The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism

Consenso brasileiro para o diagnóstico e tratamento do hipertireoidismo: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia

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ABSTRACTS

Introduction: Hyperthyroidism is characterized by increased synthesis and release of thyroid hormones by the thyroid gland. Thyrotoxicosis refers to the clinical syndrome resulting from excessive circulating thyroid hormones, secondary to hyperthyroidism or due to other causes. This article describes evidence-based guidelines for the clinical management of thyrotoxicosis. **Objective:** This consensus, developed by Brazilian experts and sponsored by the Department of Thyroid Brazilian Society of Endocrinology and Metabolism, aims to address the management, diagnosis and treatment of patients with thyrotoxicosis, according to the most recent evidence from the literature and appropriate for the clinical reality of Brazil. **Materials and methods:** After structuring clinical questions, search for evidence was made available in the literature, initially in the database Medline, PubMed and Embase databases and subsequently in SciELO – Lilacs. The strength of evidence was evaluated by Oxford classification system was established from the study design used, considering the best available evidence for each question. **Results:** We have defined 13 questions about the initial clinical approach for the diagnosis and treatment that resulted in 53 recommendations, including the etiology, treatment with antithyroid drugs, radioactive iodine and surgery. We also addressed hyperthyroidism in children, teenagers or pregnant patients, and management of hyperthyroidism in patients with Graves' ophthalmopathy and various other causes of thyrotoxicosis. **Conclusions:** The clinical diagnosis of hyperthyroidism usually offers no difficulty and should be made with measurements of serum TSH and thyroid hormones. The treatment can be performed with antithyroid drugs, surgery or administration of radioactive iodine according to the etiology of thyrotoxicosis, local availability of methods and preferences of the attending physician and patient. Arq Bras Endocrinol Metab. 2013;57(3):205-32

Keywords
Thyrotoxicosis; Graves' disease; toxic nodular goiter; antithyroid drugs

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RESUMO

Introdução: O hipertireoidismo é caracterizado pelo aumento da síntese e liberação dos hormônios tireoidianos pela glândula tireoide. A tireotoxicose refere-se à síndrome clínica decorrente do excesso de hormônios tireoidianos circulantes, secundário ao hipertireoidismo ou não. Este artigo descreve diretrizes baseadas em evidências clínicas para o manejo da tireotoxicose. **Objetivo:** O presente consenso, elaborado por especialistas brasileiros e patrocinado pelo Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia, visa abordar o manejo, diagnóstico e tratamento dos pacientes com tireotoxicose, de acordo com as evidências mais recentes da literatura e adequadas para a realidade clínica do país. **Materiais e métodos:** Após estruturação das questões clínicas, foi realizada busca das evidências disponíveis na literatura, inicialmente na base de dados do Medline-PubMed e posteriormente nas bases Embase e SciELO – Lilacs. A força das evidências, avaliada pelo sistema de classificação de Oxford, foi estabelecida a partir do desenho de estudo utilizado, considerando-se a melhor evidência disponível para cada questão. **Resultados:** Foram definidas 13 questões sobre a abordagem clínica inicial visando ao diagnóstico e ao tratamento que resultaram em 53 recomendações, incluindo investigação etiológica, tratamento com drogas antitireoidianas, iodo radioativo e cirurgia. Foram abordados ainda o hipertireoidismo em crianças, adolescentes ou pacientes grávidas e o manejo do hipertireoidismo em pacientes com oftalmopatia de Graves e com outras causas diversas de tireotoxicose. **Conclusões:** O diagnóstico clínico do hipertireoidismo, geralmente, não oferece dificuldade e a confirmação diagnóstica deverá ser feita com as dosagens das concentrações séricas de TSH e hormônios tireoidianos. O tratamento pode ser realizado com drogas antitireoidianas, administração de radioiodoterapia ou cirurgia de acordo com a etiologia da tireotoxicose, as características clínicas, disponibilidade local de métodos e preferências do médico-assistente e paciente. Arq Bras Endocrinol Metab. 2013;57(3):205-32

Descritores

Tireotoxicose; doença de Graves; bócio nodular tóxico; drogas antitireoidianas

1) INTRODUCTION

Hyperthyroidism is characterized by increased synthesis and release of thyroid hormones by the thyroid gland. Thyrotoxicosis refers to the clinical syndrome resulting from excessive circulating thyroid hormones (thyroxine, T4; triiodothyronine, T3), secondary to hyperthyroidism or due to other causes. T3--thyrotoxicosis refers to an isolated increase in serum levels of T3 along with normal T4 levels and suppressed levels of thyroid-stimulating hormone (TSH).

The clinical manifestations commonly found in hyperthyroidism are listed in table 1. Usually, thyroid hormone levels correlate with clinical presentation. The signs and symptoms secondary to adrenergic stimulation, such as tachycardia and anxiety, are more evident in young patients and in patients with a large goiter (1-2) (**A**). Although weight loss is a frequent finding, some patients, especially the youngest ones, might report weight gain due to an increased appetite (3) (**B**). In the elderly, cardiopulmonary symptoms such as tachycardia (or atrial fibrillation), dyspnea, and edema are typical. The term "apathetic thyrotoxicosis" is used to describe patients with no symptoms besides weakness and asthenia (2,4) (**A,D**).

2) HOW SHOULD PATIENTS WITH THYROTOXICOSIS BE ASSESSED AND THE INITIAL MANAGEMENT PERFORMED?

Patients suspected of having thyrotoxicosis must be subjected to a careful medical interview and physical examination to establish the diagnosis and etiology (Table 2). The time from symptom onset, the use of medications, exposure to iodine (*e.g.*, through tests using iodinated contrast or use of compounds with high iodine content), pregnancy, and family history of autoimmune thyroid diseases must be investigated. Upon physical examination, measurements of body weight, arterial pressure, and heart rate are particularly important. Sinus tachycardia and systolic arterial hypertension are common findings. Atrial fibrillation can also be present, particularly among older adults. Ocular signs such as eyelid retraction, fixed or frightened stare, and the lid-lag sign are due to adrenergic hyperactivity

and can be present in thyrotoxicosis of any etiology. Conversely, signs such as conjunctival and palpebral hyperemia, eyelid swelling, chemosis, paralysis of the extraocular muscles, and exophthalmos are characteristic of the ophthalmopathy of Graves' disease (GD). In thyrotoxicosis, the skin is usually warm and wet, and fine, rapid tremors of outstretched hands, proximal muscle weakness, and hyperreflexia are frequent findings. Infiltrative dermopathy (pretibial myxedema) is a rare manifestation in GD. Palpation and auscultation of the thyroid gland allow for the assessment of size and consistence, the presence of nodules, or thyroid murmur. Goiter of variable size is usually observed in GD and toxic multinodular goiter (TMNG). Pain, either spontaneous or on thyroid palpation, is characteristic of subacute thyroiditis, whereas the presence of a single nodule points to hyperfunctioning follicular adenoma.

The initial laboratory assessment of patients with clinical suspicion of thyrotoxicosis includes measurement of the serum levels of TSH and thyroid hormones. Measurement of TSH by means of ultrasensitive methods (functional sensitivity < 0.02 mlU/mL) is the most sensitive method for thyrotoxicosis diagnosis (sensitivity 95%, specificity 92%) (5) (**B**). Whenever possible, the free thyroxine fraction (FT4) should be measured since abnormalities in the carrier proteins of the thyroid hormones (secondary to the use of medication or other specific clinical conditions) can alter the total concentration of T4 or T3 (6,7) (**D,B**). Except for the very rare cases of hyperthyroidism secondary to TSH-secreting pituitary adenoma (< 1%, see section 13) and the thyroid hormone resistance syndrome (an autosomal dominant disease with an incidence of 1:40,000 live births, see section 13), excess circulating thyroid hormones, independent from the cause, results in TSH suppression (usually < 0.1 mIU/ml). In overt hyperthyroidism, both serum FT4 and T3 levels are increased, whereas TSH is undetectable. In the early stages of GD, as well as in functioning adenomas, T3 can exhibit an isolated increase, a clinical condition known as "T3 thyrotoxicosis". In cases with suspicion of factitious thyrotoxicosis (intake of thyroid hormones), low or undetectable levels of serum thyroglobulin can help establish the diagnosis (8) (**D**).

Measurement of the anti TSH-receptor antibody (TRAb) is not usually required to diagnose Graves' hyperthyroidism and is only indicated in selected cases. As a rule, TRAb should be measured in pregnant women with ongoing or past history of GD to assess the risk of neonatal thyrotoxicosis due to transplacental antibody transfer (9) (**B**), in the differential diagnosis of gestational thyrotoxicosis (10) (**B**), and in euthyroid individuals with exophthalmos, especially when it is bilateral.

Iodine is a crucial element for the synthesis of thyroid hormones, and thus, iodine uptake is an excellent indicator of thyroid function. The rate of iodine uptake by the thyroid can be assessed using radioactive iodine (^{131}I or ^{123}I), which allows one to distinguish the causes of thyrotoxicosis associated with increased uptake (hy-

Table 1. Clinical manifestations of hyperthyroidism

Symptoms	%	Signs	%
Nervousness	99	Tachycardia	100
Excessive sweating	91	Goiter	97
Intolerance to heat	89	Tremor	97
Palpitations	89	Warm and wet skin	90
Fatigue	88	Thyroid murmur	77
Weight loss	85	Eye disorders	71
Dyspnea	75	Atrial fibrillation	10
Weakness	70	Gynecomastia	10
Increased appetite	65	Palmar erythema	8
Ocular complaints	54		
Limb edema	35		
Increased frequency of bowel movements	33		
Diarrhea	23		
Menstrual disorders	20		
Anorexia	9		
Weight gain	2		

Table 2. Radioiodine uptake (^{123}I or ^{131}I) in the different causes of thyrotoxicosis

Normal or increased uptake
Graves' disease
Multinodular goiter and toxic adenoma
Trophoblastic disease
TSH-secreting pituitary adenoma
Thyroid hormone resistance
Low or absent uptake
Painless (silent) thyroiditis
Amiodarone-induced thyroiditis
Subacute (granulomatous, De Quervain's) thyroiditis
Iatrogenic thyrotoxicosis
Factitious intake of thyroid hormones
Struma ovarii
Acute thyroiditis
Extensive metastases of thyroid follicular carcinoma

perthyroidism) from those with low or no iodine uptake (Table 2) (11) (**B**). Iodine uptake is usually increased in patients with GD and TMNG and is virtually absent in thyroiditis and factitious thyrotoxicosis. Iodine uptake also decreases in the individuals who have used iodinated radiological contrast media in the previous 30-60 days or consume iodine-rich diets (*e.g.*, seaweed). Interestingly, iodine uptake can be present in amiodarone users, despite its high iodine content (12) (**B**).

Thyroid scintigraphy shows the distribution of the radioactive marker across the gland and has limited indications in the assessment of thyrotoxicosis. Thyroid scintigraphy is characteristically diffuse in GD and heterogeneous in TMNG (high-uptake intertwined with low-uptake areas). The main indication for scintigraphy is the suspicion of hyperfunctioning follicular adenoma (hot nodule) (11) (**B**).

Thyroid ultrasound (US) is not routinely indicated for the assessment of hyperthyroidism and is usually limited to cases when a nodule is discovered by palpation (13) (**D**). Nevertheless, when an iodine uptake test cannot be performed, is contraindicated (pregnancy and breastfeeding), or does not result in a diagnosis (recent exposure to iodine), thyroid Doppler US can help to establish the etiologic diagnosis (14,15) (**C,D**). Thyroid Doppler flowmetry can contribute to the differential diagnosis between the amiodarone-induced thyrotoxicosis subtypes (types 1 and 2) as well as between GD and destructive thyroiditis (14,16) (**C,D**).

Treatment with beta-blockers must be considered for symptomatic patients with suspected or diagnosed thyrotoxicosis (17,18) (**B,D**). These agents reduce the heart rate, arterial pressure, tremor, emotional lability, and exercise intolerance (18) (**D**). The non-selective beta-blocker propranolol is the most widely used; however, cardioselective beta-blockers (atenolol, metoprolol) or with shorter half-life (esmolol) can also be prescribed (19,20) (**B,C**). The usual dose of propranolol and atenolol per oral route varies from 20-80 mg every 6-12 hours and from 50-100 mg once per day, respectively, and must be adjusted according to the clinical response (21) (**D**). Calcium channel blockers (*e.g.*, verapamil and diltiazem) can be used orally when beta-blockers are contraindicated (22,23) (**B**).

Recommendation 1

The diagnosis of Graves' hyperthyroidism can be established with relative confidence in patients with moderate to severe symptoms of thyrotoxicosis, recent ophthalmopathy, and diffuse goiter. In these cases no additional tests are needed to investigate its etiology.

Recommendation 2

Clinical suspicion of thyrotoxicosis must be confirmed by concomitant measurement of the serum levels of TSH and thyroid hormones (**B**). TSH is low or undetectable in most patients with thyrotoxicosis, and high FT4 and/or T3 levels confirm the diagnosis.

Recommendation 3

Measurement of serum TRAb levels is indicated in pregnant women with ongoing or past history of GD, to assess the risk of neonatal thyrotoxicosis due to transplacental antibody transfer, in the differential diagnosis of gestational thyrotoxicosis (first trimester), and in euthyroid individuals with ophthalmopathy (**B**).

Recommendation 4

Radioactive iodine uptake (^{123}I or ^{131}I) is useful for the differential diagnosis of thyrotoxicosis, in particular, to distinguish between GD and TMNG from thyroiditis (**B**). This test is contraindicated during pregnancy and breastfeeding (**A**).

Recommendation 5

Thyroid US is not routinely indicated for the assessment of thyrotoxicosis (**B**). Doppler flowmetry can be useful in the differential diagnosis of the amiodarone-induced thyrotoxicosis subtypes (**B**).

Recommendation 6

Prescription of beta-blockers is indicated for symptomatic patients with suspected or diagnosed thyrotoxicosis (**B**).

3) HOW SHOULD PATIENTS WITH HYPERTHYROIDISM SECONDARY TO GD BE TREATED?

GD is the most common cause of thyrotoxicosis, and its pathogenesis includes formation of TRAbs, which bind to the TSH receptors at the thyroid follicular cell membrane, causing gland hyperfunction. The excess of thyroid hormones due to Graves' hyperthyroidism can be controlled by inhibition of the hormone synthe-

sis with antithyroid drugs (ATDs), destruction of the thyroid tissue using radioactive iodine (^{131}I), or total thyroidectomy (TT). Each of these three treatment modalities has advantages and disadvantages, and the latter two are considered definitive treatments. The choice of modality must be grounded on clinical and socioeconomic characteristics as well as physician and patient preferences.

A. USE OF ATDS AS AN INITIAL TREATMENT FOR GRAVES' HYPERTHYROIDISM

ATD prescription is the only therapeutic option that allows for a cure without surgical intervention or radiation exposure. The ATDs are thionamides and include propylthiouracil (PTU), methimazole (MMI), and carbimazole; the latter is not available in Brazil. These agents inhibit thyroid hormone synthesis by interfering with the use of intrathyroid iodide and the coupling reaction, both of which are catalyzed by thyroid peroxidase (24) (**D**). Thionamides also exhibit immunomodulating effects, although the mechanism has not yet been elucidated. High doses of PTU inhibit the peripheral conversion of T_4 into T_3, which is an additional benefit when a faster control of thyrotoxicosis is desired. However, due to the hepatotoxic effects of PTU and the reduction of the efficacy of ^{131}I in a possible future treatment (see below), its use as first treatment must be restricted to cases of severe hyperthyroidism, thyrotoxic crisis, and the first trimester of pregnancy (25,26) (**B,D**). MMI use is associated with aplasia cutis congenita and is contraindicated in the first trimester of pregnancy (27) (**C**).

The initial dose of MMI in patients with mild to moderate thyrotoxicosis is 10-30 mg in a single daily dose. In cases of severe hyperthyroidism, the daily dose can vary from 40-60 mg (28) (**B**). Most patients achieve euthyroidism following six to eight weeks of treatment. In this stage, the dose can be gradually reduced; the maintenance doses of MMI and PTU are 5-10 mg/day and 50-100 mg/day, respectively.

Mild side effects occur in 1%-5% of the patients using thionamides and include skin rash, itch, urticaria, and arthralgia. When these symptoms do not disappear spontaneously, one ATD can be replaced by another, although cross reactions occur in up to 50% of patients. Antihistamines can be used to control the skin manifestations (24) (**D**). Severe side effects occur in approximately 1% of patients and include severe polyarthritis and agranulocytosis and, more rarely, aplastic anemia, thrombocytopenia, toxic hepatitis (PTU), vasculitis, lupus-like syndrome, hypoprothrombinemia (PTU), and hypoglycemia (MMI) (29,30) (**B,C**). Agranulocytosis is the most frequent severe side effects and occurs in 0.5% of patients using ATDs (31) (**C**). Therefore, at treatment onset, the patients should be advised to discontinue the ATD and consult their doctor when fever, odynophagia, or lesions in the oral mucosa occur. When the diagnosis is confirmed, the patient must be admitted to the hospital to be treated with broad-spectrum antibiotics and granulocyte colony-stimulating factor (1-5 µg/kg/day per the subcutaneous route) (32) (**D**). When a severe side effect occurs, the drug must be immediately and permanently discontinued.

Monitoring of thyroid function is performed by measuring FT4 and total T3 4-6 weeks after the onset of treatment and then every four to eight weeks until euthyroidism is achieved with the lowest drug dose. From that moment onwards, clinical and laboratory assessment should be performed every two to three months. TSH levels can remain suppressed for several months following the onset of treatment and must not be used for monitoring in the initial stage (33,34) (**B**).

ATDs must be discontinued following 12-24 months of treatment. The rate of GD remission varies from 30%-50% (35,36) (**B,A**). Patients with long-standing disease, large goiter, and high T3 levels (> 500 ng/dL) exhibit higher probabilities of relapse (33,34,37) (**B**). As most relapses occur within the first months following ATD discontinuance, it is recommended to monitor the thyroid function on a monthly basis for the first six months and then every three months; following the first year of remission, the patient must be monitored once per year, indefinitely (38-40) (**B**).

Recommendation 7

Treatment with ATDs is effective for the control of Graves' hyperthyroidism and can be used as the initial treatment in an attempt to achieve remission of the autoimmune disorder. The rate of disease remission following 12-24 months of treatment varies from 30%-50% (**B**).

Recommendation 8

Due to the potential hepatotoxic effects of PTU, its use as a first treatment must be restricted to cases of severe hyperthyroidism, thyrotoxic crisis, and the first

trimester of pregnancy (**B**). MMI use has been associated with aplasia cutis congenita, and thus, it is contraindicated in the first trimester of pregnancy (**C**).

Recommendation 9

Variable degrees of side effects occur in 1%-5% of the patients using thionamides. Whenever a severe side effect occurs, the ATD must be immediately and permanently discontinued (**D**).

B. USE OF ^{131}I AS INITIAL TREATMENT FOR PATIENTS WITH GRAVES' HYPERTHYROIDISM

^{131}I was introduced into clinical practice in the mid-1940s and is currently widely used in the treatment of hyperthyroidism. Along with surgery, ^{131}I is classified as a definitive treatment of hyperthyroidism. ^{131}I is considered a simple and safe therapy and is the least expensive compared with the other therapeutic modalities available, including ATDs (41-43) (**B,D,D**).

Radioiodine is the first therapeutic choice for patients in whom ATDs and/or surgery are contraindicated as well as in cases of hyperthyroidism relapse following treatment with ATDs. It must also be considered as initial treatment when definitive and fast control of hyperthyroidism is desired, *e.g.*, in older adults and patients with heart disease as well as in fertile women who plan to become pregnant in the future to avoid the risks posed by hyperthyroidism during pregnancy and the postpartum period. This treatment is contraindicated during pregnancy, breastfeeding, in the presence of suspected or confirmed thyroid cancer, and for women who plan to become pregnant in less than four to six months. Pregnancy tests must be performed for all fertile women before ^{131}I is administered (43) (**D**).

^{131}I is administered orally, dissolved in water or in capsules, and is quickly absorbed and organified by the thyroid follicular cells. ^{131}I-induced radiation triggers an inflammatory response followed by local destruction and progressive fibrosis resulting in reduction of the gland volume, which is more pronounced in the first year following dose administration (43) (**D**). No special dietary recommendations are required; the patients must simply avoid consuming excessive amounts of iodine (*e.g.*, multivitamins). Previous use of beta-blockers must be considered in highly symptomatic cases and/or with increased risk of complications were thyrotoxicosis to become worse (17,18) (**B,D**).

Prior treatment with ATD to avoid exacerbation of the clinical manifestations of thyrotoxicosis is controversial. Prospective randomized studies that assessed thyroid hormone levels following ^{131}I administration found a significant reduction of the FT4 and T3 levels in both the patients pretreated or not with MMI (1,44) **(A)**. When pretreatment with an ATD is performed, the drug must be discontinued for four to seven days prior to ^{131}I administration. Pretreatment with MMI does not influence the efficacy of the treatment of hyperthyroidism (45) (**A**), but pretreatment with PTU can result in increased therapeutic failure (46,47) (**B**). Reintroduction of MMI 7 days after ^{131}I treatment appears to avoid thyrotoxicosis exacerbation without interfering with treatment efficacy (48) (**B**).

The ^{131}I dose can be either fixed or calculated for each individual patient based on the iodine uptake and gland volume (49) (**D**). Prospective trials found that fixed doses and individualized regimens exhibit similar efficacy with regard to the cure rates for hyperthyroidism (50,51) (**A**). The dose is usually calculated as microcuries (uCi) or megabecquerels (MBq) per gram (g) of thyroid tissue based on the thyroid size and 24-hour iodine uptake. A dose of 160-200 uCi/g [5.9-7.4 MBq/g] is recommended to ensure successful treatment. Alternatively, fixed dose of 10-15 mCi [370-555] can be prescribed (52-54) (**B,D,D**). Administration of low iodine doses represents an attempt at curing hyperthyroidism without causing hypothyroidism; however, this approach exhibits high rates of therapeutic failure (55) (**B**). Higher doses are recommended for patients with comorbidities that might worsen with persistent hyperthyroidism and under conditions of increased radioresistance (large goiter, severe hyperthyroidism) (42,56) (**D**). When doses are calculated, activity typically falls within a range of 5-15 mCi ^{131}I (corresponding to 185-555 MBq).

Therapeutic failure occurs in approximately 20% of the patients treated with ^{131}I. The factors associated with higher failure rates are large goiter (> 50 ml), high iodine uptake (> 90%), and high serum T3 levels (> 500 ng/mL) at diagnosis (45) (**A**).

The use of glucocorticoids has not been effective in improving hyperthyroidism; however, glucocorticoids are indicated as prophylaxis against appearance or progression of ophthalmopathy in GD as well as for the treatment of thyrotoxic crisis (see section 10).

Recommendation 10

Radioiodine therapy is effective for the control of Graves' hyperthyroidism and can be used as initial treatment, especially in patients with low probabilities of remission with ATD therapy, when definitive and fast control of thyrotoxicosis is required, or when ATD use and/or surgery are contraindicated (**A**).

Recommendation 11

Treatment with ^{131}I is contraindicated during pregnancy, breastfeeding, and in the presence of suspected thyroid nodule or confirmed thyroid cancer. Radioactive iodine should also be avoided in women who plan to become pregnant in less than four to six months (**D**).

Recommendation 12

Radioactive iodine is administered orally in fixed or calculated doses. Pretreatment with beta-blockers and ATD should be considered in patients with risk of complications (**B**).

C. WHAT ACTIONS SHOULD BE TAKEN IN CASES OF RELAPSE FOLLOWING A THERAPEUTIC DOSE OF ^{131}I?

The rate of satisfactory response to treatment with ^{131}I resulting in hypothyroidism or euthyroidism is approximately 80%-90% (42,43) (**D**). Hypothyroidism occurs not only due to the effect of radiation on the gland but also to the natural history of the autoimmune disease. A large goiter with hypoechogenicity on ultrasound, the presence of anti-thyroid peroxidase (anti-TPO) antibodies, and high ^{131}I doses increase the probability of hypothyroidism (42,45,52) (**D,A,B**).

The response to ^{131}I administration should be assessed through the signs and symptoms of thyrotoxicosis, thyroid size and function. Follow-up one to two months after the administration of radioactive iodine should include measurements of FT4 and total T3. If the patient remains hyperthyroid, monitoring should be repeated every four to six weeks. When hyperthyroidism persists six months after treatment, administration of another dose of ^{131}I should be considered. Suppressed TSH levels associated with normal total T3 and FT4 levels does not call for further treatment, but the patient should be closely monitored for relapse or development of hypothyroidism (43) (**D**).

Clinical features associated with therapeutic failure are as follows: male gender; smoking; large goiter (larger than 50 g); high 24-hour iodine uptake; and very high T3 levels (> 500 mg/dL) (45) (**A**). The presence of autonomous tissue exhibiting functional differences in iodine uptake and organification can represent an additional cause of therapeutic failure in some cases (57) (**B**). Persistence of high TRAb levels and increased blood flow on thyroid Doppler also increase the probability of relapse (42,52) (**D,B**). A second dose of ^{131}I is usually recommended for patients who do not respond to the first therapeutic dose (58) (**D**). Use of lithium (900 mg/day for 12 days) (59) (**B**) or surgery should be considered for the small fraction of patients with hyperthyroidism refractory to ^{131}I.

In the long term, in addition to hypothyroidism, patients treated with ^{131}I exhibit a low but significant risk of cardiovascular events, but it is not known whether this is an effect of hyperthyroidism or of the treatment (56) (**D**). There is no evidence pointing to an increased risk of thyroid cancer or increased mortality by any other type of neoplasm (42,60,61) (**D,B,B**). However, it is described a small increase in the incidence of tumors in patients with hyperthyroidism after 5 years of treatment with ^{131}I, relative to the general population of 118.9 *vs.* 94.9 per 10,000 person-years (RR = 1.25 1.08 to 1.46 with 95% CI). This increased incidence is related to the dose of ^{131}I, especially in the age groups 50-59 years (RR = 1.44) or more than 70 years (RR = 1.39), particularly for renal tumors (RR = 2.32), stomach (RR = 1.75) and breast cancer (RR = 1.07) (60) (**B**). Some men exhibit a mild, subclinical, and reversible decrease in testosterone and luteinizing hormone levels. The offspring of patients treated with ^{131}I do not exhibit a higher prevalence of congenital anomalies compared with the overall population (42,62) (**D,C**). Women are advised to wait four to six months before attempting conception to ensure they achieve stable euthyroidism; men are recommended to wait three to four months. Breastfeeding should be avoided for at least six weeks following radioiodine administration (42) (**D**).

Recommendation 13

The response to ^{131}I should be monitored by clinical and laboratory follow-up. If the patient remains thyrotoxic, measurement of T3 and FT4 should be performed every four to six months. When hyperthyroidism persists six months after treatment with ^{131}I, administration of an additional dose should be considered. Suppressed TSH levels associated with total T3 and FT4

within the normal range points to the need for monitoring for possible relapse (**D**).

D. When is thyroidectomy indicated for patients with GD?

Surgery is the oldest treatment for GD (63) (**B**). Its main aim is to achieve fast and definitive control of the thyroid hormone excess effects. That goal is achieved by removing all or most of the functioning thyroid gland tissue.

The indications for surgery in the treatment of GD are not well established in the literature; some authors classify them as absolute and relative. A large goiter causing compressive symptoms, suspected or confirmed malignant thyroid nodule, pregnant women who fail to achieve disease control through ATDs, refusal of ^{131}I treatment, women planning to become pregnant within a period of four to six months, and intolerance to ATD are classified as absolute indications. Relative indications include large goiter, severe ophthalmopathy, poor adherence, and lack of response to ATD treatment (63,64) (**B**).

The advantages offered by thyroidectomy over the other treatment modalities include the fast normalization of the thyroid hormone levels and a greater effectiveness in cases with compressive symptoms. Disadvantages include cost, the need for hospitalization, and the risks associated with surgery (hypoparathyroidism, recurrent laryngeal nerve injury, bleeding, infection, scarring, and hypothyroidism) (42) (**D**). Liu and cols. (65) (**B**) analyzed 58 patients with GD treated by means of surgery and found that the main indications were the following: persistence of disease following clinical treatment (47%); patient preference (21%); multinodular disease or cold nodule (20%); failure of ^{131}I treatment (16%); and ophthalmopathy (12%).

Once the choice of surgical treatment is made, certain pre- and postoperative measures are crucial. Previous administration of ATD, with or without beta-blockers, must be considered to control thyroid function and reduce the risk of thyrotoxic crisis, which can be triggered by surgical stress, anesthesia, and gland manipulation (66) (**B**). Administration of potassium iodide or a saturated solution of potassium iodide (SSKI) 7-10 days before surgery can reduce the intraglandular blood flow and vascularization and thus blood loss during surgery. The doses suggested are as follows: SSKI (50 mg/drop), one drop three times per day, or Lugol's solution (6 mg/drop), 5-10 drops three times per day (67,68) (**B**).

During the immediate postoperative period, symptoms (paresthesia, cramps) and signs (Chvostek's and Trousseau's signs) of hypocalcemia must be evaluated, and serum calcium levels should be monitored (especially in symptomatic patients). Use of calcium supplements per the oral route and calcitriol reduces the risk of symptomatic hypocalcemia and the need to administer calcium per the intravenous route (69) (**B**). In case of clinical manifestations of recurrent laryngeal nerve dysfunction, the vocal folds mobility should be evaluated through laryngoscopy in the postoperative period for diagnosis (70) (**D**). Although partial (PT) or subtotal (TST) thyroidectomy have been the first-choice surgical procedures for many decades, the amount of remaining gland tissue required to maintain the euthyroid state cannot be established. The probability of relapse varies from 5%-20% when residual tissue remains (71,72) (**B**), whereas the risk of relapse following total thyroidectomy (TT) is virtually zero (73) (**B**). The risk of permanent paralysis of the recurrent laryngeal nerve is 0.9% with TT and 0.7% with TST. Transient hypocalcemia is observed in 9.6% of the patients who underwent TT and in 7.4% of those submitted to TST (whereas the risk of definitive hypoparathyroidism is 0.9% and 1.0%, respectively) (73) (**B**). Thus, when surgery is indicated for the treatment of GD, the procedure of choice is TT, performed by an experienced surgeon (more than 100 thyroidectomies/year) whenever possible (74) (**B**). Thyroid hormone replacement therapy with levothyroxine sodium should be initiated on the following day after surgery when TT is performed.

Recommendation 14

Surgical treatment (total thyroidectomy) is indicated for patients with GD that exhibit a large goiter associated with compressive symptoms, suspected or confirmed malignant nodule, pregnant women who do not achieve control of disease using ATDs, and for patients intolerant to ATDs who refuse radioactive iodine treatment (**B**).

4) HOW SHOULD PATIENTS WITH GD AND THYROID NODULES BE ASSESSED AND TREATED?

Thyroid cancer occurs in less than 2% of patients with GD, and most of the tumors are papillary microcarci-

nomas with an excellent prognosis (75,76) (**D,B**). Patients with GD and thyroid nodules on palpation and/or thyroid US must be assessed before therapeutic administration of ^{131}I. Nodules larger than 1 cm should be subjected to fine-needle aspiration biopsy (FNAB) under US guidance to rule out malignancy. Nodules smaller than 1 cm require additional assessment when the US findings are ambiguous, there is association with enlarged cervical lymph nodes, the patient has a previous history of head and/or neck irradiation, or a family history of thyroid cancer (13,77) **(D)**. When the nodules exhibit indeterminate or malignant cytology, TT should be indicated (13,77) **(D)**.

Recommendation 15

Patients with GD and thyroid nodules larger than 1 cm should be evaluated according to the general criteria suggested for nodule management before the administration of a therapeutic dose of ^{131}I **(B)**.

5) HOW SHOULD PATIENTS WITH HYPERTHYROIDISM DUE TO TMNG AND TOXIC ADENOMA (TA) BE TREATED?

TMNG and TA are the main causes of hyperthyroidism among older adults, occuring frequently in areas characterized by poor iodine intake (70) (**D**). TA commonly results from activating mutations of the TSH receptor. TMNG is a result of the natural history of non-toxic multinodular goiter (MNG) when autonomous areas become evident, and is also often caused by mutations in the TSH receptor (78) (**D**). In this case, the control of hyperthyroidism achieved using ATD is only transitory, and the treatment choice should be radioactive iodine ablation or thyroidectomy. Percutaneous ethanol injection under US guidance or laser thermal ablation can be used as alternative treatment in select cases (70) (**D**).

A. THERAPY WITH ATDS IN PATIENTS WITH TMNG OR TA

Treatment of hyperthyroidism with ATDs in patients with non-autoimmune nodular disease does not induce remission. Nevertheless, patients with TMNG or TA and severe hyperthyroidism must be treated with ATDs to achieve euthyroidism as preparation for surgery. The first-choice drug in this context is MMI at a dose of 10-30 mg/day. However, older adults with contraindications for surgery or ^{131}I administration can be treated continuously with low MMI doses (79) (**D**).

Recommendation 16

Patients with TMNG or TA and severe hyperthyroidism should be treated with ATDs as preparation for surgery or ^{131}I therapy. The drug of choice is MMI (10-30 mg/day) which should be used until euthyroidism is achieved. Instead, in those patients with mild/moderate hyperthyroidism or moderate-sized goiter, beta-blockers can be used (**D**).

Recommendation 17

In older adults in whom surgery or ^{131}I are contraindicated, continuous treatment with low MMI doses should be considered (**D**).

B. INDICATION FOR ^{131}I THERAPY IN PATIENTS WITH TMNG OR TA

Administration of ^{131}I is indicated for the treatment of TMNG or TA when surgery is contraindicated or refused by the patient (42) (**D**). Radioactive iodine therapy is particularly indicated for older adults with comorbidities and a 24-hour iodine uptake high enough to allow for appropriate uptake of ^{131}I. Beta-blockers are indicated for older adults with cardiovascular disease who are at risk for tachyarrhythmias following ^{131}I dosing (21,80,81) (**D,D,C**).

Therapy with ^{131}I is contraindicated for pregnant women or those who plan to become pregnant within a six-month period, and breastfeeding mothers. As the incidence of thyroid cancer is the same in single nodules and multinodular goiter (82) (**B**), patients with TMNG must undergo to FNAB to cytological analysis of the suspected malignant nodule and/or dominant nodule before the therapeutic dose of ^{131}I is administered (13,26,83) (**D,D,B**).

The ^{131}I uptake is frequently low in TMNG which requires high therapeutic doses and, consequently, need for hospitalization. The use of recombinant TSH provides an alternative, as it increases ^{131}I uptake and thus promotes a greater reduction of the TMNG (83) (**B**). Radioactive iodine treatment in TMNG patients usually results in a 40%-50% reduction of the goiter size 6-36 months later and improves the compressive symptoms even in patients with a large goiter (84) (**B**). Approximately 40%-50% of patients present hypothyroidism following treatment (82) (**B**). The ^{131}I dose calculated on

the basis of the goiter size to release 150-250 µCi per gram of tissue corrected for the 24-hour ^{131}I uptake is usually higher than the one needed for the treatment of GD and, usually, varies from 30-50 mCi ^{131}I. Although in TA, the uptake is concentrated in the dominant nodule, hypothyroidism may also occur following ^{131}I, and its incidence increases with the time elapsed since ^{131}I use. The dose of ^{131}I used for the treatment of TA is similar to the one used for TMNG (150-250 µCi per gram corrected for the 24-hour ^{131}I uptake) and calculated based on the nodule size. Thus, the total dose is usually smaller (10-20 mCi) (85) (**B**). The patients with TA subjected to an appropriate therapeutic dose of ^{131}I rarely require a second dose (42) (**B**).

Recommendation 18

Patients with TMNG or TA with contraindications or refuse surgical treatment are candidates for treatment with ^{131}I (**D**). Symptomatic patients must first be treated with ATDs and beta-blockers, while the mild cases should be treated with beta-blockers only (**C**).

Recommendation 19

The therapeutic doses of ^{131}I recommended for patients with TMNG or TA range from 150-250 µCi per gram of tissue corrected for the 24-hour ^{131}I uptake (**B**).

C. INDICATIONS FOR THYROIDECTOMY IN PATIENTS WITH TMNG OR TA

Surgery is the first therapeutic choice in patients with TMNG or TA (86) (**B**). The patients can be previously treated with ATDs and beta-blockers until euthyroidism is achieved. For this purpose, the choice drug is MMI in a dose of 10-30 mg/day. Relapse following TT is less than 1%, and indications for TT include thyroid dysfunction, compressive symptoms (dyspnea and dysphagia), suspected or confirmed malignancy, and intrathoracic or substernal goiter (70,87,88) (**D,D,B**). As TA is characterized by single lesions, TP by means of total lobectomy (removal of the nodule-affected lobe, and extension of resection through the isthmus up to the contralateral lobe) is indicated (70,87,88) (**D,D,B**).

Follow-up after TT sould follow the recommendations described in section 3, including assessment of possible postoperative complications (hypocalcemia, vocal cord dysfunction) and thyroid hormone replacement therapy with levothyroxine (**D**).

Patients who underwent TT virtually never require further surgery (89,90) (**B**). However, when hyperthyroidism relapses following TP or TST, completion of TT is indicated after the assessment of the remaining thyroid lobe by means of US (70) (**D**). If treatment with ^{131}I is chosen instead, the remaining tissue must be evaluated as to the presence of nodules, and whenever they are found, the nodules should be assessed following the recommended criteria (13,70,87,88) (**D,D,D,B**).

Recommendation 20

Surgical treatment offers satisfactory results of achieving control of hyperthyroidism in patients with TMNG and TA. TT is the first-choice definitive treatment of TMNG, whereas lobectomy is indicated for TA (**B**).

Recommendation 21

Pre-surgical care, complications, and postoperative follow-up are similar to the ones described for the surgical treatment of GD (**D**).

6) USE OF OTHER THERAPEUTIC MODALITIES FOR TMNG AND TA

Ethanol provides a therapeutic alternative for the treatment of cystic (91-93) (**B**) and autonomous nodules (94-98) (**B,B,B,B,C**). Ethanol injection is well tolerated, and most patients report only mild pain during the procedure (96) (**B**). This procedure is effective, safe, inexpensive, and has long-term satisfactory results. However, this modality tends to be rejected in the case of solid thyroid nodules. Ablation of solid nodules by means of percutaneous laser ablation (97-99) (**C,D**) or radiofrequency has proven to be effective in the treatment of benign thyroid nodules regardless of the extension of their solid component (100) (**D**).

Recommendation 22

Sclerotherapy of cystic or autonomous nodules is a safe therapeutic option when the traditional treatments (surgery or ^{131}I) are contraindicated or refused by the patient (**B**).

7) HOW SHOULD THYROTOXIC CRISIS BE DIAGNOSED AND MANAGED?

The diagnosis of thyrotoxic crisis or storm is basically clinical. Its manifestations are the same as thyrotoxi-

cosis, but highly exacerbated and include tachycardia (usually > 140 beats per minute), heart failure, hyperthermia, agitation, anxiety, delirium, psychosis, coma, nausea, vomiting, diarrhea, abdominal pain, liver failure, and jaundice. In 1993, Burch and Wartofsky suggested a score for an objective assessment of these patients, including cutoff points for the diagnosis of thyrotoxic crisis (Table 3) (101) (**B**). More recently, new criteria have been proposed, including the same disorders as listed previously: the combination of thyrotoxicosis and manifestations in other organic systems (disorders of the central nervous system, tachycardia, heart failure, gastrointestinal disorders, and fever) (102) (**B**).

The laboratory assessment of thyroid function exhibits the same pattern as in hyperthyroidism (increased serum levels of thyroid hormones and TSH suppression). As the diagnosis depends on the clinical assessment, it is recommended that patients suspected of thyrotoxic crisis be treated as if they actually present this condition. Known triggers of thyrotoxic crisis include abrupt discontinuation of ATDs, thyroid and non-thyroid surgery, and severe acute illnesses (infections, diabetic ketoacidosis, vascular events) (66) (**B**).

Treatment must be initiated using multiple medications to block the adrenergic system and the synthesis and release of thyroid hormones. For that purpose, thionamides, beta-blockers, and inorganic iodine compounds are used (Table 4). The supportive management is also important and must be preferentially conducted in the intensive care setting (66) (**B**).

The use of beta-blockers seeks to control the signs and symptoms of adrenergic hyperactivation. Although propranolol is the most frequently used drug, cardioselective beta-blockers (atenolol, metoprolol) or drugs with a shorter half-life (esmolol) can also be prescribed (20) (**C**). For patients in whom beta-blockers are contraindicated, diltiazem represents an alternative option (22) (**B**).

The use of thionamides seeks to block the synthesis of thyroid hormones, which begins 1-2 hours following administration. The first choice agent for the treatment of thyrotoxic crisis is PTU because it induces additional blocking of the peripheral conversion of T4 into T3, particularly when high doses are used (Table 2) (103) (**B**). Both drugs can be administered per alternative (rectal or intravenous) routes when the oral route is not available (104-109) (**C,B,C,C,B,C**) (Table 5). When patients develop severe side effects or allergy to thionamides, TT is recommended. Preparation for surgery must be performed with beta-blockers, glucocorticoids, and iodine solutions over 5-7 days, and thyroidectomy is performed between days 8 and 10 (110) (**C**). The use of iodine solutions seeks to block the release of the thyroid hormones already synthesized and must be preceded by thionamide administration. The two iodide compounds available are Lugol's solution and SSKI. These agents can also be administered per the rectal route. In addition, iodinated contrast media (iopanoic acid and sodium ipodate) can be used, which has an additional advantage of simultaneously blocking the thyroid hormone release and the peripheral conversion of T4 into T3 (111) (**B**). Similar to the iodine solutions, the use of contrast media must be preceded by blocking thyroid hormone synthesis using thionamides.

Table 3. Burch-Wartofsky's diagnostic criteria

Thermoregulatory dysfunction (temperature ºC)	Scoring points
37.2 – 37.7	5
37.8 – 38.2	10
38.3 – 38.8	15
38.9 – 39.4	20
39.4 – 39.9	25
> 40.0	30
Effects on the central nervous system	
Mild (agitation)	10
Moderate (*delirium*, psychosis, extreme lethargy)	20
Severe (seizures, coma)	30
Gastrointestinal and liver dysfunction	
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular dysfunction (heart rate)	
99 – 109	5
110 – 119	10
120 – 129	15
130 – 139	20
≥ 140	25
Atrial fibrillation	10
Heart failure	
Mild (peripheral edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
History of triggering factor	
Negative	0
Positive	10

The score for all items is added. Scores > 45 are highly suggestive of thyrotoxic storm, 25-45 are suggestive of thyrotoxic storm, and < 25 indicates that this condition is improbable. Adapted from: Burch HB, Wartofsky L. Endocrinol Metab Clin North Am. 1993;22:263.

Table 4. Drugs used in the treatment of thyrotoxic crisis

Beta-blockers	
Propranolol	PO: 60-80 mg every 4-6 hours. IV: 0.5-1.0 mg in 10 minutes, followed by 1-2 mg every 10 minutes
Esmolol	IV: loading dose 250-500 mcg/kg followed by infusion of 50-100 mcg/kg per minute
Atenolol	PO: 50-200 mg once per day
Metoprolol	PO: 100-200 mg once per day
Nadolol	PO: 40-80 mg once per day
Thionamides	
Propylthiouracil	PO: 200-400 mg every 4-6 hours
Methimazole	PO: 20-25 mg every 4-6 hours
Iodine solutions	
Lugol's solution	PO: 4-10 drops every 6-8 hours
SSKI	PO: 5 drops every 6 hours
Iodinated contrast media reagents	
Iopanoic acid	PO: 0.5-1 g once per day
Sodium ipodate	PO: 1-3 g once per day
Glucocorticoids	
Hydrocortisone	IV: 100 mg every 8 hours
Dexamethasone	IV: 2 mg every 6 hours

PO: oral route (per os); IV: intravenous route. The oral doses can be administered per nasogastric or nasoenteric tube. SSKI: saturated solution of potassium iodide.

Table 5. Alternative administration routes of thionamides

Propylthiouracil	
Enema	8-12 50 mg capsules dissolved in 90 mL of sterilized water
Suppository	200 mg dissolved in polyethylene glycol base
.	Dissolve tablets in isotonic saline solution with alkaline pH (using sodiumhydroxide)
Methimazole	
Suppository	1,200 mg dissolved in 12 mL of water with 2 drops of polysorbate 80 mixed 52 mL of cacao butter
Intravenous	Dissolve tablets in isotonic saline solution and filter using a 0.22-µm filter

High doses of glucocorticoids reduce the peripheral conversion of T4 into T3. In addition, there is evidence that the adrenal reserve is reduced in patients with severe hyperthyroidism, and thus, hormone replacement treatment might be needed (112) (**B**). The use of cholestyramine to reduce the enterohepatic circulation has also been described (113) (**C**). The use of plasmapheresis has been reported to improve the clinical and laboratory parameters in patients who failed to respond to the treatments described above (114) (**C**).

The triggering factor of the thyrotoxic crisis should be identified and must be the target of aggressive treatment. In addition, hyperthermia must be treated. Salicylates must be avoided because they can increase the free fraction of thyroid hormones (66) (**B**). Intravenous hydration is recommended as well as multivitamin replacement, particularly thiamine.

Recommendation 23

The diagnosis of thyrotoxic storm is established based on clinical criteria (**D**). Its treatment includes beta-blockers, ATD, iodinated compounds, and glucocorticoids (**B**). Total thyroidectomy should be considered for patients who do not respond for clinical management (**C**). The patients must be given supportive treatment in the intensive care unit, and the triggering factors should be identified and treated (**B**).

8) HOW SHOULD CHILDREN OR ADOLESCENTS WITH GD BE TREATED?

Children with GD can be treated with ATDs, ^{131}I, or thyroidectomy. Although ATDs are used as an initial treatment, most pediatric patients will require definitive treatment by means of ^{131}I or surgery (115) (**B**).

A. USE OF ATDS AS AN INITIAL TREATMENT IN CHILDREN WITH GD

As some children achieve remission of GD after using ATDs for one or two years, this therapeutic approach is still considered the first line of treatment in most cases (26) (**D**).

Euthyroidism is achieved virtually in all cases during treatment with ATDs (116) (**B**). However, the remission rates are modest whereas relapse rates are high. The remission rate following initial treatment with ATD for two years is approximately 30% (113,117) (**B**). The factors associated with remission are relatively low levels of thyroid hormones, faster response to treatment, and age (115) (**B**). The hyperthyroidism relapse rate is 60% in one year after treatment and 70% in two years, and the associated risk factors are non-Caucasian ethnicity, high TRAb and FT4 levels at diagnosis. On the other hand, the risk of relapse decreases with age and length of the first ATD course (118) (**B**).

The length of ATD therapy seems to be a key element in the treatment of GD, with longer periods of use being associated with long-lasting remission in children

(119) (**B**). A recent meta-analysis on the treatment of GD hyperthyroidism in children showed that the optimal length of ATD therapy is 12-18 months (120) (**B**). However, age and pubertal development appear to influence the length of treatment needed to achieve remission. Longer periods of treatment is usually required in prepubertal compared to pubertal children. In addition, there is a positive correlation between the TRAb concentration at diagnosis and length of ATD therapy to achieve remission (117) (**B**). Thus, MMI can be administered for one or two years, and then discontinued or reduced to assess whether the disease remission was achieved. If, under those conditions, remission is not achieved, treatment with ^{131}I or surgery must be considered according to the child's age. Alternatively, MMI can be used over longer periods. This approach can delay ^{131}I or surgery until an appropriate age. In selected cases where the use of ^{131}I or surgery is not appropriate or possible, treatment with low doses of MMI can be continued. A positive impact of longer ATD use on the remission rate of GD has recently been reported (121) (**A**).

The usual daily doses of MMI vary from 0.2-0.5 mg/kg of body weight, but the dose can vary from 0.1-1.0 mg/kg to a total maximum of 30 mg/day (116,122-127) (**B**). When MMI, thyroidectomy, and ^{131}I cannot be used, PTU can be considered an option for a short period of time in doses of 4.7-8.6 mg/kg of body weight (116) (**B**) under rigorous clinical and laboratory monitoring (see below).

The main dilemma presented by ATD therapy is their adverse reactions. Side effects occur in approximately 6%-35% of cases and are more frequent and/or severe with PTU. For that reason, MMI is the first choice ATD in the pediatric population (115,117-118,128,129) (**B**). Among the adverse effects attributed to PTU in children and adolescents, hepatotoxicity and vasculitis are the most worried (130) (**B**). The use of PTU is also associated with a higher prevalence of antineutrophil cytoplasmic antibodies, even with no evidence of vasculitis or nephritis (131) (**B**). Although MMI shows a better safety profile compared to PTU, side effects occur in up to 20% of treated children (128) (**B**). Therefore, pediatric patients should be subjected to a complete blood count and measurement of the serum bilirubin, transaminase, and alkaline phosphatase levels, before the onset of ATD administration (132,133) (**C,B**). Patients and their caregivers must be informed of the ATD side effects as well as the need to immediately contact their doctor should any of the following conditions occur: itchy rash, jaundice, acholic stool or choluria, nausea, joint pain, abdominal pain or distension, ill feeling, fatigue, fever, and pharyngitis (134) (**D**). MMI is the main drug associated with agranulocytosis, particularly when used in high doses, but this complication has been rarely reported in Latin America (0.38 cases/million inhabitants/year), with it, particularly (135,136) (**B**). There are no data available on the prevalence of agranulocytosis in children, but it is estimated to be very low (26) (**D**).

Mild and persistent skin reactions to MMI in children can be treated with antihistamines. In the case of PTU therapy, a 2- to 3-fold increase of transaminases above the upper normal limit that does not improve within one week indicates the need to discontinue treatment. Following drug withdrawal, the levels of bilirrubin, alkaline phosphatase and transaminase should be monitored weekly until the laboratory analysis shows improvement. If it does not occur, the patient should be referred to a pediatric gastroenterologist or hepatologist to further investigation (26) (**D**).

Treatment with beta-blockers improve the complaints of tachycardia, muscle weakness, tremor, and neuropsychological disorders in hyperthyroid children (134) (**D**). Cardioselective beta-blockers can be used in patients with history of reactive airway disease, but special attention should be given to its eventual exacerbation (137) (**A**).

Following the onset of ATD therapy, thyroid function tests should be assessed monthly over the first months of treatment and then every two to four months. As a function of the severity of hyperthyroidism, it may take several months before thyroid hormone levels reach the reference range (138) (**B**).

Recommendation 24

MMI is the first-choice drug for the treatment of GD hyperthyroidism in children and adolescents (**B**). PTU must be avoided given the higher incidence of severe associated side effects (**B**).

Recommendation 25

Beta-blockers can be indicated for hyperthyroid children and adolescents to control associated symptoms (**D**).

Recommendation 26

Mild or persistent skin reactions to ATD in children can be treated with antihistamines (**D**). If the patient presents a severe adverse effect during ATD treatment, it is not recommended to replace the one drug by another. Instead, it should be considered radioactive iodine administration or surgical treatment (**C**).

Recommendation 27

Children with GD should be monitored by means of clinical assessment and thyroid hormone measurement on a monthly basis at the beginning of treatment, and then every two to four months, depending on the disease control (**D**).

Recommendation 28

ATD treatment in children should be maintained for at least 12-18 months, and up to two years in order to achieve remission (**A**).

B. THE USE OF ^{131}I IN CHILDREN AND ADOLESCENTS WITH GD

Several studies have shown that treatment with ^{131}I is more effective in achieving euthyroidism as compared with ATDs (relative risk [RR], 1.70; 95% confidence interval, 1.29-2.24) in pediatric patients with GD (139-141) (**B**).

The doses of ^{131}I can be fixed or calculated based on the thyroid weight and the 24-hour ^{131}I uptake (142) (**B**). The fixed doses vary from 10-15 mCi and are most effective in smaller goiters (143-145) (**B**). When doses higher than 150 µCi ^{131}I/g thyroid tissue are administered, hypothyroidism occurs in approximately 95% of cases (142) (**B**). There are no studies comparing the dose regimens in children, but, in adults, the results were reported to be similar (146) (**D**) (see section 3).

The treatment recommended for children with GD and serum levels of total T4 > 20 ug/dL (260 nmol/L) or FT4 > 5 ng/dL (60 pmol/L) includes MMI and beta-blockers until normalization of thyroid hormone levels, prior to the use of ^{131}I (26) (**D**). In such cases, MMI must be discontinued three to five days before ^{131}I administration, and the beta-blockers should be continued until the total T4 and/or FT4 levels are normalized (26) (**D**). As the decrease in the thyroid hormone levels begins within the first week following ^{131}I administration, the use of ATD is no longer needed after this treatment (26) (**B**). The literature reports rare cases of children with severe hyperthyroidism who developed thyrotoxic crisis following MMI withdrawal and radioactive iodine administration (147)C (**C**).

There is no evidence supporting an association between treatment of hyperthyroidism with ^{131}I and cancer of the thyroid or any other site, particularly when doses > 160 µCi /g thyroid tissue are used (148,149) (**B,D**). However, based on risk projections and as a function of the exposure to low-level radiation relative to age, there is a theoretical small risk of malignant neoplasia in very young children treated with ^{131}I (150) (**B**). For that reason, it is recommended to avoid treatment with ^{131}I in very young children (< 5 years old) (149) (**D**). The use of ^{131}I is acceptable in children aged 5-10 years, when the calculated activity of ^{131}I to be administered is less than 10 mCi and in children older than 10 years old, when activity is higher than 160 µCi/g thyroid tissue (149) (**D**).

A higher incidence of hypothyroidism has been reported in children treated with ^{131}I as compared with those treated with ATD (RR, 6.46; 95% CI, 1.16-35.81). However, no significant difference has been observed in the appearance of or worsening of Graves' ophthalmopathy (RR, 1.30; 95% CI, 0.56-3.00) (141) (**B**).

Recommendation 29

Treatment with ^{131}I should be avoided in children younger than five years of age (**D**). However, in older children, radioactive iodine dosing is an effective and safe therapy and can be performed using fixed or calculated doses (**B**). Pretreatment with ATD should be considered in patients with very high levels of thyroid hormones (**D**).

C. INDICATION FOR THYROIDECTOMY IN CHILDREN OR ADOLESCENTS WITH GD

Surgery offers a definitive treatment of GD in children and adolescents and TT is the procedure most widely accepted, given the risk of relapse associated with PT (151,152) (**D,B**). This procedure is safe when performed by an experienced surgeon, requiring short hospital stays (65,151-153) (**B,D,B,B**).

The patient should be euthyroid before the surgery procedure. The use of Lugol's solution (5-10 drops three times per day) can reduce blood loss during surgery, but it is not routinely prescribed. In addition to blocking the release of thyroid hormones,

Lugol's solution reduces gland vascularization, thus decreasing the occurrence of perioperative intercurrent events. The greatest blood losses occur when a partial surgery is performed because it involves gland sectioning (65) (**B**).

Potential problems such as pain and postoperative discomfort, healing time, risks of anesthesia, and specific surgical risks (recurrent laryngeal nerve injury and transient or definitive hypoparathyroidism) are less common when surgery is performed by an experienced surgeon (151) (**D**). If the parathyroid glands are accidentally removed, they should be transplanted to a neck muscle after their identification (151-153) (**D,B,B**).

Thyroid hormone replacement therapy using levothyroxine should be initiated in the immediate postoperative period, and the dose adjusted over time according to the child's growth and development (152) (**B**).

Recommendation 30

Total thyroidectomy provides a definitive and low-risk treatment of GD hyperthyroidism in children, adolescents, and young adults (**B**).

9) HOW SHOULD HYPERTHYROIDISM IN PREGNANT WOMEN BE TREATED?

The differential diagnosis between GD and gestational hyperthyroidism is very important in pregnant women with thyrotoxicosis. Although, the clinical manifestations are similar a lack of previous history of thyroid disease and clinical signs of GD (goiter, ophthalmopathy) point to gestational hyperthyroidism. In ambiguous cases, measurement of TRAb is indicated, since 95% of patients with GD are TRAb positive (10) (**B**). During pregnancy, hyperthyroidism can result in complications such as hypertensive disease, miscarriage, premature birth, low birth weight, stillbirth, thyrotoxic crisis, and maternal heart failure (154-156) (**C,B,B**).

A. HOW SHOULD PREGNANT WOMEN WITH GD BE TREATED?

Women diagnosed with GD must be advised not to become pregnant before achieving euthyroidism and the use of contraception is strongly recommended (157) (**D**). Definitive (^{131}I or surgery) or ATD therapy should be addressed with those female patients who plan to become pregnant. Mild cases diagnosed during the first trimester, with appropriate weight gain and satisfactory obstetric conditions, can be subjected to careful monitoring without any further treatment. The main goal is to control hyperthyroidism and attain normal FT4 levels as soon as possible without inducing fetal hypothyroidism (158) (**D**).

MMI or PTU can be used, but PTU is preferentially recommended during the first trimester of pregnancy as a function of its lower transplacental transfer and the occurrence of aplasia cutis, cloacal atresia, tracheoesophageal fistula, and facial anomalies associated with the use of MMI (157,159,160) (**D,C,D**). Radioactive iodine administration is contraindicated during pregnancy (see below).

The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia. The initial dose of MMI varies from 5-15 mg/day in one single daily and PTU from 50-300 mg/day, three times per day. The serum levels of FT4 and TSH should be monitored two to four weeks following treatment onset and then every four to six weeks after euthyroidism is achieved. Then, the dose of ATD can be reduced gradually, and treatment can be eventually discontinued in one-third of patients (161) (**D**). The dose should be adjusted as a function of the FT4 concentration and should be as small as possible to maintain FT4 concentrations within or slightly above the specific range for each trimester. When reference values of hormone concentrations during pregnancy are not available, the ones for non-pregnant women should be used (157) (**D**). It is not recommended to use the T3 levels as reference for treatment because normalization of the maternal T3 concentration can result in fetal hypothyroidism (161) (**D**). Patients using MMI before pregnancy should be advised to replace it with PTU until the end of the first trimester and then to change back to MMI (157,162,163) (**D,D,B**). Other indications for PTU include intolerance to MMI and thyrotoxic crisis.

Beta-blockers are useful to control the adrenergic symptoms. Propranolol (20-40 mg two or three times per day) or atenolol (25-50 mg/day) can be used whenever necessary over short period of time since prolonged use has been associated with reduced uterine growth, fetal bradycardia, and hypoglycemia (164) (**B**).

Radioactive iodine therapy is contraindicated during pregnancy because ^{131}I crosses the placental barrier and can cause fetal goiter, hypothyroidism, and even asphyxia (165,166) (**D**). Iodinated compounds can be used over short periods in cases of thyrotoxic crisis (less than two weeks, 5-7 drops of potassium iodide, twice per day) (see section 7).

Thyroidectomy is an effective treatment in in hyperthyroid pregnant patients, it is only indicted for special cases such as severe adverse reactions to both ATD or patients with poor treatment compliance (167) (**C**). If necessary, it is recommended to be performed in the second trimester of pregnancy, ideally between weeks 22 to 24. Previous preparation of by means of beta-blockers and a short course of potassium iodide (50-100 mg/day) is advised (168) (**B**). TRAb measurements at the time of surgery allows for the assessment of the potential risk of fetal hyperthyroidism (9) (**B**).

Recommendation 31

Hyperthyroid women should be advised to not become pregnant before achieving euthyroidism (**D**).

Recommendation 32

During the first trimester of pregnancy, PTU is the recommended ATD (**C**), evenin those patients using MMI before the pregnancy (**B**). After the first trimester, MMI can be used (**D**).

Recommendation 33

Pregnant women using ATD should be monitored by measurement of FT4 and TSH every two to six weeks. FT4 concentration must be maintained at the upper levels of, or slightly above, the reference range. It is not recommended to use T3 levels as reference for treatment because normalization of the maternal T3 concentration can result in fetal hypothyroidism (**D**).

Recommendation 34

Radioactive iodine therapy is contraindicated during pregnancy (**D**).

Recommendation 35

Thyroidectomy is rarely indicated during pregnancy. If necessary, total thyroidectomy should (ideally) be performed in the second trimester between weeks 22 and 24 (**C**).

Recommendation 36

Fetal surveillance by ultrasound should be performed in patients with hyperthyroidism and/or high TRAb levels (three times above the upper normal limit). Monitoring must include fetal heart rate, fetal growth, amniotic fluid volume, and fetal goiter volume (**D**).

B. HOW SHOULD GESTATIONAL HYPERTHYROIDISM (RELATED TO HUMAN CHORIONIC GONADOTROPIN – HCG) BE TREATED?

During the first trimester of pregnancy, hyperthyroidism can be associated with hCG or its molecular variants. The clinical manifestations are variable.

Gestational transient thyrotoxicosis: gestational transient thyrotoxicosis occurs during the first trimester of pregnancy, between weeks 8 and 14, with a prevalence of 2.4% of pregnancies (169) (**B**). The thyroid gland is usually not enlarged and treatment is rarely required due to the transient nature of this condition.

Hyperemesis gravidarum: hyperemesis gravidarum represents a serious complication because it is associated with weight loss and severe dehydration (170) (**B**). Biochemical hyperthyroidism is found in most affected women. Treatment includes supportive measures to control vomiting, dehydration, and electrolytic alterations. Use of ATDs is not indicated (171) (**B**). If a differential diagnosis with GD cannot be established, a short ATD course can be instituted. Recurrence of hyperthyroidism following ATD discontinuation is a strong indication of GD and need of continuous treatment.

Recurrent gestational hyperthyroidism: some cases of recurrent hyperthyroidism during pregnancy have been described (172) (**B**). Interestingly, a mutation in the extracellular domain of the TSH receptor gene which increases its response to normal hCG levels has been reported in one patient (173) (**B**).

Recommendation 37

ATD therapy is not indicated in patients diagnosed with gestational transient thyrotoxicosis, hyperemesis gravidarum, or recurrent gestational hyperthyroidism (**B**).

Hyperthyroidism due to other causes can occur during pregnancy, including TA and TMNG. These conditions are characterized by uni- and multinodular goiter, respectively. Treatment should be performed with ATDs and definitive treatment (^{131}I or surgery) delayed until the postpartum period. After delivery, ATD treatment should continue and the patients should be given guidance as to breastfeeding. Patients who discontinued ATD during pregnancy should be advised to seek assistance if the symptoms of hyperthyroidism recur. Routine measurements of TSH and FT4 should be performed six weeks after delivery in patients whore-

main asymptomatic, and should be follow-up at regular intervals since relapse is common (174) (**B**).

Neonatal hyperthyroidism is a rare occurrence with an incidence < 1% among the newborns of hyperthyroid mothers. This syndrome is caused by the transfer of maternal thyroid-stimulating antibodies (175) (**D**). When the mother is adequately treated with ATDs, the fetus also benefits from treatment, and remains euthyroid throughout pregnancy. However, this protective effect is lost following birth, and clinical hyperthyroidism may appear, requiring ATD treatment. High TRAb titers in the third trimester of pregnancy are predictive of neonatal hyperthyroidism (176) (**D**). Therefore, TRAb measurement is recommended in weeks 26-28 of pregnancy and in women with a previous history of GD treated with ^{131}I or surgery. Pregnant patients with high TRAb levels must be subjected to fetal US to assess the presence of goiter or other signs of hyperthyroidism such as intrauterine growth restriction or heart failure (177,178) (**D**).

Some cases of central hypothyroidism have been reported in newborns of mothers with GD, whose hyperthyroidism was not well controlled during pregnancy. This phenomenon might be explained by the transfer of high amounts of maternal T4 to the fetus, resulting in suppression of the fetal pituitary gland. Diagnosis is established after birth, with low levels of FT4 associated to normal-to-low TSH levels or not appropriated to the FT4 levels. The newborn thyroid function becomes normal after a few weeks or months; however, treatment with thyroxine and long-term follow-up are recommended (179,180) (**B**).

Breastfeeding is permitted to during ATD therapy. Nevertheless, it is recommended to use the smallest dose possible. A maximum of 300 mg/day of PTU or 20-30 mg/day of MMI is recommended (181) (**D**). The children should be monitored by means of thyroid function testing.

Recommendation 38

TRAb measurement is recommended in pregnant patients with a past or ongoing history of GD in weeks 20-24 of pregnancy.

10) HOW SHOULD HYPERTHYROIDISM IN PATIENTS WITH GRAVES' OPHTHALMOPATHY (GO) BE TREATED?

GO occurs in about 50% of patients with GD whereas 20%-30% of the cases shows significant clinical findings that require a more aggressive and specific treatment (182) (**B**). The two major traits of GO are its activity and severity (183) (**B**). GO progresses from an active (inflammatory) phase to stabilization (plateau), and finally to an inactive phase (184) (**D**). A practical approach to the assessment of the degree of activity of GO is to apply the clinical activity score (CAS) (185) (**A**). The CAS score includes the following: swelling of the eyelid; redness of the eyelid; redness of the conjunctiva; chemosis; swollen caruncle; spontaneous eye pain; and eye pain with movement. GO is considered to be active when at least three of these items are present. The assessment of GO severity, in turn, is based on the changes exhibited by the soft tissues, eye proptosis, involvement of the extrinsic extraocular muscles and the optic nerve, or corneal affection (183) (**B**).

ATD treatment does not appear to impact the progression of eye disease. Nevertheless, it is believed that ATDs induce an indirect beneficial effect upon correcting the hyperthyroid state, especially when associated with a reduction of TRAb levels (186) (**D**). A potential disadvantage of this strategy is the risk of hyperthyroidism relapse (34) (**B**). During relapse, the autoimmune process can be reactivated, with a consequent increase in the levels of TRAb and other antibodies. Although the connection between the immune response against antigens shared by the thyroid and the orbit is not fully elucidated, reactivation and progression of GO is likely to occur (182) (**D**).

Recommendation 39

Patients with Graves' hyperthyroidism and GO can be treated with ATDs. However, that strategy is disadvantageously associated with high rates of relapse, which can exert a negative impact on the progression of GO (**B**).

Randomized studies have shown that radioactive iodine treatment for hyperthyroidism is associated with increased risk for appearance or progression of GO in 15%-30% of cases (187,188) (**A**). Exacerbation is most frequently observed among the individuals diagnosed with GO before treatment and can be prevented with the use of corticosteroids per oral route (182,187) (**A**). The usual protocol recommends prednisone (or equivalent oral steroid) at a dose of 0.5 mg/kg over two to three months (186) (**A**). However, smaller doses of 0.2 mg/kg used over shorter periods (six weeks) exhibited a similar efficacy (189) (**B**).

Appearance or exacerbation of GO following ^{131}I treatment occurs in a small fraction of patients and some risk factors have been identified: a) recent onset of hyperthyroidism (188) (**A**); b) pre-existing GO (especially if in the active stage) (182) (**B**); c) severe hyperthyroidism (very high levels of thyroid hormones) (190) (A); d) high serum TSH levels (186) (**D**); e) high serum TRAb levels (186) (**D**); and f) smoking (188) (**A**). Radioactive iodine administration to patients without signs of GO or with minimally active or inactive GO in the absence of risk factors is rarely associated with a poorer ocular status (186) (**D**). Nevertheless, a retrospective study suggests that GO following treatment with radioactive iodine can occur also in patients without risk factors (191) (**B**). In spite of these findings, it is believed that even if ^{131}I administration may be deleterious in the short term, it has a potential benefice in the long term (182) (B). The use of ^{131}I is associated with increases in TRAb levels. However, even though high TRAB levels may help on identifying patients using ATDs at higher risk of developing GO, the correlation between the increased TRAb levels following use of radioactive iodine and worsening of GO is not yet clear (187) (**A**).

Recommendation 40

Treatment of hyperthyroidism with ^{131}I is associated with worsening of GO, especially in the patients with previous GO (**B**), moderate-to-severe activity (**A**) and smoking history (**A**). In these patients as well as in patients with risk factors for the appearance or progression of GO (**D**), prophylaxis with corticosteroids should be considered (**D**).

Surgery does not appear to exert any significant effect on the progression of GO. Randomized controlled studies did not find significant difference in the progression of GO between TT and ST (61,183,192) (**C,B,B**). TT or ^{131}I alone are not associated with full ablation of the thyroid tissue, even when hypothyroidism ensues (193) (**D**). In a recent randomized study, patients subjected to total ablation of the thyroid tissue as treatment of hyperthyroidism and concomitant intravenous corticotherapy associated with orbital radiotherapy exhibited a better overall response to immunosuppression; however, the difference between the groups was not significant, and the parameters of eye opening and proptosis exhibited the best indices (194) (**B**). Therefore, the usefulness of this approach must be tested in studies with longer follow-up periods.

Recommendation 41

Surgical treatment of hyperthyroidism does not appear to have significant effects on patients with GO (**B**).

The modality of treatment of Graves' hyperthyroidism with GO can be select as a function of the degree of GO. GO is classified according to its severity and inflammatory activity as mild inactive, moderate-to--severe active, moderate-to-severe inactive, or severe sight-threatening GO.

MILD INACTIVE GO

Recommendation 42

The method chosen for the treatment of hyperthyroidism does not appear to influence eye disorders. If ^{131}I is selected, prophylaxis with corticosteroids per oral route is not usually indicated, unless the patient present risk factors for GO progression (**B**).

MODERATE-TO-SEVERE ACTIVE GO

Recommendation 43

The choice of the hyperthyroidism treatment modality is controversial. The use of ATDs alone usually restores euthyroidism which favors improvement of GO. However, in addition to the lack of evidence in the literature, the increased risk of relapse and maintenance of the gland activity associated with oscillations in the thyroid hormone levels can exert a negative effect on GO progression (42,184,187,194,195) (**D,D,D,D,B**). Based on this, a second line of treatment suggests that in this type of patient, the gland must be ablated following the establishment of euthyroidism using ATDs (194) (**D**).

MODERATE-TO-SEVERE INACTIVE GO

Recommendation 44

The choice of hyperthyroidism treatment modality is less critical. Prophylaxis with corticosteroids per oral route can be avoided in the absence of risk factors (186) (**D**).

SEVERE SIGHT-THREATENNG GO

Recommendation 45

Most patients in this category exhibit optic neuropathy or severe corneal affection. Hyperthyroidism must be

treated by means of ATDs (186) (**D**). Treatment with ^{131}I or surgery must be deferred until the eye condition improves (186) (**D**).

11) HOW SHOULD DRUG-INDUCED THYROTOXICOSIS BE TREATED?

Treatment of iodine-induced thyrotoxicosis is complex because an iodine-enriched thyroid makes treatment with ^{131}I unfeasible for several weeks and reduces the efficacy of ATD treatment. Clinical treatment with ATDs should be performed over a prolonged period, and the patients might have to wait six to nine months after iodine withdrawal before ^{131}I can be administered. Potassium perchlorate can be concomitantly used to induce release of inorganic iodine and prevent iodine uptake by the thyroid (196) (**D**).

Amiodarone-induced thyrotoxicosis (AIT) is classified as type I when there is excessive thyroid hormone synthesis and release and as type II, which is a form of destructive thyroiditis. Amiodarone must be discontinued whenever possible. However, due to its long half-life and the lack of response of AIT types I and II to drug withdrawal, pharmacological treatment is usually needed. Type I AIT requires high doses of ATDs because the high intrathyroid iodine content reduces the efficacy of these agents (197) (**D**). Potassium perchlorate (1 g/day) can be added to ATD treatment to block iodine uptake and thus reduce its intraglandular content; however, it must be used over limited periods of time to avoid nephrotoxicity and effects on the bone marrow (198) (**B**). In addition, lithium carbonate (900-1,350 mg/day) can be included in the therapeutic regimen over four to six weeks to reduce the thyroid hormone synthesis and release (199) (**B**). In type I AIT, thyrotoxicosis can relapse and never achieve remission, thus requiring definitive treatment by means of ^{131}I (when amiodarone is withdrawn) or surgery. In type II AIT, discontinuation of amiodarone does sometimes suffice, and euthyroidism is achieved in three to five months. Administration of glucocorticoids (prednisone 0.5 to 1 mg/kg/day or dexamethasone 3 to 6 mg/day over two or three months) can accelerate the clinical and biochemical recovery (200) (**D**). In mixed forms of AIT, or in cases where its type cannot be accurately distinguished, treatment must consist of a combination of ATD and glucocorticoids (197,198,200) (**D,B,D**). TT is indicated when immediate control is required such as in cases of thyrotoxic crisis, severe heart failure, or untreatable arrhythmias.

Treatment with interferon-alpha (IFN-alpha) can cause destructive thyroiditis or induce GD in 21% and 17% of patients, respectively. Treatment of hyperthyroidism does not require discontinuation of IFN-alpha. Beta-blockers can be used in the thyrotoxic phase of destructive thyroiditis, whereas ATDs must be used in the treatment of Graves' hyperthyroidism (201) (**C**). Thyroid function usually normalizes when treatment with IFN-alpha is discontinued. However, these patients present an increased risk of developing autoimmune thyroid dysfunction in the future.

Treatment with interleukin-2 (IL-2) can cause thyrotoxicosis in 5% of the cases (202) (**D**). Treatment of the thyroid dysfunction should be performed as described above for IFN-alpha.

Recommendation 46

In drug-induced thyrotoxicosis secondary to iodine overload (iodine and type I AIT), treatment must be performed using high ATD doses (**D**). In type II AIT, amiodarone withdrawal may suffice and glucocorticoids can also be used (**B**). In IFN-alpha (**C**) and IL-2--induced (**D**) thyrotoxicosis, it should be considered the drug discontinuation and beta-blockers can be used to alleviate the symptoms.

12) HOW SHOULD THYROTOXICOSIS ASSOCIATED WITH THYROIDITIS BE TREATED?

Destructive thyroiditis is characterized by thyroid inflammation, consequent deregulated release of thyroid hormones secondary to the destruction of the thyroid follicles, and proteolysis of the stored thyroglobulin (203) (**D**). Thyroiditis can manifest as neck pain (acute and subacute thyroiditis) or be "silent" (painless thyroiditis).

The clinical manifestations of thyrotoxicosis are usually mild, compared with other causes of hyperthyroidism, and self-limiting (lasting two to six weeks) (204) (**B**). Therefore, treatment with beta-blockers is recommended only for symptomatic patients (18) (**D**). The use of thionamides is not recommended because in this case, thyrotoxicosis does not derive from increased production of thyroid hormones. The use of radioactive iodine is also contraindicated because the iodine uptake is characteristically low in thyroiditis (26,203,205)

(**D**). There are reports on the use of iodinated contrast media in rare cases of more severe thyrotoxicosis to achieve faster control of the thyroid hormone levels (206) (**C**).

Recommendation 47

Beta-blockers are recommended for the treatment of thyrotoxicosis associated with thyroiditis (**D**). In the patients with more severe clinical manifestations, the use of iodinated contrast media should be considered (**C**).

13) THYROTOXICOSIS DUE TO OTHER CAUSES BE TREATED?

A. HOW SHOULD THYROTOXICOSIS DUE TO TSH-SECRETING TUMORS BE ASSESSED AND TREATED?

The TSH-secreting tumors represent less than 1% of the pituitary tumors and usually cause diffuse goiter and clinical thyrotoxicosis (207) (**B**). In contrast to GD, the levels of TSH are high or inappropriately normal relative to the serum thyroid hormone levels (207) (**B**). These tumors also secrete prolactin in up to 25% of cases, growth hormone in up to 25%, both in 1%, and gonadotropins in 1%. The tumor diameter is usually larger than 1 cm, which allows for easy identification on cranial magnetic resonance imaging (MRI) (208) (**D**).

The treatment of TSH-secreting tumors consists in surgical removal, preferentially after achieving euthyroidism using ATDs. Administration of octreotide reduces the serum levels of TSH in more than 50% of the cases, and most patients achieve euthyroidism with a reduction in tumor size in 20%-50% of cases (207) (**B**). Bromocriptine can also be used, although with poorer results (208) (**D**). The patients whose tumors were not fully ressected may benefit from the use of octreotide as an adjuvant, as well as patients with contraindications for surgery (207) (**B**).

The differential diagnosis between TSH-secreting tumors and thyroid hormone resistance is important because although their laboratory parameters are similar, their treatment strategies are quite different. The patients with pituitary tumors usually exhibit an elevated alpha subunit of TSH, blocked response of TSH to thyrotropin-releasing hormone (TRH), increased levels of sex hormone-binding globulin, evident clinical signs of thyrotoxicosis, and anatomical anomalies on cranial MRI.

Recommendations 48

The diagnosis of TSH-secreting tumors is established on the grounds of inappropriately high serum TSH levels associated to elevated T3 and T4 levels (**B**), presence of pituitary adenoma on MRI (**D**), and lack of family history or genetic tests compatible with thyroid hormone resistance. Pituitary surgery is indicated for tumor removal. The use of octreotide should be considered in patients with incomplete tumor removal or contraindications to surgery (**B**).

B. HOW SHOULD THYROTOXICOSIS DUE TO THYROID HORMONE RESISTANCE BE ASSESSED AND TREATED?

The patients with thyroid hormone resistance syndrome (THRS) present high serum T3 and T4 concentrations associated with high or inappropriately normal serum TSH levels, which is characteristic of reduced sensitivity of the pituitary thyrotrophs. Refetoff and cols. (1967) described, for the first time, the clinical syndrome in 2 deaf-mute individuals with goiter and delayed bone age. Their serum thyroid hormone levels were elevated, contrasting with the symptoms of hypothyroidism. Administration of exogenous thyroxine did not induce the expected metabolic effects or suppress the TRH-stimulated TSH (209) (**C**).

A THRS diagnosis is established on the grounds of high serum T3 and FT4 levels associated with non-suppressed TSH in the absence of thyroid hormone transporter defects or antibody interference in immunologic assays, the absence of TSH suppression with supraphysiological levels of thyroid hormone, and eventual presence of this syndrome in other relatives. As described above, the differential diagnosis of a TSH-secreting tumor can be achieved through the measurement of subunit alpha of TSH and/or demonstration of the etiopathogenic genetic anomalies of THRS, such as mutations of the thyroid hormone receptor (TR) beta (210) (**C**).

Treatment is not required in most cases where the resistance to the thyroid hormones appears to be appropriately compensated by an endogenous increase in thyroid hormones. The patients with greater resistance at the pituitary level and exhibiting symptoms of hyperthyroidism may benefit from symptomatic treatment using beta-blockers (209,211) (**C,D**). Treatment with liothyronine (LT3) can improve the symptoms of attention deficit and hyperactivity in children (212) (**B**).

Recommendation 49

Patients with thyroid hormone resistance syndrome may exhibit hyperthyroidism and be mistaken for cases of TSH-secreting pituitary tumors. The differential diagnosis between these conditions is important because patients with thyroid hormone resistance usually do not require treatment or benefit from the use of beta-blockers alone and, eventually, LT3 (**C**).

C. HOW SHOULD THYROTOXICOSIS DUE TO *STRUMA OVARII* BE ASSESSED AND TREATED?

Struma ovarii is a rare form of ovarian teratoma that is entirely or predominantly composed of thyroid tissue. It is usually benign, although it can be malignant in 5%-37% of the cases (213) (**C**). The ectopic thyroid tissue can include cancer cells and produce thyroid hormones with the consequent development of thyrotoxicosis in 5%-10% of patients. In addition, this tumor can, eventually, be associated GD (214,215) (**D,C**). Differential diagnosis with other causes of hyperthyroidism is based on the low radioactive iodine uptake and the presence of an ovarian tumor on imaging studies (213,215). Treatment consists in the surgical removal of the tumor after achieving euthyroidism through ATD treatment. Postoperative use of radioactive iodine allows for the elimination of residual thyroid and ovarian malignant cells.

Recommendation 50

The diagnosis of *Struma ovarii* must be considered in patients with thyrotoxicosis, low iodine uptake, and the presence of an ovarian tumor on imaging studies. If the diagnosis is confirmed, the treatment consists in the surgical removal of the tumor (**C**).

D. HOW SHOULD THYROTOXICOSIS DUE TO GONADOTROPIN HYPERSECRETION BE ASSESSED AND TREATED?

The production of very high levels of hCG can stimulate the TSH receptor and thus cause hyperthyroidism in patients with choriocarcinoma, molar pregnancy (hydatidiform mole), or testicular cancer (216-218) (**C,C,B**). The differential diagnosis with other causes of thyrotoxicosis is based on low thyroid ^{131}I uptake, high serum gonadotropin levels, and presence of the corresponding producing tumor. Treatment consists in the removal of tumors after achieving euthyroidism by means of ATDs.

Recommendation 51

Patients with thyrotoxicosis, low thyroid ^{131}I uptake, high gonadotropin levels, and choriocarcinoma, molar, or testicular tumors must be treated by means of surgical resection of the tumor after achieving euthyroidism with ATDs (**B**).

E. HOW SHOULD FACTITIOUS THYROTOXICOSIS BE ASSESSED AND TREATED7?

Factitious thyrotoxicosis is a serious problem in Brazil, mainly due to the abuse of thyroid hormones for weight-loss purposes (219) (**B**). Diagnosis can be difficult in the cases of inappropriate use without a medical prescription because the patients may omit this information. Diagnosis can also be a challenge in the cases of accidental use due to food contamination or pharmaceutical error (220) (**C**). The differential diagnosis is based on the absence of goiter, suppressed thyroglobulin levels, and low ^{131}I uptake. Patients who ingest T3 or a combination of T4 and T3 exhibit disproportionally high T3 levels. Treatment consists in discontinuation of the ingestion/administration of thyroid hormones and use of beta-blockers to control the symptoms (**B**).

Recommendation 52

A diagnosis of factitious thyrotoxicosis must be considered in patients exhibiting symptoms of thyroid hormone excess without goiter or other manifestations suggestive of thyroid disease. Undetectable levels of serum thyroglobulin and low ^{131}I uptake confirm the diagnosis. Treatment consists in discontinuance of the inappropriate intake of thyroid hormones and the use of beta-blockers to control the symptoms (**B**).

F. HOW SHOULD THYROTOXICOSIS DUE TO FUNCTIONING METASTASES OF DIFFERENTIATED THYROID CANCER BE ASSESSED AND TREATED?

Rare cases of hyperthyroidism secondary to functioning metastases of follicular tumors, usually associated with very large or extensive lesions causing thyrotoxicosis, have been described (221) (**C**). Those tumors are easy to identify and must be treated by means of surgical resection and/or ^{131}I combined with ATD to achieve euthyroidism.

Recommendation 53

The patients with extensive follicular thyroid carcinoma lesions or metastases may exhibit hyperthyroidism. Treatment can be surgical or by means of ^{131}I administration (**C**).

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REFERENCES

1. Andrade VA, Gross JL, Maia AL. Effect of methimazole pretreatment on serum thyroid hormone levels after radioactive treatment in Graves' hyperthyroidism. J Clin Endocrinol Metab. 1999;84(11):4012-6.
2. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab. 2010;95(6):2715-26.
3. Nordyke RA, Gilbert FI Jr, Harada AS. Graves' disease. Influence of age on clinical findings. Arch Intern Med. 1988;148(3):626-31.
4. Woeber KA. Thyrotoxicosis and the heart. N Engl J Med. 1992;327(2):94-8.
5. de los Santos ET, Starich GH, Mazzaferri EL. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. Arch Intern Med. 1989;149(3):526-32.
6. Rajatanavi R, Braverman LE. Euthyroid hyperthyroxinemia. J Endocrinol Invest. 1983;6(6):493-505.
7. Rajatanavin R, Liberman C, Lawrence GD, D'Arcangues CM, Young RA, Emerson CH. Euthyroid hyperthyroxinemia and thyroxine-binding prealbumin excess in islet cell carcinoma. J Clin Endocrinol Metab. 1985;61(1):17-21.
8. Mariotti S, Martino E, Cupini C, Lari R, Giani C, Baschieri L, et al. Low serum thyroglobulin as a clue to the diagnosis of hyperthyroidism factitia. N Engl J Med. 1982;307(7):410-2.
9. Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, Noel M, et al. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. J Clin Endocrinol Metab. 2005;90(11):6093-8.
10. Vos XG, Smit N, Endert E, Tijssen JG, Wiersinga WM. Frequency and characteristics of TBII-seronegative patients in a population with untreated Graves' hyperthyroidism: a prospective study. Clin Endocrinol (Oxf). 2008;69(2):311-7.
11. Al-Shariff A, Abujbara AA, Chiacchio S, Ajlouni KM, Mariani G. Contribution of radioiodine uptake measurement and thyroid scintigraphy to the differential diagnosis of thyrotoxicosis. Hell J Nucl Med. 2010;13(2):132-7.
12. Bogazzi F, Martino E, Dell'Unto E, Brogioni S, Cosci C, Aghini-Lombardi F, et al. Thyroid color flow Doppler sonography and radioiodine uptake in 55 consecutive patients with amiodarone-induced thyrotoxicosis. J Endocrinol Investigation. 2003;26(7):635-40.
13. Maia AL, Ward LS, Carvalho GA, Graf H, Maciel RM, Maciel LM, et al. Thyroid nodules and differentiated thyroid cancer: Brazilian consensus. Arq Bras Endocrinol Metab. 2007;51(5):867-93.
14. 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(1):41-5.
15. 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.
16. Bogazzi F, Bartalena L, Brogioni S, Mazzeo S, Vitti P, Burelli A, et al. Color flow Doppler sonography rapidly differentiates type I and type II amiodarone-induced thyrotoxicosis. Thyroid. 1997;7(4):541-5.
17. Trzepacz PT, Klein I, Roberts M, Greenhouse J, Levey GS. Graves' disease: an analysis of thyroid hormone levels and hyperthyroid signs and symptoms. Am J Med. 1989;87(5):558-61.
18. Geffner DL, Hershman JM. Beta-adrenergic blockade for the treatment of hyperthyroidism. Am J Med. 1992;93(1):61-8.
19. McDevitt DG, Nelson JK. Comparative trial of atenolol and propranolol in hyperthyroidism. Br J Clin Pharmacol. 1978;6(3):233-7.
20. Duggal J, Singh S, Kuchinic P, Butler P, Arora R. Utility of esmolol in thyroid crisis. Can J Clin Pharmacol. 2006;13(3):292-5.
21. Henderson JM, Portmann L, Van Melle G, Haller E, Ghika JA. Propranolol as an adjunct therapy for hyperthyroid tremor. Eur Neurol. 1997;37(3):182-5.
22. Milner MR, Gelman KM, Phillips RA, Fuster V, Davies TF, Goldman ME. Double-blind crossover trial of diltiazem versus propranolol in the management of thyrotoxic symptoms. Pharmacotherapy. 1990;10(2):100-6.
23. Kelestimur F, Aksu A. The effect of diltiazem on the manifestations of hyperthyroidism and thyroid function tests. Exp Clin Endocrinol Diabetes. 1996;104(1):38-42.
24. Cooper DS. Antithyroid drugs. N Engl J Med. 2005;352(9):905-17.
25. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 2004;10(8):1018-23.
26. Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011;17(3):456-520.
27. Shivakumar SK, Dwarakanath S, Swaroop G, Venkataramana NK. Aplasia cutis congenita of the scalp: therapeutic modalities. Neurol India. 2006;54(3):312-13.
28. Reinwein D, Benker G, Lazarus JH, Alexander WD. A prospective randomized trial of antithyroid drug dose in Graves' disease therapy. J Clin Endocrinol Metab. 1993;76(6):1516-21.
29. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clin Endocrinol (Oxf). 2004;61(5):589-94.
30. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: what have we learned? J Clin Endocrinol Metab. 1997;82(6):1727-33.
31. Fibbe WE, Claas FHJ, Van der Star-Dijkstra W, Schaafsma MR, Meyboom RH, Falkenburg JH. Agranulocytosis induced by propylthiouracil: evidence of a drug dependent antibody reacting with granulocytes, monocytes and haematopoietic progenitor cells. Br J Haematol. 1986;64(2):363-73.
32. Cooper DS. The side effects of antithyroid drugs. The Endocrinologist. 1999;9:457-67.
33. Schleusener H, Schwander J, Fischer C, Holle R, Holl G, Badenhoop K, et al. Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. Acta Endocrinol. 1989;120(6):689-701.
34. Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid. 1997;7(3):369-75.

35. Tamai H, Nakagawa T, Fukino O, Ohsako N, Shinzato R, Suematsu H, et al. Thionamida therapy in Graves' disease: relation of relapse rate to duration of therapy. Ann Intern Med. 1980;92(4):488-90.
36. Allannic H, Fauchet R, Orgiazzi J, Madec AM, Genetet B, Lorcy Y, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab. 1990;70(3):675-9.
37. Benker G, Rjenwein D, Kahaly G, Teglu L, Alexander WD, Fassbinder J, et al. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. Clin Endocrinol (Oxf). 1998;49(4):451-7.
38. Wood LC, Ingbar SH. Hypothyroidism as a late sequela in patient with Graves' disease treated with antithyroid agents. J Clin Invest. 1979;64(5):1429-36.
39. Hedley AJ, Young RE, Jones SJ, Alexander WD, Bewsher PD. Antithyroid drugs in the treatment of hyperthyridism of Graves' disease: long-term follow-up of 434 patients. Clin Endocrinol (Oxf). 1989;31(2):209-18.
40. Berglund J, Christensen SB, Dymling JF, Hallengren B. The incidence of recurrence and hypothyroidism following treatment with antithyroid drugs, surgery or radioiodine in all patients with thyrotoxicosis in Malmo during the period 1970-1974. J Intern Med. 1991;229(5):435-42.
41. Cruz Júnior AF, Takahashi MH, Albino CC. Tratamento clínico com drogas antitireoidianas ou dose terapêutica de Iodo-131 no controle do hipertireoidismo na doença de Graves: avaliação dos custos e benefícios. Arq Bras Endocrinol Metab. 2006;50(6):1096-101.
42. Hegedus L. Treatment of Graves' hyperthyroidism: evidence-based and emerging modalities. Endocrinol Metab Clin North Am. 2009;38(2):355-71.
43. Ross DS. Radioiodine therapy for hyperthyroidism. N Engl J Med. 2011;364(6):542-50.
44. Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after (131)I ablation for Graves' disease. J Clin Endocrino Metab. 2001;86(7):3016-21.
45. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab. 2001;86(8):3488-93.
46. Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves' disease. Thyroid. 2004;14(7):525-30.
47. Imseis RE, Vanmiddlesworth L, Massie JD, Bush AJ, Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab. 1998;83(2):685-7.
48. Bonnema SJ, Bennedbaek FN, Gram J, Veje A, Marving J, Hegedus L. Resumption of methimazole after 131I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomized clinical trial. Eur J Endocrinol. 2003;149(6):485-92.
49. Abraham P, Acharya S. Current and emerging treatment options for Graves' hyperthyroidism. Ther Clin Risk Manag. 2010;2(6):29-40.
50. Jarløv AE, Hegedüs L, Kristensen LO, Nygaard B, Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? Clin Endocrinol (Oxf). 1995;43(3):325-9.
51. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrino Metab. 2003;88(3):978-83.
52. Allahabadia A, Dykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism – prognostic factors for outcome. J Clin Endocrinol Metab. 2001;86(8):3611-17.
53. van Isselt JW, de Klerk JM, Lips CJ. Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science? Eur J Nucl Med Mol Imag. 2007;34(11):1883-4.
54. de Rooij A, Vandenbroucke JP, Smit JW, Stokkel MP, Dekkers OM. Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. Eur J Endocrinol. 2009;161(5):771-7.
55. Boelaert K, Syed AA, Manji N, Sheppard MC, Holder RL, Gough SC, et al. Prediction of cure and risk of hypothyroidism in patients receiving 131I for hyperthyroidism. Clin Endocrinol (Oxf). 2009;70(1):129-38.
56. Abraham P, Acharya A. Current and emerging treatment options for Graves' hyperthyroidism. Ther Clin Risk Manag. 2010;6:29-40.
57. Flower MA, al-Saadi A, Harmer CL, McCready VR, Ott RJ. Dose-response study on thyrotoxic patients undergoing positron emission tomography and radioiodine therapy. Eur J Nucl Med. 1994;21(6):531-6.
58. Cooper DS. Hyperthyroidism. Lancet. 2003;362(9382):459-68.
59. Bogazzi F, Giovannetti C, Fessehatsion R, Tanda ML, Campomori A, Compri E, et al. Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: a cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. J Clin Endocrinol Metab. 2010;95(1):201-8.
60. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer. 2007;109(10):1972-9.
61. Verburg FA, Luster M, Lassmann M, Reiners C. (131)I therapy in patients with benign thyroid disease does not conclusively lead to a higher risk of subsequent malignancies. Nuklearmedizin. 2011;50(3):93-9.
62. Ceccarelli C, Canale D, Battisti P, Caglieresi C, Moschini C, Fiore E, et al. Testicular function after 131I therapy for hyperthyroidism. Clin Endocrinol. 2006;65(4):446-52.
63. Stalberg P, Svensson A, Hessman O, Akerstrom G, Hellman P. Surgical treatment of Graves' disease: evidence-based approach. World J Surg. 2008;32(7):1269-77.
64. Yip J, Lang BH, Lo CY. Changing trend in surgical indication and management for Graves' disease. Am J Surg. 2012;203(2):162-7.
65. Liu J, Bargren A, Schaefer S, Chen H, Sippel RS. Total thyroidectomy: a safe and effective treatment for Graves' disease. J Surg Res. 2011;168(1):1-4.
66. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocr Metab Clin North Am. 2006;35(4):663-86.
67. Ansaldo GL, Pretolesi F, Varaldo E, Meola C, Minuto M, Borgonovo G, et al. Doppler evaluation of intrathyroid arterial resistances during preoperative treatment with Lugol's iodide solution in patients with diffuse toxic goiter. J Am Coll Surg. 2000;191(6):607-12.
68. Erbil Y, Ozluk Y, Giris M, Salmaslioglu A, Issever H, Barbaros U, et al. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. J Clin Endocrinol Metab. 2007;92(6):2182-9.
69. Bellantone R, Lombardi CP, Raffaelli M, Boscherini M, Alesina PF, De Crea C, et al. Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? Surgery. 2002;132(6):1109-12.
70. Portefield JR Jr, Thompson GB, Farley DR, Grant CS, Richards MI. Evidence-based management of toxic multinodular goiter (Plummer' Disease). World J Surg. 2008;32(7):1278-84.

71. Winsa B, Rastad J, Akerstrom G, Johansson H, Westermark K, Karlsson FA. Retrospective evaluation of subtotal and total thyroidectomy in Graves' disease with and without endocrine ophthalmopathy. Eur J Endocrinol. 1995;132(4):406-12.
72. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery. 1996;120(6):1020-4.
73. Palit TK, Miller CC, 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res. 2000;90(2):161-5.
74. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg. 1998;228(3):320-30.
75. Stocker DJ, Burch HB. Thyroid cancer yield in patients with Graves' disease. Minerva Endocrinol. 2003;28(3):205-12.
76. Kikuchi S, Noguchi S, Yamashita H, Uchino S, Kawamoto H. Prognosis of small thyroid cancer in patients with Graves' disease. Br J Surg. 2006;93(4):434-9.
77. Camargo R, Corigliano S, Friguglietti C, Gauna A, Harach R, Munizaga F, et al. Latin American thyroid society. Latin American thyroid society recommendations for the management of thyroid nodules. Arq Bras Endocrinol Metab. 2009;53(9):1167-75.
78. Krohn K, Führer D, Bayer Y, Eszlinger M, Brauer V, Neumann S, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. Endocr Rev. 2005;26(4):504-24.
79. Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet. 2012;379(9821):1155-66.
80. Becker DV, Hurley JR. Complications of radioiodine treatment of hyperthyroidism. Semin Nucl Med. 1971;1(4):442-60.
81. Koornstra JJ, Kerstens MN, Hoving J, Visscher KJ, Schade JH, Gort HB, et al. Clinical and biochemical changes following 131I therapy for hyperthyroidism in patients not pretreated with antithyroid drugs. Neth J Med. 1999;55(5):215-21.
82. Papini E, Guglielmi R, Bianchini A, Creszenci A, Taccogna S, Nardi F, et al. Risk of malignancies in non-palpable thyroid nodules: predictive value of ultrasound and colo-Doppler features. J Clin Endocrinol Metab. 2002;87(5):1941-6.
83. Graf H, Pacini F, Pinchera A, Leung A, Vaisman M, Reiners C, et al. Modified-release recombinant human TSH (MRrhTSH) augments the effect of 131I therapy in benign multinodular goiter: results from a multicenter international, randomized, placebo-controlled study. J Clin Endocrinol Metab. 2011;96(5):1368-76.
84. Hegedus L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev. 2003;24(1):102-32.
85. Zakavi SR, Mousavi Z, Davachi B. Comparison of four different protocols of I-131 therapy for treating single toxic thyroid nodule. Nucl Med Commun. 2009;30(2):169-75.
86. Erickson D, Gharib H, Li H, van Heerden JA. Treatment of patients with toxic multinodular goiter. Thyroid. 1998;8(4):277-82.
87. Wahl RA, Rimpl I, Saalabian S, Schabram J. Differentiated operative therapy of thyroid autonomy (Plummer's disease). Exp Clin Endocrinol Diabetes. 1998;106 suppl 4:S78-84.
88. Kang AS, Grant CS, Thompson GB, van Heerden JA. Current treatment of nodular goiter with hyperthyroidism (Plummer's Disease): surgery versus radioiodine. Surgery. 2002;132(6):916-23.
89. Vidal-Trecan GM, Stahl JE, Eckman MH. Radioiodine or surgery for toxic thyroid adenoma: dissecting an important decision. A cost-effectiveness analysis. Thyroid. 2004;14(11):933-45.
90. Vaiman M, Nagibin A, Hagag P, Kessler A, Gavriel H. Hypothyroidism following partial thyroidectomy. Otolaryngol Head Neck Surg. 2008;138(1):98-100.
91. Lippi F, Ferrari C, Manetti L, Rago T, Santini F, Monzani F, et al. Treatment of solitary authonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. J Clin Endocrinol Metab. 1996;81(9):3261-4.
92. Braga-Basaria M, Trippia MA, Stolf AR, Mesa C Jr, Graf H. Treatment of autonomous and cystic thyroid nodules with intranodular ethanol injection. Rev Assoc Med Bras. 2002;48(4):335-40.
93. Yano Y, Sugino K, Akaishi J, Uruno T, Okuwa K, Shibuya H, et al. Treatment of autonomously functioning thyroid nodules at a single institution: radioiodine therapy, surgery, and ethanol injection therapy. Ann Nucl Med. 2011;25(10):749-54.
94. Monzani F, Caraccio N, Goletti O, Lippolis PV, Casolaro A, Del Guerra P, et al. Five-year follow-up of percutaneous ethanol injection for the treatment of hyperfunctioning thyroid nodules: a study of 117 patients. Clin Endocrinol (Oxf). 1997;46(1):9-15.
95. Janowitz P, Ackmann S. Long-term results of ultrasound-guided ethanol injections in patients with autonomous thyroid nodules and hyperthyroidism. Med Klin (Munich). 2001;96(8):451-6.
96. Valcavi R, Frasoldati A. Ultrasound-guided percutaneous etanol injection therapy in thyroid cystic nodules. Endocr Pract. 2004;10(3):269-75.
97. Tarantino L, Francica G, Sordelli I, Sperlongano P, Parmeggiani D, Ripa C, et al. Percutaneous ethanol injection of hyperfunctioning thyroid nodules: long-term follow-up in 125 patients. AJR Am J Roentgenol. 2008;190(3):800-8.
98. Dossing H, Bennebaek FN, Karstrup S, Hegedüs L. Benign solitary solid cold thyroid nodules: US-guided interstitial laser photocoagulation-initial experience. Radiology. 2002;225(1):53-7.
99. Papini E, Guglielmi R, Bizarri G, Pacella CM. Ultrasound-guided laser termal ablation for treatment of benign thyroid nodules. Endocrine Practice. 2004;10(3):276-83.
100. Baek JB, Lee JH, Valcavi R, Pacella CM, Rhim H, Gyu D. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol. 2011;12(5):525-40.
101. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993;22(2):263-77.
102. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012;22(7):661-79.
103. Laurberg P, Vestergaard H, Nielsen S, Christensen SE, Seefeldt T, Helleberg K, et al. Sources of circulating 3,5,3'-triiodothyronine in hyperthyroidism estimated after blocking of type 1 and type 2 iodothyronine deiodinases. J Clin Endocrino Metab. 2007;92(6):2149-56.
104. Giles HG, Roberts EA, Orrego H, Sellers EM. Disposition of intravenous propylthiouracil. J Clin Pharmacol. 1981;21(11-12 Pt1):466-71.
105. Nabil N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. J Clin Endocrino Metab. 1982;54(1):180-1.
106. Walter RM Jr, Bartle WR. Rectal administration of propylthiouracil in the treatment of Graves' disease. Am J Med. 1990;88(1):69-70.
107. Yeung SC, Go R, Balasubramanyam A. Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm. Thyroid. 1995;5(5):403-5.
108. Jongjaroenprasert W, Akarawut W, Chantasart D, Chailurkit L, Rajatanavin R. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. Thyroid. 2002;12(7):627-31.
109. Hodak SP, Huang C, Clarke D, Burman KD, Jonklaas J, Janicic-Kharic N. Intravenous methimazole in the treatment of refractory hyperthyroidism. Thyroid. 2006;16(7):691-5.

110. Baeza A, Aguayo J, Barria M, Pineda G. Rapid preoperative preparation in hyperthyroidism. Clin Endocrinol (Oxf). 1991;35(5):439-45.

111. Robuschi G, Manfredi A, Salvi M, Gardini E, Montermini M, d'Amato L, et al. Effect of sodium ipodate and iodide on free T4 and free T3 concentrations in patients with Graves' disease. J Endocrinol Invest. 1986;9(4):287-91.

112. Tsatsoulis A, Johnson EO, Kalogera CH, Seferiadis K, Tsolas O. The effect of thyrotoxicosis on adrenocortical reserve. Eur J Endocrinol. 2000;142(3):231-5.

113. Solomon BL, Wartofsky L, Burman KD. Adjunctive cholestyramine therapy for thyrotoxicosis. Clin Endocrinol (Oxf). 1993;38(1):39-43.

114. Vyas AA, Vyas P, Fillipon NL, Vijayakrishnan R, Trivedi N. Successful treatment of thyroid storm with plasmapheresis in a patient with methimazole-induced agranulocytosis. Endocr Pract. 2010;16(4):673-6.

115. Glaser NS, Styne DM. Organization of Pediatric Endocrinologists of Northern California Collaborative Graves' Disease Study Group. Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. Pediatrics. 2008;121:e481-8.

116. Dötsch J, Siebler T, Hauffa BP, Doeker B, Andler W, Bettendorf M, et al. Diagnosis and management of juvenile hyperthyroidism in Germany: a retrospective multicenter study. J Pediatr Endocrinol Metab. 2000;13(7):879-85.

117. Poyrazoğlu S, Saka N, Bas F, Isguven P, Dogu A, Turan S, et al. Evaluation of diagnosis and treatment results in children with Graves' disease with emphasis on the pubertal status of patients. J Pediatr Endocrinol Metab. 2008;21(8):745-51.

118. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J. French Childhood Graves' Disease Study Group. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab. 2008;93(10):3817-26.

119. Barrio R, López-Capapé M, Martinez-Badás I, Carrillo A, Moreno JC, Alonso M. Graves' disease in children and adolescents: response to long-term treatment. Acta Paediatr. 2005;94(11):1583-9.

120. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2010;20:CD003420.

121. Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab. 2012;97(1):110-9.

122. Perrild H, Grüters-Kieslich A, Feldt-Rasmussen U, Grant D, Martino E, Kayser L, et al. Diagnosis and treatment of thyrotoxicosis in childhood. A European questionnaire study. Eur J Endocrinol. 1994;131(5):467-73.

123. Mussa GC, Corrias A, Silvestro L, Battan E, Mostert M, Mussa F, et al. Factors at onset predictive of lasting remission in pediatric patients with Graves' disease followed for at least three years. J Pediatr Endocrinol Metab. 1999;12(4):537-41.

124. Slyper AH, Wyatt D, Boudreau C. Effective methimazole dose for childhood Graves' disease and use of free triiodothyronine combined with concurrent thyroid-stimulating hormone level to identify mild hyperthyroidismand delayed pituitary recovery. J Pediatr Endocrinol Metab. 2005;18(6):597-602.

125. Cassio A, Corrias A, Gualandi S, Tato' L, Cesaretti G, Volta C, et al. Influence of gender and pubertal stage at diagnosis on growth outcome in childhood thyrotoxicosis: results of a collaborative study. Clin Endocrinol (Oxf). 2006;64(1):53-7.

126. Sato H, Harada S, Yokoya S, Tanaka T, Asayama K, Mori M, et al. Treatment for childhood-onset Graves' disease in Japan: results of a nationwide questionnaire survey of pediatric endocrinologists and thyroidologists. Thyroid. 2007;17(1):67-72.

127. Smith J, Brown RS. Persistence of thyrotropin (TSH) receptor antibodies in children and adolescents with Graves' disease treated using antithyroid medication. Thyroid. 2007;17(11):1103-7.

128. Rivkees SA, Stephenson K, Dinauer C. Adverse events associated with methimazole therapy of graves' disease in children. Int J Pediatr Endocrinol. 2010;2010:176970.

129. Lazar L, Kalter-Leibovici O, Pertzelan A, Weintrob N, Josefsberg Z, Phillip M. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. J Clin Endocrinol Metab. 2000;85(10):3678-82.

130. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab. 2010;95(7):3260-7.

131. Sato H, Hattori M, Fujieda M, Sugihara S, Inomata H, Hoshi M, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves' disease treated with propylthiouracil. J Clin Endocrinol Metab. 2000;85(11):4270-3.

132. Jafarzadeh A, Poorgholami M, Izadi N, Nemati M, Rezayati M. Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism. Clin Invest Med. 2010;33(5):271-9.

133. Sarinnapakorn V, Noppavetchwich P, Sunthorntepwarakul T, Deerochanawong C, Ngongamrut S. Abnormal liver function test in Graves' disease: a prospective study of comparison between the hyperthyroid state and the euthyroid state. J Med Assoc Thai. 2011;94(Suppl 2):S11-6.

134. Sandrini R, França SN, Lacerda L, Graf H. Treatment of hyperthyroidism in infancy and adolescence. Arq Bras Endocrinol Metab. 2001;45(1):32-6.

135. Hamerschlak N, Maluf E, Biasi Cavalcanti A, Avezum Júnior A, Eluf-Neto J, Passeto Falcão R, et al. Incidence and risk factors for agranulocytosis in Latin American countries--the Latin Study: a multicenter study. Eur J Clin Pharmacol. 2008;64(9):921-9.

136. Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, et al. Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. Thyroid. 2009;19(6):559-63.

137. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. Ann Intern Med. 2002;137(9):715-25.

138. Sato H, Minagawa M, Sasaki N, Sugihara S, Kazukawa I, Minamitani K, et al. Comparison of methimazole and propylthiouracil in the management of children and adolescents with Graves' disease: efficacy and adverse reactions during initial treatment and long-term outcome. J Pediatr Endocrinol Metab. 2011;24(5-6):257-63.

139. Chen DY, Chen TH. Comparison of efficacy of 131I and antithyroid drugs in the treatment of Graves' disease in children. Chin J Pediatr. 2005;43(7):507-9.

140. Hu B, Wei YF, Huang C, Chen LX. The treatment strategy for pediatric Graves' disease and the relevant problems of radioiodine treatment. J Med Forum. 2006;27:67-8.

141. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves' disease. Cochrane Database Syst Rev. 2008;16(CD006294).

142. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. Pediatrics. 2003;111(4 Pt1):745-9.

143. Zantut-Wittmann DE, Ramos CD, Santos AO, Lima MM, Panzan AD, Facuri FV, et al. High pre-therapy [99mTc]pertechnetate thyroid uptake, thyroid size and thyrostatic drugs: predictive factors

of failure in [131I]iodide therapy in Graves' disease. Nucl Med Commun. 2005;26(11):957-63.

144. Nebesio TD, Siddiqui AR, Pescovitz OH, Eugster EA. Time course to hypothyroidism after fixed-dose radioablation therapy of Graves' disease in children. J Pediatr. 2002;141(1):99-103.
145. Monte O, Calliari LEP, Longui CA. Utilização do 131I no tratamento da doença de Basedow-Graves na infância e adolescência. Arq Bras Endocrinol Metab. 2004;48(1):166-70.
146. Kalinyak JE, McDougall IR. How should the dose of iodine-131 be determined in the treatment of Graves' hyperthyroidism? J Clin Endocrinol Metab. 2003;88(3):975-7.
147. Kadmon PM, Noto RB, Boney CM, Goodwin G, Gruppuso PA. Thyroid storm in a child following radioactive iodine (RAI) therapy: a consequence of RAI versus withdrawal of antithyroid medication. J Clin Endocrinol Metab. 2001;86(5):1865-7.
148. Freitas JE, Swanson DP, Gross MD, Sisson JC. Iodine-131: optimal therapy for hyperthyroidism in children and adolescents? J Nucl Med. 1979;20(8):847-50.
149. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. J Clin Endocrinol Metab. 2007;92(3):797-800.
150. Imaizumi M, Usa T, Tominaga T, Neriishi K, Akahoshi M, Nakashima E, et al. Radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors 55-58 years after radiation exposure. JAMA. 2006;295(9):1011-22.
151. Cheetham TD, Hughes IA, Barnes ND, Wraight EP. Treatment of hyperthyroidism in young people. Arch Dis Child. 1998;78(3):207-9.
152. Feliciano DV, Lyons JD. Thyroidectomy is optimal treatment for Graves' disease. J Am Coll Surg. 2011;212(4):714-20.
153. Sugino K, Ito K, Nagahama M, Kitagawa W, Shibuya H, Ito K. Surgical management of Graves' disease-10-year prospective trial at a single institution. Endocr J. 2008;55(1):161-7.
154. Kriplani A, Buckshee K, Bhargava VL, Takkar D, Ammini AC. Maternal and perinatal outcome in thyrotoxicosis complicating pregnancy. Eur J Obstet Gynecol Reprod Biol. 1994;54(3):159-63.
155. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol. 1989;160(1):63-70.
156. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstet Gynecol. 1994;84(6):946-9.
157. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Thyroid. 2011;21(10):1081-125.
158. Mandel SJ, Cooper DS. The use of antithyroid drugs in pregnancy and lactation. J Clin Endocrinol Metab. 2001;86(6):2354-9.
159. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. Methimazole embryopathy: delineation of the phenotype. Am J Med Genet. 1999;83(1):43-6.
160. Clementi M, Di Gianantonio E, Cassina M, Leoncini E, Botto LD, Mastroiacovo P. SAFE-Med Study Group Treatment of hyperthyroidism in pregnancy and birth defects. J Clin Endocrinol Metab. 2010;95(11):E337-41.
161. Hamburger JI. Diagnosis and management of Graves' disease in pregnancy. Thyroid. 1992;2(3):219-24.
162. Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid. 2009;19(7):673-4.
163. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. J Clin Endocrinol Metab. 2009;94(6):1881-2.
164. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens. 1999;12(6):541-7.
165. Galina MP, Avnet ML, Einhorn A. Iodides during pregnancy. An apparent cause of neonatal death. N Engl J Med. 1962;267:1124-7.
166. Stoffer SS, Hamburger JI. Inadvertent 131I therapy for hyperthyroidism in the first trimester of pregnancy. J Nucl Med. 1976;17(2):146-9.
167. Bruner JP, Landon MB, Gabbe SG. Diabetes mellitus and Graves' disease in pregnancy complicated by maternal allergies to antithyroid medication. Obstet Gynecol. 1988;72(3 Pt 2):443-5.
168. Momotani N, Hisaoka T, Noh J, Ishikawa N, Ito K. Effects of iodine on thyroid status of fetus versus mother in treatment of Graves' disease complicated by pregnancy. J Clin Endocrinol Metab. 1992;75(3):738-44.
169. Glinoer D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest. 1993;16(11):881-8.
170. Bashiri A, Neumann L, Maymon E, Katz M. Hyperemesis gravidarum: epidemiologic features, complications and outcome. Eur J Obstet Gynecol Reprod Biol. 1995;63(2):135-8.
171. Bouillon R, Naesens M, Van Assche FA, De Keyser L, De Moor P, Renaer M, et al. Thyroid function in patients with hyperemesis gravidarum. Am J Obstet Gynecol. 1982;143(8):922-6.
172. Nader S, Mastrobattista J. Recurrent hyperthyroidism in consecutive pregnancies characterized by hyperemesis. Thyroid. 1996;6(5):465-6.
173. Rodien P, Bremont C, Sanson ML, Parma J, Van Sande J, Costagliola S, et al. Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. N Engl J Med. 1998;339(25):1823-6.
174. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007;92(8):S1-47.
175. Momotani N, Ito K. Treatment of pregnant patients with Basedow's disease. Exp Clin Endocrinol. 1991;97(2-3):268-74.
176. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. Thyroid. 1992;2(2):155-9.
177. Chan GW, Mandel SJ. Therapy insight: management of Graves' disease during pregnancy. Nat Clin Pract Endocrinol Metab. 2007;3(6):470-8.
178. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007;92(8):S1-47.
179. 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. J Clin Endocrinol Metab. 2003;88(12):5851-7.
180. Lee YS, Loke KY, Ng SC, Joseph R. Maternal thyrotoxicosis causing central hypothyroidism in infants. J Paediatr Child Health. 2002;38(2):206-8.
181. Mestman JH. Hyperthyroidism in pregnancy. Best Pract Res Clin Endocrinol Metab. 2004;18(2):267-88.

182. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998;338(2):73-8.

183. Jarhult J, Rudberg C, Larsson E, Selvander H, Sjovall K, Winsa B, et al. Graves' disease with moderate-severe endocrine ophthalmopathy-long term results of a prospective, randomized study of total or subtotal thyroid resection. Thyroid. 2005;15(10):1157-64.

184. Wiersinga WM, Prummel MF. Graves' ophthalmopathy: a rational approach to treatment. Trends Endocrinol Metab. 2002;13(7):280-7.

185. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997;47(1):9-14.

186. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158(3):273-85.

187. Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf). 2008;69(6):943-50.

188. Traisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, et al. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. J Clin Endocrinol Metab. 2009;94(10):3700-7.

189. Lai A, Sassi L, Compri E, Marino F, Sivelli P, Piantanida E, et al. Lower dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. J Clin Endocrinol Metab. 2010;95(3):1333-7.

190. Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med. 1992;326(26):1733-8.

191. Vannucchi G, Campi I, Covelli D, Dazzi D, Curro N, Simonetta S, et al. Graves' orbitopathy activation after radioactive iodine therapy with and without steroid prophylaxis. J Clin Endocrinol Metab. 2009;94(9):3381-6.

192. Witte J, Goretzki PE, Dotzenrath C, Simon D, Felis P, Neubauer M, et al. Surgery for Graves' disease: total versus subtotal thyroidectomy-results of a prospective randomized trial. World J Surg. 2000;24(11):1303-11.

193. DeGroot LJ. Radioiodine and the immune system. Thyroid. 1997;7(2):259-64.

194. Leo M, Marcocci C, Pinchera A, Nardi M, Megna L, Rocchi R, et al. Outcome of Graves' orbitopathy after total thyroid ablation and glucocorticoid treatment: follow-up of a randomized clinical trial. J Clin Endocrinol Metab. 2012;97(1):E44-8.

195. Azizi F, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. Eur J Endocrinol. 2005;152(2):695-701.

196. Lawrence JE, Lamm SH, Braverman LE. The use of perchlorate for the prevention of thyrotoxicosis in patients given iodine rich contrast agents. J Endocrinol Invest. 1999;22(5):405-7.

197. Bogazzi F, Bartalena L, Gasperi M, Braverman LE, Martino E. The various effects of amiodarone on thyroid function. Thyroid. 2001;11(5)511-9.

198. Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. J Clin Endocrinol Metab. 1996;81(8):2930-3.

199. Dickstein G, Shechner C, Adawi F, Kaplan J, Baron E, Ish-Shalom S. Lithium treatment in amiodarone-induced thyrotoxicosis. Am J Med. 1997;102(5):454-8.

200. Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart. 1998;79(2):121-7.

201. Koh LK, Greenspan FS, Yeo PP. Interferon-alfa induced thyroid dysfunction: three clinical presentation and a review of the literature. Thyroid. 1997;7(6):891-6.

202. Hamnvik OP, Larsen PR, Marqusee E. Thyroid dysfunction from antineoplastic agents. J Natl Cancer Inst. 2011;103(21):1572-87.

203. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003;348(26):2646-55.

204. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab. 2003;88(5):2100-5.

205. Pearce EN. Diagnosis and management of thyrotoxicosis. BMJ. 2006;332(7554):1369-73.

206. Chopra IJ, van Herle AJ, Korenman SG, Viosca S, Younai S. Use of sodium ipodate in management of hyperthyroidism in subacute thyroiditis. J Clin Endocrinol Metab. 1995;80(7):2178-80.

207. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, et al. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol. 2003;148(4):433-42.

208. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev. 1996;17(6):610-38.

209. Refetoff S, DeWind LT, DeGroot LJ. Familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab. 1967;27(2):279-94.

210. Adams M, Matthews C, Collingwood TN, Tone Y, Beck-Peccoz P, Chatterjee KV. Genetic analysis of 29 kindreds with generalized and pituitary resistance to thyroid hormone. J Clin Invest. 1994;94(2):506-15.

211. Beck-Peccoz P, Chatterjee VK. The variable clinical phenotype in thyroid hormone resistance syndrome. Thyroid. 1994;4(1):225-32.

212. Weiss RE, Stein MA, Refetoff S. Behavioral effects of liothyronine (L-T3) in children with attention deficit hyperactivity disorder in the presence and absence of resistance to thyroid hormone. Thyroid. 1997;7(3):389-93.

213. Zakhem A, Aftimos G, Kreidy R, Salem P. Malignant struma ovarii: report of two cases and selected review of the literature. J Surg Oncol. 1990;43(1):61-5.

214. Ross DS. Syndromes of thyrotoxicosis with low radioactive iodine uptake. Endocrinol Metab Clin North Am. 1998;27(1):169-85.

215. Kung AW, Ma JT, Wang C, Young RT. Hyperthyroidism during pregnancy due to coexistence of struma ovarii and Graves' disease. Postgrad Med J. 1990;66(772):132-3.

216. Soutter WP, Green-Thompson RW. The management of choriocarcinoma causing severe hyperthyroidism. Br J Obstet Gynaecol. 1981;88(9):938-43.

217. Rajatanavin R, Chailurkit LO, Srisupandit S, Tungtrakuls S, Bunyaratvej S. Case reports: trophoblastic hyperthyroidism: clinical and biochemical features of five cases. Am J Med. 1988;85(2):237-41.

218. Giralt SA, Dexeus F, Amato R, Sella A, Logothetis C. Hyperthyroidism in men with germ cell tumors and high levels of beta-human chorionic gonadotropin. Cancer. 1992;69(5):1286-90.

219. Sichieri R, Andrade R, Baima J, Henriques J, Vaisman M. TSH levels associated with slimming pill use in a population-based study of Brazilian women. Arq Bras Endocrinol Metabol. 2007;51(9):1448-51.

220. Hedberg CW, Fishbein DB, Janssen RS, Meyers B, McMillen JM, MacDonald KL, et al. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. N Engl J Med. 1987;316(16):993-8.

221. Kasagi K, Takeuchi R, Miyamoto S, Misaki T, Inoue D, Shimazu A, et al. Metastatic thyroid cancer presenting as thyrotoxicosis: report of three cases. Clin Endocrinol (Oxf). 1994;40(3):429-34.