mg once daily. However, propylthiouracil should be prescribed only in the first trimester as it can cause hepatotoxicity. Propranolol cannot be given as it can cause growth retardation and respiratory depression in the neonate.Treatment with iodides and radioiodine are contraindicated in pregnant patients.

Breast feeding mothers should be given lower doses of

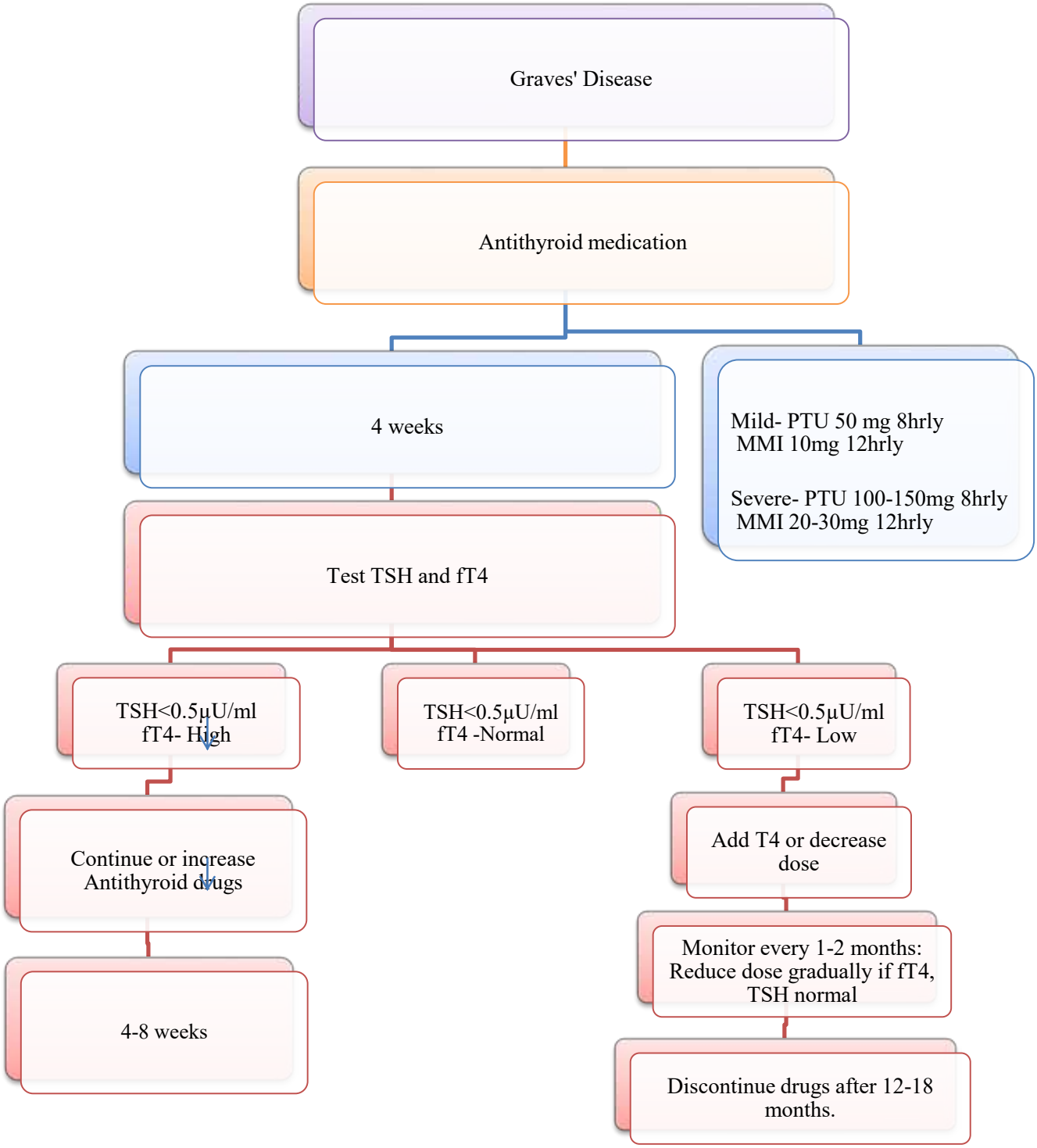

Fig. 6: Treatment of Graves' disease, fT4: Free thyroxine, MMI: Methimazole

these drugs. Thyroid function test should be conducted every 4-6 weeks.[7,8]

SICK EUTHYROID SYNDROME

Euthyroid syndrome is a condition in which there is a disregulation in the feedback mechanism and is caused by starvation, severe infection, liver failure etc. In such patients T3 and T4 levels will be abnormal and or suppressed TSH.[6]

DRUGS CAUSING THYROID DYSFUNCTION

Amiodarone induced thyroid dysfunction occurs more commonly.If the patient has thyroid abnormality, amiodarone can be continued along with an added levothyroxine replacement therapy.Thyroid function test should be checked prior to taking this medication and every 6 months after taking amiodarone.[4,5]

THYROIDITIS

Thyroiditis is the inflammation of the thyroid caused by a group of disorders like Hashimoto's thyroiditis,

Table 5: Drugs	
↓ TSH Production	↑ TSH Production
Alpha adrenergic blockers	Dopamine receptor antagonist
Serotonin Antagonists	Opioids
Dopamine analogues	Ephedrine, Theophylline
Glucocorticoids	Haloperidol, chlorpromazine
Somatostatin analogues	Selective Serotonin Reuptake Inhibitors

postpartum thyroiditis, subacute thyroiditis (De Quervain's thyroiditis), silent thyroiditis, acute thyroiditis and radiation induced thyroiditis. Subacute thyroiditis is caused by viral infection and acute thyroiditis is caused by bacteria or any other infectious organism. Main aim is to treat these patients according to the type and clinical presentation.

CONCLUSION

Abnormal TSH is considered as the primary method to differentiate between thyroid disorders. Other supporting investigations include serum fT4,fT3 and thyroid antibodies. Patients with subclinical hypothyroidism and hyperthyroidism need to be treated on the basis of symptoms and risk factors. Other conditions like sick euthyroid syndrome, thyroid resistance and assay interference must be considered while managing patients with abnormal TSH. Algorithm for treating patients with abnormal TSH must be followed and treated based on their investigations and diagnosis.One should consider referral to a tertiary centre endocrinologist if there is challenge in diagnosing and managing the patients.

REFERENCE

1. Melmed S, Polonsky KS, Larsen PR et al editors. Williams Textbook of Endocrinology. 13th ed. India: RELX India Pvt. Ltd; 2016.
2. Shargel L, Mutnick AH, Souney PF, Swanson LN editors. Comprehensive Pharmacy Review. 8thed New Delhi: Wolters Kluwer (India) Pvt Ltd; 2013.
3. Jameson and Groot D editors. Endocrinology: Adult and Pediatric Volume 2. 7th ed. India: Reed Elsevier India Pvt. Ltd; 2016.
4. Wass J, Owen K, Turner H editors. Oxford handbook of endocrinology and diabetes. 3rd ed. India: Oxford University Press; 2014.
5. Kennedy L and Basu A editors. Problem solving in Endocrinology and Metabolism;UK: Atlas Medical Publishing Ltd; 2007.
6. Garber JR, Cobin RH, Gharib H, et al. Clinical Practice Guidelines For Hypothyroidism In Adults: Cosponsored By The American Association Of Clinical Endocrinologists And The American Thyroid Association 2012; 18:e9-e15.
7. Ross DS, Burch HB, Cooper DS, et al. American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis. 2016 Mary Ann Liebert, Inc.DOI: 10.1089/thy.2016.0229.
8. Sharma S, Sethi GR, et al editors. Standard treatment guidelines. A manual for medical therapeutics. 4th ed. New Delhi: Wolters Kluwer (India) Pvt Ltd; 2015.