Review

Management of Graves Disease
A Review

Henry B. Burch, MD; David S. Cooper, MD

IMPORTANCE Graves disease is the most common cause of persistent hyperthyroidism in adults. Approximately 3% of women and 0.5% of men will develop Graves disease during their lifetime.

OBSERVATIONS We searched PubMed and the Cochrane database for English-language studies published from June 2000 through October 5, 2015. Thirteen randomized clinical trials, 5 systematic reviews and meta-analyses, and 52 observational studies were included in this review. Patients with Graves disease may be treated with antithyroid drugs, radioactive iodine (RAI), or surgery (near-total thyroidectomy). The optimal approach depends on patient preference, geography, and clinical factors. A 12- to 18-month course of antithyroid drugs may lead to a remission in approximately 50% of patients but can cause potentially significant (albeit rare) adverse reactions, including agranulocytosis and hepatotoxicity. Adverse reactions typically occur within the first 90 days of therapy. Treating Graves disease with RAI and surgery result in gland destruction or removal, necessitating life-long levothyroxine replacement. Use of RAI has also been associated with the development or worsening of thyroid eye disease in approximately 15% to 20% of patients. Surgery is favored in patients with concomitant suspicious or malignant thyroid nodules, coexisting hyperparathyroidism, and in patients with large goiters or moderate to severe thyroid eye disease who cannot be treated using antithyroid drugs. However, surgery is associated with potential complications such as hypoparathyroidism and vocal cord paralysis in a small proportion of patients. In pregnancy, antithyroid drugs are the primary therapy, but some women with Graves disease opt to receive definitive therapy with RAI or surgery prior to becoming pregnant to avoid potential teratogenic effects of antithyroid drugs during pregnancy.

CONCLUSIONS AND RELEVANCE Management of Graves disease includes treatment with antithyroid drugs, RAI, or thyroidectomy. The optimal approach depends on patient preference and specific patient clinical features such as age, history of arrhythmia or ischemic heart disease, size of goiter, and severity of thyrotoxicosis. Physicians should be familiar with the advantages and disadvantages of each therapy to best counsel their patients.

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Author Affiliations: Endocrinology Service, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland (Burch); Uniformed Services University of Health Sciences, Bethesda, Maryland (Burch); The Johns Hopkins University School of Medicine, Baltimore, Maryland (Cooper).

Corresponding Author: David S. Cooper, MD, Division of Endocrinology, Diabetes, & Metabolism, The Johns Hopkins University School of Medicine, 1830 E Monument St, Ste 333, Baltimore, MD 21287 (dscooper@jhmi.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Graves disease is an autoimmune thyroid disorder caused by stimulating antibodies to the thyrotropin (thyroid-stimulating hormone [TSH]) receptor on thyroid follicular cells. It is the most common cause of hyperthyroidism with 20 to 30 cases per 100 000 individuals each year.[1] Approximately 3% of women and 0.5% of men develop Graves disease during their lifetime.[1] The peak incidence of Graves disease occurs among patients aged 30 to 60 years, but all ages are affected. Recent data suggest a possible increased incidence among young African Americans.[2] The purpose of this review is to provide an evidence-based update of therapy options for Graves disease.

Methods

We searched PubMed and the Cochrane databases for English-language studies published from June 2000 through October 1, 2015, for randomized clinical trials (RCTs), meta-analyses, systematic reviews, and observational studies (search terms are reported in eAppendix in the Supplement). We also manually searched the references of selected articles, reviews, meta-analyses, and practice guidelines. Selected articles were mutually agreed upon by the authors. Emphasis was given to selection of RCTs and meta-analyses and to consideration of information of interest to a general medical readership.

Clinical Presentation

Most patients with Graves disease have overt hyperthyroidism and a variety of characteristic symptoms and physical findings (**Table 1**).[3] Some of the more prevalent symptoms include palpitations, tremulousness, heat intolerance, weight loss, and anxiety. Physical findings include tachycardia, proptosis, thyroid enlargement, and tremor. Older patients are less symptomatic than younger patients.[4] Atrial fibrillation is common in elderly thyro-

toxic men with underlying cardiovascular disease,[5] and weight loss with a decrease in appetite is common among older patients with hyperthyroidism.[4] Possible laboratory findings in Graves disease include leukopenia, hypercalcemia due to increased osteoclastic activity, increased bone alkaline phosphatase, and mild-to-moderate transaminase elevation.[3] Substantially reduced bone mineral density should warrant thyroid function evaluation in postmenopausal women.[6]

Diagnosis

The diagnosis of Graves disease can often be established based on clinical features, elevated levels of thyroxine (T_4) and triiodothyronine (T_3), and undetectable levels of TSH. If the diagnosis is uncertain, additional testing may include measuring TSH-receptor antibodies (TRAb), radioactive iodine (RAI) uptake, or thyroid ultrasound with Doppler, each of which can confirm the diagnosis of Graves disease.[7] The differential diagnosis for thyrotoxicosis is summarized in **Table 2** and includes toxic multinodular goiter, painless thyroiditis, and drug-induced thyroiditis. Pregnant women should not undergo isotopic studies. Postpartum thyrotoxicosis may be caused by destructive thyroiditis or Graves disease, both of which can be distinguished using Doppler flow on ultrasound and TRAb testing (increased flow and positive TRAb results suggest Graves disease; normal or diminished flow and negative TRAb suggest postpartum thyroiditis).[8]

RAI radioactive iodine

T_3 triiodothyronine

T_4 thyroxine

TRAb thyrotropin-receptor antibody

TSH thyrotropin (previously thyroid-stimulating hormone)

Pathogenesis

Hyperthyroidism in Graves disease results from immunoglobulins that stimulate the TSH receptor on thyrocytes.[9] Levels of these anti-TRAbs correlate with disease activity and likely cause Graves orbitopathy by binding to TSH receptors in retroorbital tissues.[9] Factors contributing to the development of TRAb include HLA type, the postpartum state, tobacco smoking, physical or emotional stress,[10] and antigen release following thyroid injury such as radiation exposure.[11]

Management

Overview of Management

Hyperthyroidism due to Graves disease is treated with 1 of the following approaches: (1) use of antithyroid drugs to normalize thyroid hormone production; (2) destruction of the thyroid using RAI; or (3) surgical removal of the thyroid (**Figure**, **Table 3**).

Thionamide antithyroid drug therapy, which in the United States includes methimazole and propylthiouracil, results in a remission in approximately 40% to 50% of patients treated for 12 to 18 months[18,19] (range, 10%-90%).[13] Higher remission rates occur in patients with milder disease and smaller goiters, but for the average patient, laboratory factors do not predict remission.[20] The principal disadvantage of thionamide therapy is adverse effects. Use of RAI therapy allows an expeditious return to euthyroidism but results in permanent hypothyroidism in more

Table 1. Symptoms and Signs of Thyrotoxisosis[a]

	Prevalence, %[b]
Symptoms	
Fatigue	70
Weight loss (poor appetite)[c]	60
Heat intolerance	55
Tremulousness	55
Palpitations	50
Diaphoresis (heat intolerance)[d]	45
Increased appetite[d]	40
Nervousness (anxiety)[d]	40
Hyperdefecation	20
Neck fullness	20
Dyspnea	10
Eye symptoms (pain, redness, swelling, diplopia)	10
Weight gain	10
Physical findings	
Tachycardia	80
Diffuse palpable goiter with an audible bruit	70
Increased pulse pressure	50
Tremor	40
Warm moist palms	35
Periorbital edema and proptosis	25

[a] Data were adapted from *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text*.[3]

[b] Values have been rounded.

[c] Poor appetite, weight loss, congestive heart failure, and atrial fibrillation are more prevalent among elderly patients with thyrotoxisosis.

[d] Symptom less prevalent among elderly patients with thyrotoxisosis.

than 80% of patients and a 15% to 20% risk of inducing or aggravating Graves orbitopathy.[21]

Thyroidectomy typically requires antithyroid drug pretreatment to restore euthyroidism preoperatively and may result in permanent hypoparathyroidism in 4% of patients or vocal cord paralysis in less than 1%.[22]

The choice of therapy requires consideration of patient values and clinical features that would predict a successful outcome.[7] Among clinical endocrinologists in North America, 58.6% favor RAI for initial treatment of uncomplicated Graves disease, 40.5% prefer a prolonged course of antithyroid drugs, and fewer than 1% recommend thyroidectomy.[23] Conversely, a majority of endocrinologists outside of North America (67%-85%) prefer primary antithyroid drug therapy.[24] A trial of 179 patients randomized to the 3 previously mentioned modalities showed similar quality-of-life scores 14 to 21 years later.[25] Two cost analyses have shown RAI to be the least-expensive approach and surgery the most expensive for treating Graves disease.[26,27] Novel therapies currently under investigation for Graves disease include small molecules that will block the interaction between TRAb and the TSH receptor.[9,28]

β-Adrenergic–Blocking Drugs

β-Blockers are important in the initial management of Graves disease until thyroid hormone levels can be normalized. β-Blocking

Table 2. Differential Diagnosis of Thyrotoxicosis

Diagnosis	Clinical Findings	Laboratory Results	Imaging Findings	Other Features
Graves disease	Diffuse goiter, orbitopathy	Increased FT_4 and T_3, low TSH, positive TSH-receptor antibody	Elevated 24-h RAI uptake (often >30%-50%), diffuse uptake on scan, increased vascularity on Doppler-flow ultrasound	Typically seen in younger age groups and women
Toxic multinodular goiter	Multinodular goiter	Increased FT_4, T_3, or both	Multiple hyperfunctioning nodules on imaging	More common in older persons, women, and in areas of relative iodine deficiency
Solitary toxic nodule	Large (>3 cm) solitary thyroid nodule	Increased FT_4, T_3, or both	Solitary hyperfunctioning nodule with suppression of the paranodular tissue and contralateral lobe	More common in older persons, women, and in areas of relative iodine deficiency
Painless thyroiditis	Mild hyperthyroidism and small nonpainful goiter; self-limited condition (usually <2-3 mo)	Variable elevation of FT_4 (often 1.6-2.0 × ULN), increased T_3 (often 1.0-1.5 × ULN), usually positive anti-TPO antibodies	Absent to very low (0%-5%) 24-h RAI uptake, normal or decreased vascularity on Doppler-flow ultrasound	Has a predilection for the postpartum period and is also associated with lithium use; may recur over years
Subacute de Quervain thyroiditis	Painful enlarged thyroid that often occurs after an upper respiratory tract infection	Variable elevation of FT_4 (often 1.6-2.0 × ULN), increased T_3 (often 1.0-1.5 × ULN), very high ESR (typically >50 mm/h)	Absent to very low (0%-5%) 24-h RAI uptake	Usually not associated with permanent sequelae
Drug-induced thyroiditis	Mildly enlarged thyroid	Variable elevation of FT_4 (often 1.6-2.0 × ULN), increased T_3 (often 1.0-1.5 × ULN)	Absent to very low (0%-5%) 24-h RAI uptake	Associated with use of amiodarone, lithium, interferon-α, sorafenib and other multikinase inhibitors
Iodine-induced hyperthyroidism	Hyperthyroidism in days to months after iodine exposure in patients with preexisting thyroid disease, typically a multinodular goiter	Variable elevation of FT_4 (often 1.6-2.0 × ULN), increased T_3 (often 1.0-1.5 × ULN)	Absent to very low (0%-5%) 24-h RAI uptake	Associated with iodine exposure usually in the form of amiodarone or iodinated contrast agents
Ingestion of thyroid hormone	Thyrotoxic symptoms and signs without an enlarged thyroid	Elevated T_4 and T_3 in patients ingesting T_4; elevated T_3 with low FT_4 in patients ingesting T_3	Absent to very low (0%-5%) 24-h RAI uptake	May be intentional or inadvertent
Struma ovarii	Thyrotoxic symptoms and signs without an enlarged thyroid	Elevated FT_4 and T_3	Increased RAI uptake over the pelvis	May rarely be malignant
Molar pregnancy and choriocarcinoma	Thyrotoxic signs and symptoms with an enlarged thyroid	Elevated FT_4 (often 1.6-2.0 × ULN) and T_3 (often 1.6-2.0 × ULN)	Elevated 24-h RAI uptake (>30%-50%)	Caused by high levels of hCG, which has thyroid-stimulating action when present in high serum concentrations

Abbreviations: ESR, erythrocyte sedimentation rate; FT_4, free thyroxine; hCG, human chorionic gonadotropin; RAI, radioactive iodine; T_3, triiodothyronine; T_4, thyroxine; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone); ULN, upper limit of normal.

agents relieve many symptoms, especially palpitations, tremulousness, anxiety, and heat sensitivity. Although some β-blockers, including propranolol, atenolol, and metoprolol, can decrease the conversion of T_4 to T_3 in peripheral tissues,[29] this is only at high doses (eg, >160 mg/d of propranolol).[30] Typical starting doses for propranolol range from 40 to 160 mg per day, preferably as the long-acting preparation. Both atenolol and metoprolol are effective treatments for thyrotoxicosis and may be given once or twice daily. Higher doses may be required (eg, 160-320 mg/d of propranolol) because drug clearance is increased in hyperthyroidism.[31]

β-Blocking drugs should be used cautiously in patients with asthma, congestive heart failure, bradyarrhythmias, and Raynaud phenomenon. In these patients, calcium-channel blocker therapy is an alternative to β-blocking drugs for heart rate control.[32] In patients who are acutely ill, intravenous use of propranolol or the rapidly acting cardioselective β-blocker esmolol is recommended because of these drugs' rapid onset and short duration of action.[33]

Antithyroid Drug Therapy

The thionamide antithyroid drugs methimazole and propylthiouracil inhibit thyroid hormone synthesis by interfering with thyroid peroxidase (TPO) (Table 3).[34] In addition, propylthiouracil blocks peripheral T_4-to-T_3 conversion, which may benefit patients with

thyroid storm. Antithyroid drug therapy also is associated with a normalization of TRAb levels over time in many patients, which is potentially important in mediating remissions after long-term therapy.[14]

Methimazole or carbimazole (which is converted to methimazole in the serum) are almost exclusively used in antithyroid drug therapy.[23,35] Propylthiouracil is not used for primary treatment because of hepatotoxicity but is indicated for patients who are intolerant of methimazole, pregnant women during the first trimester (see below), and patients in thyroid storm.[7,33] Antithyroid drugs can be used as primary treatment (given for 12-18 months), and they are also used as pretreatment in selected patients prior to RAI therapy and in most patients prior to surgery.[34] The usual starting dose for methimazole is 10 to 30 mg per day, depending on the severity of the patient's hyperthyroidism. Most patients do not require more than 30 to 40 mg per day. Methimazole can be given as a single daily dose, which improves medication adherence. However, in severe hyperthyroidism, a split dose may be more effective initially.[36] Higher methimazole doses may achieve faster normalization of thyroid function and are used in more severe thyrotoxicosis (eg, FT_4 >3 times greater than the reference range) but are also associated with more adverse effects.[37]

Thyroid function tests are performed at 2 to 6 weeks after drug initiation to document improvement with shorter intervals

Figure. Summary of the Biosynthesis of Thyroid Hormone and Overview of the Management of Graves Disease

A Biosynthesis of thyroid hormone

B Primary treatments for Graves Disease

A, Thyroid hormone synthesis begins with iodide uptake by thyroid follicular cells followed by oxidation of iodide by thyroid peroxidase (TPO) using endogenously generated H_2O_2. TPO catalyzes the subsequent steps of thyroid hormone synthesis—iodination of tyrosine residues in thyroglobulin to form iodotyrosines and coupling of 2 iodotyrosines to form the iodothyronines bound to thyroglobulin. The iodothyronines are stored in the follicular lumen as colloid then ingested by thyroid follicular cells. Within the follicular cells, thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are released from thyroglobulin and enter the bloodstream.

B, Options for the management of Graves disease include antithyroid drug therapy such as methimazole, radioactive iodine (RAI) treatment, and surgery. Left, Antithyroid drug (ATD) therapy interferes with new thyroid hormone synthesis and reduces serum levels of T_4 and T_3 until they are normal. Most

patients also have normalization of TSH-receptor antibody (TRAb) levels.[12] ATD therapy is generally continued for 12 to 18 months before the possibility of remission is assessed by measuring TRAb levels. ATD therapy is stopped if the TRAb level is normal. Center, Radioactive iodine (RAI, ^{131}I) is taken up by thyroid follicular cells and incorporated into thyroid hormone. Ionizing radiation damages thyroid follicular cell DNA and gradually destroys the gland. T_4 and T_3 levels decline resulting in hypothyroidism, which is treated by replacement with levothyroxine. Levels of TRAb generally increase following RAI treatment and may remain elevated for prolonged periods of time.[12] Right, Surgery (total thyroidectomy) is performed when thyroid function has normalized following 1 to 3 months of pretreatment with methimazole. Thyroid hormone replacement therapy is started after surgery prior to discharge from the hospital. DIT indicates diiodotyrosine; MIT, monoiodotyrosine.

Table 3. Primary Treatments for Graves Disease

Modality	Advantages	Hypothyroidism After Therapy	Mechanism of Action	Other Considerations
Antithyroid drugs (methimazole, carbimazole, propylthiouracil)	Nonablative (remission in ≈50% of patients; higher rates in those with milder disease and lower TRAb values)[13,14]	No (but can occur with excessive dosing)	Interference with new thyroid hormone synthesis	Careful dose titration needed to control hyperthyroidism and avoid hypothyroidism (starting doses of methimazole are 10-30 mg/d depending on severity) Potential for nonadherence Possible drug reactions (see Table 4 for details)
Potassium iodide	Potentially useful in patients with allergy to antithyroid drugs	No	Inhibition of thyroid hormone synthesis and release Decreased thyroid vascularity (used prior to thyroidectomy)	Limited data on utility as solo therapy Patients may escape from therapeutic effect
Radioactive iodine (131-I)	Usually curative (≈85% of patients are euthyroid or hypothyroid after a single dose)[7]	80% Rate of hypothyroidism at 1 year with high-dose therapy (≥200 μCi/g of thyroid tissue)[7]	Destruction of thyroid by emitted beta particles	Potential for onset or exacerbation of thyroid eye disease in 15% to 20% of patients (especially those who smoke and who have more severe disease)[15] Patient nonacceptance because of fear of radiation Transient worsening of thyroid function in ≈10% of patients (justifying antithyroid drug pretreatment in older patients and those with cardiovascular disease)[16] Contraindicated in pregnant and lactating women May be preferred in women considering pregnancy in 6 to 12 months Need for radiation precautions Least expensive
Surgery (total thyroidectomy)	Definitive (10%-15% recurrence rate with subtotal thyroidectomy vs 0% with near total thyroidectomy)[7]	Inevitable after total thyroidectomy	Physical removal of thyroid tissue	Usual preparation involves antithyroid drug treatment and potassium iodide therapy Pain, scarring, recuperation time Possible surgical complications (transient [≈25%] and permanent [≈4%] hypoparathyroidism; recurrent laryngeal nerve palsy [<1%])[17] Lower rates with more experienced surgeons May be preferred in women considering pregnancy in less than 6 months Preferred in patients with large goiters, coexisting suspicious or malignant nodules, or primary hyperparathyroidism Preferred in patients with significant thyroid eye disease who cannot take antithyroid drugs Most expensive form of therapy

(2-3 weeks) appropriate in more severe disease. For the first 3 to 6 months, both serum free T_4 and T_3 or free T_3 should ideally be monitored because some patients normalize their free T_4 levels but T_3 levels remain elevated.[38] Testing serum TSH levels are usually not helpful for the first 1 to 2 months because levels can remain suppressed due to the antecedent hyperthyroidism. After attaining euthyroidism, patients should be evaluated every 2 to 3 months for the next 12 to 18 months, with adjustment of the drug to maintain euthyroidism. After the first 6 months, the dose can usually be decreased with maintenance doses of 5 to 10 mg per day. The ability to maintain euthyroidism with low-dose antithyroid drugs is a predictor of remission.[39]

Patients receiving primary methimazole are treated for 12 to 18 months; a time frame supported by an RCT with findings that remission rates are not improved after more than 18 months of therapy.[18] In patients whose TRAb levels have normalized, the drug can be tapered off or stopped based on signs that the patient is in remission, defined as remaining biochemically euthyroid beyond 1 year after drug discontinuation. In patients in whom TRAb have normalized, the relapse rates are 20% to 30% over 3 to 5 years of follow-up.[12,40,41] In patients who relapse, definitive treatment with RAI or surgery should be considered, although many opt for another course of medical therapy.[42] Some experts recommend chronic, perhaps even lifelong antithyroid drug treatment.[43,44]

Antithyroid Drug Adverse Effects
Minor adverse effects such as pruritic rash and arthralgias occur in approximately 5% of patients receiving methimazole, and typically begin within the first few weeks of starting therapy (**Table 4**).[34] A mild rash may resolve with continued therapy or with antihistamines but may be severe enough to require drug discontinuation. These patients may be switched to propylthiouracil but 30% to 50% have a similar reaction.[45] The more severe adverse effects of antithyroid drugs include agranulocytosis, hepatotoxicity, and antineutrophil cytoplasmic antibody–positive vasculitis. Prior to initiation of antithyroid drug therapy, the potential adverse effects should be discussed with the patient (and a document explaining such effects preferably also provided).

Agranulocytosis occurs in approximately 1 in 500 patients,[46] is dose-related with methimazole,[48] and almost always develops within the first 90 days of drug initiation.[46] Agranulocytosis can also develop upon reexposure to the drug after an interval of years.[49] The typical presentation is high fever and severe pharyngitis,[50] and patients should be advised to contact their physician if these symptoms develop. A recent survey of antithyroid drug–treated patients concluded that 61% were unfamiliar with the symptoms of agranulocytosis.[51] Treatment includes immediate drug cessation, hospitalization, and administration of broad-spectrum antibiotics and hematopoietic growth factor therapy.[52,53]

Table 4. Adverse Reactions to Antithyroid Drugs

Drug Reactions	Methimazole/Carbimazole	Propylthiouracil	Comments
Minor			
Rash, gastrointestinal distress	Incidence 1% to 5% (dose-related)[34]	Incidence 1% to 5%[34]	Rash and itching may be manageable with antihistamine therapy; cross-reactivity for rash with the alternate drug in 30% to 50% of patients[45]
Major			
Agranulocytosis	Incidence is approximately 0.2%[46] (dose-related [rare with doses ≤10 mg/d]), almost always develops in the first 90 days of therapy	Incidence is approximately 0.2%,[46] almost always develops in the first 90 days of therapy	Due to the potential for cross-reactivity, attempting to use the other drug is not recommended
Hepatotoxicity	Incidence is less than 0.1%,[34] usually cholestatic, mean time to onset is 36 days[47]	Incidence is less than 0.1%,[34] usually hepatocellular, median time to onset is 120 days	Due to different hepatotoxicity profiles, the alternate drug could be tried in severely ill patients with mild-to-moderate hepatotoxic reactions to 1 drug
Antineutrophilic cytoplasmic antibody–positive vasculitis (typically pANCA with myeloperoxidase [MPO]-ANCA)	Rare with methimazole	Incidence uncertain; treated patients may have circulating antineutrophilic cytoplasmic antibodies and remain asymptomatic; can occur months or years after initiation of drug therapy	Asian populations may be predisposed; skin, kidney, and lung involvement are most common

Because leukopenia can be a manifestation of Graves disease, a white blood cell count and differential should be performed prior to starting antithyroid drug therapy, and therapy should be reconsidered should the granulocyte count be less than 1.5×10^9/L.[7] Whether the white blood cell count should be monitored is controversial: Some patients develop a slow decrease in white blood cell count, which reverses when the drug is stopped.[46,54] A recent international survey found that 48% of clinicians routinely monitor white blood cell count in patients taking antithyroid drugs.[23]

Methimazole-induced hepatotoxicity is frequently cholestatic,[55] whereas propylthiouracil use has been associated with hepatocellular injury, including fulminant hepatic failure, leading to death or the need for liver transplantation.[56] Recently, 2 Asian studies reported that methimazole can produce hepatocellular toxicity similar to that seen with propylthiouracil.[57,58] The frequency of severe hepatotoxicity with antithyroid drug therapy is uncertain but was 0.3 per 1000 patient years for methimazole or carbimazole and 0.7 per 1000 patient years for propylthiouracil in one of these reports.[57] Hepatic dysfunction generally occurs within the first few days to 3 months after drug initiation, and prompt recognition and discontinuation of antithyroid drug therapy is vital. Routine monitoring of liver function is not known to limit the severity of antithyroid drug hepatotoxicity[7] but is performed by the majority of clinical endocrinologists.[23] The presence of underlying liver disease, liver function abnormalities, or both is not a contraindication to methimazole,[59] but both antithyroid drugs are generally avoided in patients with baseline transaminases greater than 3 to 5 times the upper limit of normal.

Antineutrophil cytoplasmic antibody–associated vasculitis occurs much more frequently with propylthiouracil than it does with methimazole or carbimazole[60,61] and can occur after months to years of therapy. Typically, patients present with polyarthritis, fever, and purpura, and more severely affected individuals develop glomerulonephritis and pneumonitis. Therapy involves stopping the drug and possible use of glucocorticoids and other immunotherapies.[47]

RAI Therapy

Within the thyroid gland, RAI is incorporated into thyroid hormone, releasing beta particles that cause ionizing damage to thyroid follicular cells, resulting in gradual destruction of the gland (Table 3). The speed with which hypothyroidism occurs depends on the size of the thyroid, the RAI uptake, the degree of thyrotoxicosis, and the activity of RAI administered.

The goal of RAI therapy is to render the patient hypothyroid. Most patients develop hypothyroidism 2 to 3 months after a single 12- to 15-mCi (444-555 MBq) administration of RAI. Occasional patients require a longer time, with repeat treatment generally not considered before 6 months after the initial therapy. Patients with a delayed response to RAI often require antithyroid drug therapy while awaiting the beneficial effects of ablation therapy. The destruction of thyroid tissue occasionally results in transient worsening of thyrotoxicosis in the weeks following RAI therapy.[62,63] Five percent to 15% of Graves disease patients require a second administration of RAI.[64-66]

Pretreatment with antithyroid drugs before administering RAI is not required, with certain notable exceptions. Due to the risk of transient worsening of thyrotoxicosis after RAI, patients who are older or have comorbidity such as coronary artery disease may benefit from pretreatment.[67] Two RCTs comparing pretreatment and no pretreatment with antithyroid drugs before RAI therapy found that a small proportion (10%-20%) of patients in both groups experienced initial worsening; however, those who were not pretreated developed substantially higher thyroid hormone levels than those who became worse after receiving antithyroid drug pretreatment.[16,68] In patients requiring pretreatment, antithyroid drugs should be stopped 2 to 3 days prior to RAI therapy and then restarted 3 to 5 days later[69,70] to permit RAI incorporation into the thyroid hormone. Antithyroid drug adjunctive therapy before RAI may decrease the efficacy of RAI (as shown in a meta-analysis[71] from 2007), but this is not clinically significant with moderate activities of RAI.

RAI therapy is contraindicated in pregnant or breastfeeding women.[72] Because RAI is concentrated in breast milk, women who

Table 5. Effect of Radioactive Iodine Therapy on Graves Orbitopathy

Source[a]	No. of Patients Randomized	Developing New or Worsened Eye Disease Following Treatment, No./Total No. (%)		
		Methimazole	Thyroidectomy	Radioactive Iodine
Tallstedt et al,[73] 1992	114[b]	4/38 (10.5)	6/37 (16.2)	13/39 (33.3)
Bartalena et al,[74] 1998	443[c]	4/148 (2.7)	Not applicable	23/150 (15.3)
Traisk et al,[21] 2009	313	32/150 (21.3)	Not applicable	63/163 (38.7)

[a] All sources were randomized clinical trials.

[b] Includes only patients who were aged 35 to 55 years.

[c] Number of patients includes 145 patients who were treated with radioactive iodine and concurrent corticosteroids.

have stopped breastfeeding within the past 6 weeks or who have continued evidence of lactation should also avoid RAI therapy to limit breast exposure to radioisotopes. Following RAI therapy for Graves disease, it is recommended that the patient sleep alone for 3 to 6 days after a 10- to 15-mCi dose, and for 15 to 18 days in the case of a pregnant partner.[72] During the day, the patient should keep a distance of 3 feet from adults and 6 feet from pregnant women and children following receipt of 10 to 15 mCi of RAI.[72]

Adverse effects associated with RAI therapy include rare transient anterior neck pain due to radiation thyroiditis and transient worsening of thyrotoxicosis. Three RCTs and a meta-analysis from 2008 have shown that RAI therapy is associated with new or worsened Graves orbitopathy compared to antithyroid drug therapy or thyroidectomy (Table 5).[21,73-75] Tobacco smoking is associated with orbitopathy in general[76] and is a risk factor for worsening orbitopathy following RAI therapy.[73,74] Corticosteroids given at the time of RAI help prevent worsening orbitopathy following RAI therapy,[74] particularly in patients with preexisting orbitopathy.[77] A recent guideline recommended corticosteroid prophylaxis in patients with mild Graves orbitopathy and risk factors for worsening disease (such as tobacco smoking) and in patients with moderate Graves orbitopathy (such as proptosis >3 mm above the upper limit of normal and periorbital soft tissue inflammation), regardless of risk factors, with avoidance of RAI in patients with active and moderate to severe sight-threatening Graves orbitopathy.[7]

Several studies have examined the risk of malignancy following therapy with RAI for thyrotoxicosis. In the largest study of 35 593 hyperthyroid patients treated with RAI between 1946 and 1964, there was no increase in cancer deaths compared with background population rates and a small increase in thyroid cancer in patients treated for nodular causes of hyperthyroidism but not Graves disease.[78]

Following RAI therapy, serial thyroid hormone measurement should be done at 2- to 6-week intervals. Patients should be started on levothyroxine therapy immediately when free T_4 levels fall below the normal range[7] because untreated hypothyroidism is another risk factor for the worsening of orbitopathy.[73] Weight gain following correction of thyrotoxicosis is a common and concern for some patients,[79] likely due to the continued excessive caloric intake despite a return to normal metabolism.

Surgery for Hyperthyroidism Caused by Graves Disease
Surgery was the first definitive treatment for Graves disease, but with the development of antithyroid drugs and RAI therapy in the 1940s and 1950s, surgery is now recommended by fewer than 1% of experts for the initial management of Graves disease (Table 3).[23] However, recent data indicate that surgery has become the main definitive therapy (vs RAI) in some US centers, particularly among patients with low socioeconomic status.[80,81] Indications for surgery include very large goiters with compressive symptoms, concomitant suspicious thyroid nodules, concurrent hyperparathyroidism requiring surgery, and patient preference.[7] Women with Graves disease who plan to become pregnant within the next 6 months sometimes select thyroidectomy rather than RAI because of theoretical concerns related to radiation exposure prior to pregnancy and also known sustained increases in TRAb titers after RAI, which could increase the risk of neonatal thyroid dysfunction. Patients who are intolerant of antithyroid drug therapy and do not wish to be treated with RAI or who have active Graves orbitopathy are surgical candidates. Complications of surgery include transient and permanent hypoparathyroidism and recurrent laryngeal nerve damage in roughly 1% to 4% of patients.[82] Surgical complications occur less frequently when performed by more experienced surgeons,[22] and clinicians should consider referring these patients to high-volume centers.[22]

Traditionally, patients opting for surgery are prepared with antithyroid drug therapy for 1 to 3 months until they are euthyroid. In 1 RCT, intraoperative blood loss was less in patients who received potassium iodide as Lugol solution, 10 drops 3 times daily for 10 days before surgery (blood loss of 54 mL vs 109 mL; $P < .001$).[83] In addition to reducing thyroid vascularity, iodide has acute inhibitory effects on new thyroid hormone synthesis, referred to as the Wolff-Chaikoff effect. In patients with moderate to severe thyrotoxicosis requiring urgent surgery or patients who are intolerant to antithyroid drugs, preparation with β-blocking drugs plus SSKI (2 drops by mouth 3 times daily), dexamethasone (2 mg orally or intravenously 4 times daily), and cholestyramine (4 g 4 times daily) has been recommended.[33,84] Patients who are not biochemically euthyroid at the time of surgery are at an increased risk for thyroid storm.[33]

Potassium Iodide Therapy in Patients Allergic to Antithyroid Drugs and as Primary Therapy
Since the introduction of antithyroid drugs in the 1940s-1950s, potassium iodide has been avoided as primary medical therapy in patients with Graves disease, owing to the escape from the Wolff-Chaikoff inhibitory effect on thyroid hormone synthesis. However, in a 2014 report from Japan, 30 patients with mild Graves disease received primary treatment with potassium iodide (50-100 mg/d). After 12 months, control of thyroid function was comparable with that seen in patients receiving low-dose methimazole treatment.[15] Another retrospective analysis from Japan reported that 29 of 44 (66%) patients treated with potassium iodide experienced remission or long-term control of hyperthyroidism, 11 (25%) patients escaped from the Wolf-Chaikoff effect, and 3 derived no benefit at all.[85] These data may provide another potential approach to patients with mild disease who wish to avoid definitive therapy but are unable or unwilling to take antithyroid drugs.

Extrathyroidal Manifestations of Graves Disease

Extrathyroidal manifestations of Graves disease are discernible on physical examination in 25% of all Graves disease patients (with orbitopathy), 1% (with dermopathy), and 0.1% (with acropachy [digital clubbing]).[86] Graves orbitopathy can be the most debilitating feature of Graves disease, and its presence leads to a significant diminution in quality of life.[87] Orbitopathy presents as ocular inflammation, periorbital edema, proptosis, extraocular muscle enlargement and fibrosis, optic neuropathy, and lacrimal gland dysfunction.[88]

Graves dermopathy typically occurs in the pretibial area but may occur anywhere in the body exposed to repetitive trauma or pressure. It is characterized by skin thickening due to fibroblast proliferation and edema due to glycosaminoglycan elaboration.[86] Topical corticosteroids (using occlusive dressings) are usually recommended, but in 1 large study, fewer than half of patients responded to this therapy.[89]

Pregnancy

Graves disease affects 1 to 2 per 1000 pregnancies.[90,91] Untreated overt hyperthyroidism is associated with preeclampsia, heart failure, premature delivery, low birth weight, and fetal death.[17,92-96] New onset of Graves disease in pregnancy must be distinguished from gestational thyrotoxicosis resulting from elevated serum levels of human chorionic gonadotropin (hCG), which stimulate the TSH receptor. In these patients, hCG levels peak at the end of the first trimester and can cause a mild increase in serum free T_4 levels and a reciprocal decrease in serum TSH to subnormal levels in as many as 20% of pregnancies. Gestational thyrotoxicosis almost always resolves at the end of the first trimester and rarely requires treatment.[97]

The laboratory changes in thyroid function in hyperthyroid pregnant women are similar to those seen in thyrotoxic nonpregnant women. Because very high levels of TRAb can cross the placenta and be associated with neonatal Graves disease, TRAb should be measured early in the third trimester in women with active Graves disease—when levels are at their nadir. TRAb measurement should also be made in hypothyroid women treated with RAI in the past because these antibodies can persist for years.

Professional societies and the US Food and Drug Administration recommend that women undergoing treatment for hyperthyroidism with methimazole who become pregnant should be switched to propylthiouracil in the first trimester[98-100] (Box). This recommendation is based on the association between severe birth defects and in utero methimazole exposure in the first trimester.[101,102] Some women with Graves disease opt to receive definitive therapy prior to becoming pregnant to avoid potential adverse effects of antithyroid drugs during pregnancy (Box).

Thyroid hormone levels should be measured monthly throughout pregnancy (Box). Antithyroid drug therapy should be adjusted to maintain serum free T_4 levels at the upper limit of the reference range for pregnant women with mildly suppressed serum TSH levels, to avoid fetal hypothyroidism. In 30% to 50% of pregnant women, the antithyroid drug can be discontinued in the second or third trimester because of an amelioration of thyroid autoimmunity in pregnancy.[95,103] However, Graves disease often relapses in

the postpartum period, due to a rebound in autoimmunity,[104] and therefore, thyroid function should be monitored every 2 to 3 months for 1 year following delivery. Breastfeeding is safe when taking methimazole or propylthiouracil,[105] but methimazole is preferred. Thyroid function tests remained normal in infants exposed to typical therapeutic doses.[106]

Box. Special Considerations for Graves Disease Management During Pregnancy

Graves Disease Patients Who Become Pregnant While Taking Methimazole

Women should be advised to notify their physician as soon as pregnancy is confirmed

In women with long-term (>1 year) and current low-dose (eg, 5 mg/d) use of methimazole with recent normal serum thyrotropin levels, discontinuation of methimazole should be considered because the patient may be in remission

If antithyroid drugs are still necessary, medication should be switched to propylthiouracil during the first trimester at a dose ratio of approximately 1:20 (eg, 5 mg of methimazole is approximately equipotent as 100 mg of propylthiouracil)

Medication should be switched back to methimazole at the beginning of the second trimester

Serum free thyroxine (T_4) levels should be maintained at the upper end or slightly above the upper limit of reference range with a mildly suppressed serum TSH to avoid overtreatment and possible fetal hypothyroidism

Because Graves disease improves spontaneously during pregnancy, methimazole can be stopped in 30% to 50% of patients by the third trimester

Thyrotropin-receptor antibodies should be measured in the third trimester as a predictor of neonatal Graves disease

Thyroid function should be monitored during the postpartum period for possible development of postpartum thyroiditis or resurgence of Graves disease

Women Considering Pregnancy Who Are Diagnosed With Graves Disease

Methimazole is the criterion standard of care rather than risking long-term propylthiouracil therapy

Alternatively, definitive therapy with either radioiodine or surgery might be considered prior to pregnancy, thereby avoiding antithyroid drug exposure if and when the patient becomes pregnant

Conclusions

Management of Graves disease includes treatment with antithyroid drugs, RAI, or thyroidectomy. The optimal approach depends on patient preference and specific patient clinical features such as age, history of arrhythmia or ischemic heart disease, size of goiter, and severity of thyrotoxicosis. Antithyroid drugs may lead to a remission while RAI and surgery result in gland destruction or removal. In pregnancy, antithyroid drugs are the primary therapy. Since each of the treatment modalities has unique limitations and adverse consequences, physicians need to be familiar with the advantages and disadvantages of each therapy in order to best counsel their patients.

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