Chapter

Hyperthyroidism

Rushikesh Maheshwari

Abstract

Excess level of thyroid hormones in blood is thyrotoxicosis, which is responsible for clinical syndrome of hypermetabolism, sympathetic hyperactivity. Hyperthyroidism is the term used to denote the overproduction of thyroid hormones from the thyroid gland. Hyperthyroidism is possible with hyperactive thyroid gland due to multi/solitary nodular thyroid disease or Grave's disease. Thyrotoxicosis associated with thyroiditis is not hyperthyroidism. Treatment of hyperthyroidism is with anti-thyroid drugs (ATT), radio-active iodine ablation (RAI), or thyroid surgery; whereas, treatment of thyroiditis is symptomatic.

Keywords: thyrotoxicosis, hyperthyroidism, thyroiditis, anti-thyroid drugs (ATT), radio-active iodine ablation (RAI)

1. Introduction

Thyroid gland is a butterfly shaped gland located in front of neck. Thyroid gland synthesises and secretes thyroxine under influence of thyroid stimulating hormone (TSH). Hyperproduction and secretion of thyroxine is called as hyperthyroidism and presence of excess amount of thyroxine in blood is called as thyrotoxicosis. Hence presence of thyrotoxicosis does not necessarily means presence of hyperthyroidism, as thyrotoxicosis can be due to other reasons like thyroiditis, overdose of thyroxine tablets, ectopic sources like strauma ovarii producing excess thyroxine, etc. An approach to diagnose thyrotoxicosis is shown in **Figure 1**.

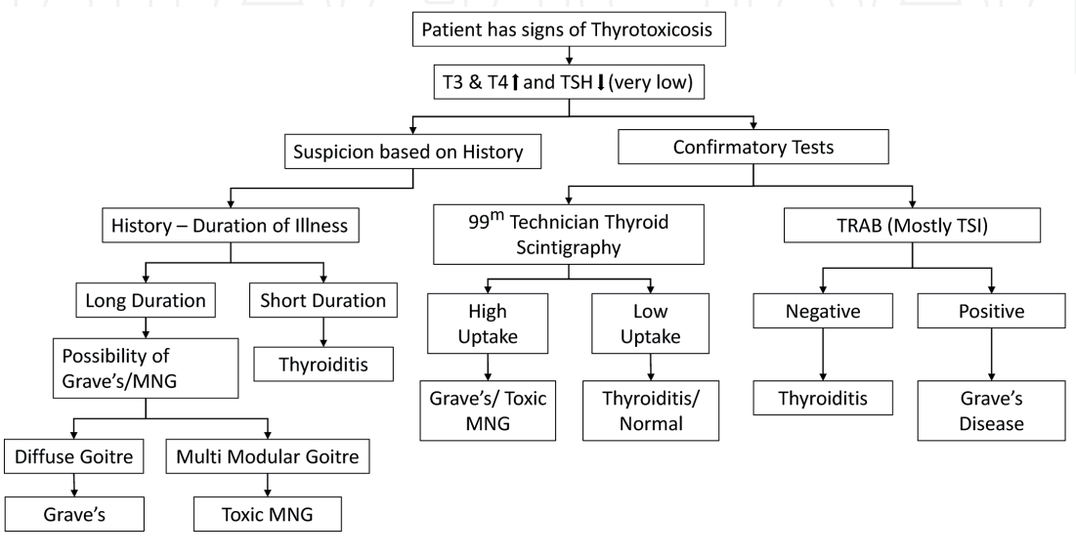

Figure 1.
Approach to thyrotoxicosis.

Treatment of thyrotoxicosis is symptomatic and the treatment of the cause, but treatment of hyperthyroidism is divided in three parts. First antithyroid drugs (ATD), radioactive iodine and thyroid surgery. The prevalence of hyperthyroidism is 1.2–1.6, 0.5–0.6 overt and 0.7–1.0% subclinical [1, 2]. The most frequent causes are Graves' disease (GD) and toxic nodular goitre.

1.1 Prevalence

Prevalence of thyroid disease varies with iodine sufficiency of the region The National health and nutrition examination survey (NHANES III) [3] and epidemic survey in UK [4] demonstrates female preponderance of thyroid diseases and lower incidence of hyperthyroidism with 1–2% prevalence in women and 1/10th in men.

2. Clinical manifestations

Hyperthyroidism can mimic other health problems, which can make it difficult to diagnose. It can also cause a wide variety of signs and symptoms like, Unintentional weight loss, palpitations, missed heartbeats, increased appetite, nervousness, anxiety and irritability, tremulousness, excess sweating, menstrual irregularity, heat intolerance, changes in bowel patterns especially more frequent bowel movements, goitre, easy fatigue, muscular weakness, insomnia, thinning of skin, hair loss. Elderly are either asymptomatic or may have palpitations, easy fatigue, etc.

Signs include tremors, warm handshake, fast tachycardia/arrhythmia, flushing over upper body, brisk reflexes, goitre and prominent eyes. Early diagnosis has become possible because of easy availability of blood investigations for thyroid.

Cause of patient's thyrotoxicosis can be guessed from presentation of patient and disease duration. Patients with hyperthyroidism have symptoms since months and dating back is usually difficult, patients of acute thyrotoxicosis due to thyroiditis usually date back their signs and symptoms. Many patients having mild thyrotoxicosis attribute their symptoms to day to day fatigue, stress, etc.

Easy access to blood tests of thyroid has made diagnosis of thyrotoxicosis easy. It is important to differentiate between thyrotoxicosis and hyperthyroidism before anti thyroid drugs are initiated.

Clinical manifestations involve multiple systems of the body as follows.

2.1 Cardiovascular system

Alterations in cardiovascular function are due to increased circulatory demand that result from the hyper metabolism, first, in heart rate, and with more severe disease, in stroke volume [5]. Widening of the pulse pressure results from the increase in systolic and decrease in diastolic pressure due to reduced peripheral resistance [6, 7].

2.2 Protein, carbohydrate, and lipid metabolism

Both synthesis and degradation rates of proteins are increased indicated by muscle wasting. Uncontrolled diabetes can be due to increased degradation rate of insulin. Lipolysis is predominantly observed [8].

2.3 Sympathetic nervous system and catecholamines

The improvement in cardiac function with β-blockade in patients with hyperthyroidism has led to the concept that there is increased sympathetic

tone or increased cardiac sensitivity to the sympathetic nervous system in these patients [9].

2.4 Nervous system

Nervousness, emotional lability, and hyperkinesia are major symptoms.

Emotional lability mental disturbance may be severe; the patient shifts positions frequently, and movements are quick, jerky, exaggerated, and often purposeless.

In children, inability to focus may lead to deterioration of school performance. A fine tremor of the hands, tongue, or lightly closed eyelids is observed on clinical examination.

2.5 Muscle

Generalised wasting associated with weight loss. The weakness is most prominent in the proximal muscles of the limbs, myopathy is also a feature of disease which involves distal muscles, ocular myopathy may mimic myasthenia gravis. Periodic paralysis of the hypokalemic type may occur together with thyrotoxicosis [10–12].

2.6 Eyes

As shown in **Figure 2**, proptosis, stare, lid lag, globe lag, dry eyes, photosensitivity, corneal ulceration, loss of vision (uncommon) are features of Graves associated orbitopathy (GAO) [13].

2.7 Skin and hair

Excessive sweating. Palmar erythema may resemble "liver palms," and telangiectasia may be present. Hair loss may increase. The nails are often soft and friable. A characteristic but uncommon finding is Plummer's nails, or onycholysis, typically involving the fourth and fifth fingers [11].

2.8 Respiratory system

Dyspnoea is common in severe thyrotoxicosis, mainly from weakness of the respiratory muscles.

2.9 Alimentary system

An increase in appetite is common but is inadequate to meet the increased caloric requirements. The frequency of bowel movements is increased and hepatic dysfunction occurs [14]. Hepatomegaly and jaundice can develop with severe, prolonged disease, and liver failure was a cause of death before the development of successful treatment for patients with Graves' disease.

2.10 Haematopoietic system

The increase in erythropoiesis results from both a direct effect of thyroid hormones on the erythroid marrow and increased production of erythropoietin. Association of pernicious anaemia can be there in 3% of Graves of which 3% have auto-antibodies to intrinsic factor; accelerated clearance of the vitamin K-dependent clotting factors. Therefore, the dosage of warfarin needs to be reduced in thyotoxicosis [15].

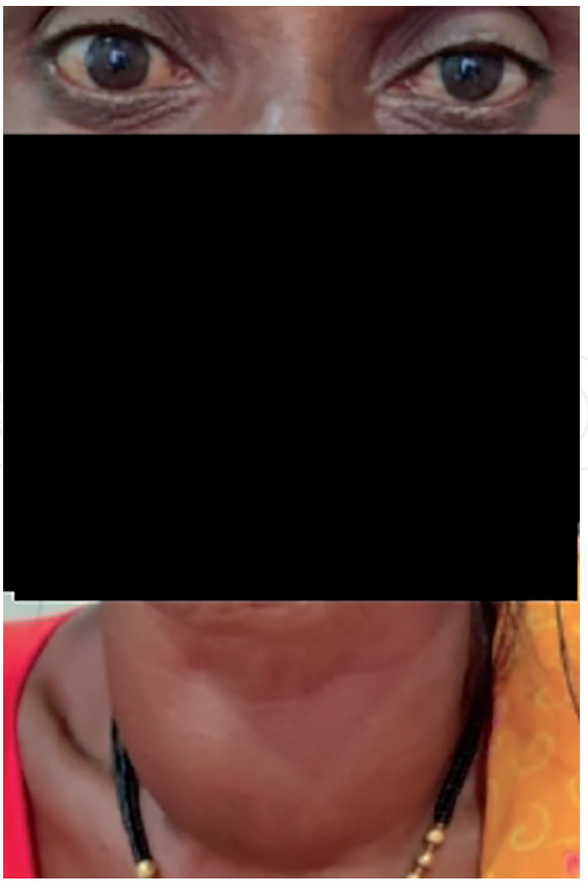

Figure 2.
Patient of Graves disease showing diffuse goitre and eye signs.

2.11 Reproductive function

Menstrual irregularity is common. Fertility may be reduced, and if conception takes place, there is an increased risk of miscarriage [16, 17]. The increased rate of conversion of androgens to estrogenic by-products may be the mechanism for gynecomastia and erectile dysfunction.

3. Graves' disease

Popularly known as Robert Graves' disease in English speaking world and as Von Basedow's disease in Europe, although disease was first described by Parry in 1825 [11].

3.1 Presentation

Graves' disease characteristics include goitre and thyrotoxicosis; common associated features include orbitopathy (GAO) and dermopathy. The thyroid histology suggests autoimmune thyroiditis with the presence of lymphocytic infiltrate.

4. Pathogenesis

4.1 The major antigen of Graves' disease: the thyrotropin receptor

The TSHR is a G protein coupled receptor. The TSHR is the primary auto antigen of Graves' disease, experimentally proven with mice antigen antibody studies [18].

5. Diagnosis

It is always better to test TSH and T4 rather than testing TSH alone, measuring both T4 & TSH increases diagnostic accuracy. In case of overt hyperthyroidism T3 and T4 are high and TSH is low and in subclinical disease T4 is usually normal TSH is usually suppressed, and T3 is normal or increased.

TSH-Receptor-Ab (TRAb) is a specific biomarker for Grave's Disease. Immunoassays used nowadays do competitive assays which measure Thyroid Receptor binding inhibitory immunoglobulins (TBII) [19]. Bioassays can differentiate between blocking and stimulating TRAB but its time consuming and a costly affair.

5.1 Imaging

Most clinicians would request thyroid ultrasound (US) and often isotope scanning is seldom available in India. Imaging tests are investigator dependant and hence experience and qualification of a person doing the test does matter, also matter is instruments used, hence a high-frequency linear probe should be used. GD is often, but not invariably, characterised by diffuse thyroid enlargement and by hypoechogenicity, both of which are assessed by ultra-sonogram and conventional grey scale analysis [20].

A colour-flow or power Doppler examination is characterised by vascular patterns and can quantify vascularity of thyroid [21]. Thyroid vascularity is significantly increased in severe Grave's disease and it typically shows a pulsatile pattern in thyroid gland which is called as "thyroid inferno" that is multiple small areas of increased intrathyroidal flow seen throughout the gland [22]. To measure accurately thyroid artery flow velocity and peak systolic velocity (PSV), it requires adjustments of pulse repetition frequency of wall filters and control of the insonation angle between 0 and 60°. The PSV is capable of differentiation between GD related thyrotoxicosis or amiodarone-induced thyrotoxicosis type 2, where the blood flow is reduced [23]. A typical US finding along with TRAB results can make diagnosis almost certain but thyroid scintigraphy is needed prior to Radioactive iodine ablation so that multinodular goitre can be differentiated [20].

6. Medical treatment

There are three ways by which GD is treated. One is by oral treatment with antithyroid drugs which reduces synthesis of thyroid hormones second is Radioactive iodine ablation where radioactive iodine is used to burn thyroid follicles and third one being thyroid surgery where thyroid gland is removed so that thyroid synthesising machinery is taken outside the body [20, 24]. ATD represent the most commonly used therapy in Europe, Asia, and in the meantime in the USA [25, 26]. The main ATD are thionamides, such as propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of the CBZ as, methimazole (MMI). CBZ is not an active substance; it has to be decarboxylated to MMI in the liver. Thionamides inhibit the coupling of iodothyronines and hence reduce the biosynthesis of TH [27]. These drugs mainly inhibit function of thyroperoxidase, reducing oxidation and the organification of iodide. ATD are indicated as a first-line treatment of GD, particularly in younger subjects, and for short-term treatment of GD before definitive RAI therapy or thyroidectomy [20]. ATD also helps to reduce TRAb levels and rates of remission of GD. PTU at very high doses also inhibits deiodination of T4 to T3 [28]. However, this effect is of use in case of thyrotoxicosis crisis but for long term use

this effect is not of much use. The starting dose of MMI is usually 10–30 mg daily in divided doses depending on the severity of hyperthyroidism (CBZ 15–60 mg/day). PTU is given 100 mg every 8 h. titration regimen is used through the Corse of disease, means as disease goes in remission, dose is gradually reduced based on severity of the illness. Thyroid function tests are reviewed 3–4 weekly intervals after initial treatment, and the dose is titrated based on T4 and T3 levels. TSH values remain suppressed for long time hence more reliable is T3 & T4 reports but measuring T4 does add value to report as sometimes overtreatment increases TSH values in short span. The usual daily maintenance doses of ATD in the titration regimen are 2.5–10 mg of MMI and 50–100 mg of PTU. Some have also advocated block and replacement regimen to avoid severe hypothyroidism during treatment where MMZ in dose of 30–50 mg daily along with thyroxin replacement is used throughout the Corse but side effects of ATD are more with this kind of regimen [28].

6.1 Adverse events

Common side effects of ATD are allergic reactions which include rash, urticaria, and arthralgia (1–5%). Minor cutaneous reactions are managed with antihistaminics without stopping the ATD. Substituting an ATD may also be helpful [28]. In the case of a serious allergic reaction like hepatitis, a lupus-like syndrome, and agranulocytosis (neutrophil count <500/mL), which occurs in 0.1–1.0% of cases, it's better to avoid ATD in patients as risk of severity of allergic reaction may increase and it's better to use alternative ways of treatment [29]. Agranulocytosis may occur abruptly within 3 months after the initiation of ATD therapy [30]. The risk of ATD-induced agranulocytosis and pancytopenia at 100 and 150 days after the initiation of ATD was 0.28 and 0.29%, respectively [31].

6.2 Beta adrenergic drugs (β blockers)

These drugs are used as second line treatment of adjunctive treatment. These reduce catecholamine response at receptor level hence this is a symptomatic treatment and not a definitive treatment. Tremulousness, palpitations, excessive sweating, eyelid retraction, and heart rate decrease; by reducing sympathetic hyperactivity which is induces by excess TH in blood. Propranolol (but not other β-adrenergic agents) may also weakly block the conversion of T4 to T3 via a mechanism independent of its effect on catecholamine signalling. Propranolol is the most widely used agent because it is relatively free from adverse effects and has a short half-life. It can be given orally in a dose of 20–60 mg every 6 or 8 h and avoided in patients with known history of bronchial asthma or COPD with respiratory problems. Hypotension with Propranolol is unusual [32].

6.3 Radioablation

Introduced in the mid-1940s, a relatively inexpensive therapy for treatment of hyperthyroidism, 131I has become the most widely used therapy, although international questionnaire studies show that geographic differences do exist. The isotope being used is 131I. It is given orally (in a capsule or in water) and is absorbed rapidly and completely, after which it is concentrated, oxidised, and organified by follicular thyroid cells. The ionising effect of β-particles, with a path length of 1–2 mm, destroys the thyroid cells by an early inflammatory response, necrosis of follicular cells, and vascular occlusion. Further chronic inflammation and fibrosis result in a decrease in thyroid size and an impaired thyroid function. So most of the patients developed Hypothyroidism following 131I therapy [33].

6.4 Dose calculation

Smallest possible dose is preferred so that to make patients euthyroid and avoid permanent hypothyroidism in patients. Dose is calculated by following algorithm:

Dose (mCi) = (80 - 200 micro Ci 131I/g thyroid × estimated thyroid gland weight (g) ÷ 24 h radioiodine uptake).

With use of above dose calculation algorithm, usual dose patients receive is 5–15 mCi and many become euthyroid followed by hypothyroidism. Dose calculation is time consuming and costly hence fixed dose activity is commonly used in many centres which simplifies and reduces cost of 131I therapy and the lack of a significant difference in outcome between patients randomised to fixed and calculated 131I doses favour the use of fixed doses. Typically a patient with Graves' disease requires 5–15 mCi, 10–29 mCi in patients with toxic nodule and toxic MNG [33]. Not all patients respond to 131I and these patients may require multiple doses at 6–12 monthly intervals. Patients who can be predicted to have poor response are: (1) age (>40 years); (2) Gender (female); (3) severe hyperthyroidism; (4) medium or large goitres (>40 g, visible); and (5) ATD pre-treatment (especially with propylthiouracil) [34].

6.5 Surgery

Thyroid surgery is oldest available treatment for hyperthyroidism and it's a definitive treatment for the illness. Being an invasive treatment and also associated complications, its least preferred now a days, but indications for the treatment include: (1) patients preference; (2) large size goitres which are causing compressive symptoms or for cosmetic reasons; (3) Graves' disease super imposed on endemic goitre with multiple cold nodules; (4) suspicion of malignancy; and (5) associated with ophthalmopathy.

6.6 Pre-operative preparation

It is mandatory to achieve normal metabolic state before patients undergo thyroid surgery or else patients may land u into thyroid storm. Normal metabolic state is generally achieved by using ATD in appropriate dose and duration. Beta blockers are also used in management to achieve eumetabolism before surgery. Once eumetabolism is achieved SSKI is added, 2–3 drops twice daily, for 7–10 days. Lugol's iodine can also be used depending on its availability.

6.7 Treatment of sub-acute thyroiditis

Treatment is usually supportive and symptomatic. Pain is relieved with NSAID's. If pain persists despite maximal NSAID's, prednisolone in a dose of 40 mg per day for 7–10 days is followed [35].

7. Special situation

7.1 Hyperthyroidism in pregnancy

Hyperthyroidism is not uncommon during pregnancy with prevalence being 0.1–0.4% of which 80% of the cases are of Grave's disease. The activity level of Graves' disease fluctuate during gestation, with exacerbation during the first trimester and improvement by late gestation related to autoimmune process of

the disease affected by gestation. Hyperthyroidism of Graves' disease may also be aggravated by high levels of HCG in the first trimester. Because nonspecific symptoms of hyperthyroidism may be mimicked by normal pregnancy, the presence of a goitre, especially with a bruit or thrill, which may point to a diagnosis of true Graves' disease. One has to be cautious before labelling diagnosis of Grave's disease and should first rule out gestational thyrotoxicosis [36–38].

Patients suspected of having hyperthyroidism require measurement of serum TSH, T4, T3 levels, and TRAb. And it's always necessary to interpret thyroid function tests in relation to the HCG-mediated decrease in serum TSH levels and the increase in T4 binding globulin concentrations that occur during normal pregnancy [39–41].

In a normal pregnancy TSH is typically suppressed specially during late first trimester and last trimester, a lady with Graves' disease, one must anticipate transplacental transfer of TRAB and fetal hyperthyroidism hence adequate treatment of a pregnant woman is necessary to avoid fetal hyperthyroidism. Fetal hyperthyroidism and inadequate treatment is associated with increased risk of medically indicated preterm delivery, intrauterine growth restriction and low birth weight, pre-eclampsia, congestive heart failure, and fetal death [42]. In addition, overtreatment of the mother with thionamides can result in iatrogenic fetal hypothyroidism [43], but under treatment of maternal hyperthyroidism may lead to central congenital hypothyroidism [44, 45].

Fetal hyperthyroidism is known to be associated with intrauterine growth restriction, fetal tachycardia, fetal goitre, advanced bone age, fetal hydrops, preterm delivery, and fetal death [46]. The diagnosis is suggested by any of these signs or abnormalities. Maternal TRAb levels able to induce fetal hyperthyroidism are usually over three times the upper normal limit. PTU and MMI or its derivative carbimazole are the mainstays of treatment. Recently, the Adverse Event Reporting System of the FDA has focused attention on the relation between hepatotoxicity and PTU [47]. This finding has led to a recommendation that PTU use in pregnancy should be limited to the first trimester, and then treatment must be switched to MMI. Use of MMI during the first trimester has been associated with a possible embryopathy.

Author details

Rushikesh Maheshwari
Private Practice at Rushikesh Endocare Superspeciality Centre, Nanded, Maharashtra, India

*Address all correspondence to: rushikeshmaheshwari@gmail.com

References

[1] Bahn RS, Burch HB, Cooper DS, et al. Management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocrine Practice. 2011;**17**:456-520

[2] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;**26**:1343-1421

[3] Vanderpump NPJ et al. The incidence of thyroid disorder in community: A twenty year follow up of Whikham survey. Clinical Endocrinology. 1995;**43**:55-68

[4] Carlae A, Pederson IB, et al. Epidemiology of subtypes of hyperthyroidism in Denmark, a population based study. European Journal of Endocrinology. 2011;**164**:801-809

[5] Burggraaf J, Tulen JH, Lalezari S, et al. Sympathovagal imbalance in hyperthyroidism. American Journal of Physiology. Endocrinology and Metabolism. 2001;**281**:E190-E195

[6] Fazio S, Palmieri EA, Lombardi G, et al. Effects of thyroid hormone on the cardiovascular system. Recent Progress in Hormone Research. 2004;**59**:31-50

[7] Kahaly GJ, Wagner S, Nieswandt J, et al. Stress echocardiography in hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism. 1999;**84**:2308-2313

[8] Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Annals of Internal Medicine. 2003;**139**:205-213

[9] Keating FR, Parkin TW, Selby JB, et al. Treatment of heart disease associated with myxedema. Progress in Cardiovascular Diseases. 1961;**3**:364-381

[10] Imaizumi M, Akahoshi M, Ichimaru S, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**:3365-3370

[11] Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. Journal of the American Medical Association. 2006;**295**:1033-1041

[12] Tachman ML, Guthrie GP Jr. Hypothyroidism: Diversity of presentation. Endocrine Reviews. 1984;**5**:456-465

[13] Mandel SJ, Larsen PR, Davies TF. Thyrotoxicosis. In: Williams Textbook of Endocrinology. 12th ed. Philadelphia, PA: Elsevier Saunders. pp. 366-400

[14] Checchi S, Montanaro A, Pasqui L, et al. L-Thyroxine requirement in patients with auotimmune hypothyroidism and parietal cell antibodies. The Journal of Clinical Endocrinology and Metabolism. 2008;**93**:465-469

[15] Lecky BRF, Williams TDM, Lightman SL, et al. Myxoedema presenting with chiasmal compression: Resolution after thyroxine replacement. Lancet. 1987;**1**:1347-1350

[16] Redmond GP. Thyroid dysfunction and women's reproductive health. Thyroid. 2004;**14**(Suppl):S5-S15

[17] Yoshimura M, Hershman JM. Thyrotropic action of human chorionic gonadotropin. Thyroid. 1995;**5**:425-434

[18] Shimojo N, Kohno Y, et al. Induction of Graves like disease in mice by immunization with fibroblasts

transfected with the thyrotropin receptor and a class II molecule. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**:11074-11079

[19] Bartalena L. Diagnosis and management of Grave's disease: A global overview. Nature Reviews. Endocrinology. 2013;**9**:724-734

[20] Smith TJ, Hegedus L. Graves' disease. The New England Journal of Medicine. 2016;**375**:1552-1565

[21] Erdogan MF, Anil C, et al. Colour flow Doppler sonography for the etiologic diagnosis of hyperthyroidism. Thyroid. 2007;**17**:223-228

[22] Ralls PW et al. Color-flow Doppler sonography in Grave's disease. American Journal of Roentgenology. 1988;**150**:781-784

[23] Kim TK, Lee EJ. The value of the mean peak systolic velocity of the superior thyroidal artery in the differential diagnosis of thyrotoxicosis. Ultrasonography. 2015;**34**:292-296

[24] Kahaly GJ, Bartalena L, Hegedus L. The American Thyroid Association/ American Association of Clinical Endocrinologists guidelines for hyperthyroidism and other causes of thyrotoxicosis: A European perspective. Thyroid. 2011;**21**:585-591

[25] Emiliano AB, Governale L, et al. Shifts in PTU and MMI prescribing practices. JCEM. 2010;**95**:2227-2233

[26] Brito JP et al. Antithyroid drugs—The most common treatment for Graves' disease in the US: A nationwide population-based study. Thyroid. 2016;**26**:1144-1145

[27] Cooper DS. Antithyroid drugs in the management of patients with Graves' disease. JCEM. 2003;**88**:3474-3481

[28] Cooper DS. Antithyroid drugs. NEJM. 2005;**352**:905-917

[29] Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clinical Endocrinology. 2004;**61**:589-594

[30] Nakamura H, Miyauchi A, et al. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. JCEM. 2013;**98**:4776-4783

[31] Watanabe N et al. Antithyroid drug induced hematopoietic damage. JCEM. 2012;**97**:E49-E53

[32] Geffner DL, Hershman JM. Beta-adrenergic blockade for the treatment of hyperthyroidism. The American Journal of Medicine. 1992;**93**(1):61-68

[33] Suryanarayana KM. Hyperthyroidism: Relevant investigations and guidelines for management. Medicine Update. 2010;**20**:440-445

[34] Allahabadia A, Daykin J, Sheppard MC, et al. Radioiodine treatment of hyperthyroidism—Prognostic factors for outcome. The Journal of Clinical Endocrinology and Metabolism. 2001;**86**(8):3611-3617

[35] Elizabeth PN, Alan FP, Lewis BE. Thyroiditis. The New England Journal of Medicine. 2003;**348**:2646-2655

[36] Mandel SJ, Cooper DS. The use of antithyroid drugs in pregnancy and lactation. The Journal of Clinical Endocrinology and Metabolism. 2001;**86**:2354-2359

[37] Glinoer D. Thyroid hyperfunction during pregnancy. Thyroid. 1998; **8**:859-864

[38] Niswander KR, Gordon M, editors. The Collaborative Perinatal Study of the National Institute of Neurologic Disease

and Stroke. Philadelphia: WB Saunders; 1972. pp. 246-249

[39] de Glinoer D et al. Regulation of maternal thyroid during pregnancy. JCEM. 1990;**71**:276-287

[40] Glinoer D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free and subunits, in relation to maternal thyroid stimulation during normal pregnancy. Journal of Endocrinological Investigation. 1993;**16**:881-888

[41] Hershman JM. Human chorionic gonadotropin and the thyroid: Hyperemesis gravidarum and trophoblastic tumors. Thyroid. 1999;**9**:653-657

[42] Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstetrics and Gynecology. 1994;**84**:946-949

[43] Davidson KM, Richards DS, Schatz DA, Fisher DA. Successful in utero treatment of fetal goiter and hypothyroidism. The New England Journal of Medicine. 1991;**324**:543-546

[44] Kempers MJ, van Tijn DA, van Trotsenburg AS, de Vijlder JJ, Wiedijk BM, Vulsma T. Central congenital hypothyroidism due to gestational hyperthyroidism: Detection where prevention failed. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**:5851-5857

[45] Papendieck P, Chiesa A, Prieto L, Gruñeiro-Papendieck L. Thyroid disorders of neonates born to mothers with Graves' disease. Journal of Pediatric Endocrinology & Metabolism. 2009;**22**:547-553

[46] De Groot L, Abalovich M, Erik K, et al. Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:2543-2565

[47] Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. The Journal of Clinical Endocrinology and Metabolism. 2009;**94**:1881-1882