

Indonesian Clinical Practice Guidelines for Hyperthyroidism

The Indonesian Society of Endocrinology
Task Force on Thyroid Diseases

Abstract

Hyperthyroidism remains as one of the major thyroid disorders in Indonesia. The Indonesian Task Force on Thyroid Diseases determined that hyperthyroidism represents a priority area in need of updated evidence-based practice guidelines. The aim of the guidelines is to provide the best evidence-based recommendations for diagnostic evaluation and management of hyperthyroidism in the adult population. The following article summarizes the guidelines.

Keywords: hyperthyroidism, clinical practice guidelines, Indonesia

Introduction

In the Republic of Indonesia, the prevalence of hyperthyroidism stands at 6.9% (latest Indonesian Basic Health Research data which was performed in 2007 with TSH cut-off level < 0.55 mIU/L). Scientific advances relevant to this topic are reported in a diverse array of literature, including subspecialty publications in endocrinology, pediatrics, nuclear medicine, and surgery, making it challenging for clinicians, especially in Indonesia, to keep abreast of new developments.

The Indonesian Clinical Practice Guidelines for Hyperthyroidism is a project of the Indonesian Task Force on Thyroid Diseases, which is a collaboration of Indonesian endocrinologists caring for individuals with hyperthyroidism. The objective of this project is to develop clinical practice guidelines on the screening, diagnosis and management of hyperthyroidism which reflect the current best evidence on optimal medical practice and incorporate local data into the recommendations. It is not the intent of these guidelines to replace clinical judgment and individual decision making. Each recommendation should be evaluated in light of these elements in order that optimal patient care is delivered.

Summary of the methodology for guidelines development

The guidelines were developed by the Indonesian Task Force on Thyroid Diseases. The Task Force reviewed available literatures on hyperthyroidism. The Task Force was able to obtain valuable feedback and suggestions to include additional evidence from the literature and to consider alternative interpretation of data. The

participants contributed to and influenced the form of the final guidelines, making it a comprehensive report from various geographical origins and medical disciplines.

Summary of recommendations

Definitions

Hyperthyroidism is a clinical condition caused by increased synthesis and secretion of hormones by the thyroid gland which affects the entire body. Thyrotoxicosis is defined as clinical manifestations related to increased thyroid hormone levels.

Epidemiology

Graves' disease (GD) persists as the most frequently-encountered etiology of hyperthyroidism causing approximately 60-80% of all cases of thyrotoxicosis worldwide. It is also more frequently found in females with a female-to-male ratio of 8:1 and apparently manifests in the third and fourth decades of life.

Clinical signs and symptoms

The signs and symptoms of hyperthyroidism are diverse and are mostly determined by the subject's age and the presence of prior organ disorders. Young patients typically complain of excessive sympathetic nerve symptoms, such as anxiety, hyperactivity and tremors, while the elderly commonly complain of cardiovascular symptoms (cardiomyopathy, arrhythmia) and unexplained weight loss.

The most commonly encountered symptoms in thyrotoxicosis are the following: nervousness and anxiety; excessive sweating, warm skin and heat intolerance; irritability; palpitations; hyperdefecation; easy fatigability;

weight loss with increased appetite (Von Muller’s paradox) and menstrual disorders.

While the most frequently observed clinical signs are as follows: thyroid gland hypertrophy or struma; hyperactivity; tachycardia or atrial fibrillation; systolic hypertension; warm and increased perspiration of the skin; tremor; muscle fatigue; ocular disorders such as Mobius’ sign (impaired ocular convergence), von Graefe’s sign (the failure of the upper eyelid to follow promptly and smoothly the downward movement of the eyeball), Joffroy’s sign (the facial muscles remain immobile when the eyeballs are rolled upward), Stellwag’s sign (infrequent and incomplete blinking of the eyes), lid lag (the upper eyelid lags behind the upper edge of the iris as the eye moves downward), exophthalmos and its following consequences e.g., conjunctivitis, corneal ulcer, palpebral edema, optic neuritis and optic atrophy.

Diagnosis of hyperthyroidism

To distinguish between hyperthyroidism and other causes of thyrotoxicosis, a radioactive iodine uptake (RAIU) should be performed. Hyperthyroidism has high RAIU while the other etiologies have low or near absent radioactive iodine uptake. The assessment of hyperthyroidism manifestations, and especially potential cardiovascular and neuromuscular complications, is essential to formulating an appropriate treatment plan.

Clinical evaluation

Biochemical evaluation of TSH and thyroid hormones is the most important initial diagnostic test for individuals suspected of hyperthyroidism/ thyrotoxic crisis based on clinical manifestations.

When there is inconsistency among the clinical signs and symptoms, or when clinical manifestations are subtle, or confirmatory biochemical testing is not readily accessible, it may be helpful to use a diagnostic index called the Wayne’ s index. This is a scoring system that has been developed since 1972 to help improve the diagnostic accuracy of clinical assessment.

Biochemical evaluation

Overt hyperthyroidism is characterized by suppressed TSH (<0.01 mU/L) and excess thyroid hormones in serum.

Serum TSH

Serum TSH measurement has the highest sensitivity and specificity of any single blood test and is used as an *initial screening* test for hyperthyroidism. In hyperthyroidism, serum TSH will be less than 0.01 mU/L or even undetectable.

Serum thyroid hormones

To assess the severity of the condition and to improve diagnostic accuracy, both TSH and free T₄ levels should be assessed at the time of the initial evaluation. In overt hyperthyroidism, usually both serum free T₄ and T₃ estimates are elevated, and serum TSH is < 0.01 mU/L or undetectable. In milder hyperthyroidism, serum T₄ and free T₄ estimates can be normal, only serum T₃ may be elevated, and serum TSH will be less than 0.01 mU/L (or undetectable) – called T₃ thyrotoxicosis. Assays for estimating free T₃ are less widely-validated than those for free T₄, and therefore measurement of total T₃ is frequently preferred in clinical practice.

Subclinical hyperthyroidism is defined as a normal serum free T₄ estimate and normal total T₃ or free T₃ estimate, with subnormal serum TSH concentration.

TRAb (thyrotropin receptor antibody)

This approach is utilized when a thyroid scan and uptake are unavailable or contraindicated (e.g., during pregnancy and lactation).

Imaging

Radioactive iodine uptake (RAIU) and thyroid scanning

RAIU should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of GD. A thyroid scan should be added in the presence of thyroid nodularity.

Table 1. Wayne’s index of signs and symptoms scoring system in diagnostic approach of hyperthyroidism

Symptoms of recent onset and/or increased severity	Scores	Signs	Only if present	Only if absent
Dyspnea on effort	(+)1	Palpable thyroid	(+3	(-) 3
Palpitations	(+2	Bruit over thyroid	(+2	(-) 2
Tiredness	(+2	Exophthalmos	(+2	-
Preference for heat	(-) 5	Lid retraction	(+2	-
Preference for cold	(+5	Lid lag	(+1	-
Excessive sweating	(+3	Hyperkinesia	(+4	(-) 2
Nervousness	(+2	Hands : hot	(+2	(-) 2
Appetite : increased	(+3	moist	(+1	(-) 1
decreased	(-) 3	Casual pulse rate :		
Weight : increased	(-) 3	> 80/min	-	(-) 3
decreased	(+3	> 90/min	(+3	-
		Atrial fibrillation	(+4	-

Total score interpretation:
 > 19 = toxic
 11-19 = equivocal
 < 11 = euthyroid/not toxic

Ultrasonography (USG)

USG is performed with the patient in the supine position and the neck hyper-extended. USG can detect thyroid lobes or lesions as small as 2 mm. It can distinguish solid nodules from simple and complex cysts. It can estimate thyroid size, give a rough estimate of tissue density, show vascular flow and velocity and aid in placing a needle for diagnostic purpose. Doppler studies may be added while executing ultrasonography.

Fine needle aspiration biopsy (FNAB)

In GD, FNAB is necessary if a nodule is found within the thyroid – to distinguish benign from malignant nodules which may occur. We recommend an USG-guided FNAB.

Management

The management of hyperthyroidism involves 3 inter-related aspects:

1. Inhibition of thyroid hormone synthesis and secretion (ATDs)
2. Destruction or reduction of thyroid tissue mass (radioactive iodine therapy or surgery)
3. Minimalization of thyroid hormone effects on peripheral tissues (beta-blocker therapy)

Judicious decision-making in choosing the most well-suited therapy depends on several factors, such as the severity of hyperthyroidism, age, struma size and the presence of comorbidities.

Specific management for Graves' Disease

There are 3 treatment modalities that can be used: antithyroid drugs (ATDs), radioactive iodine therapy and thyroidectomy.

ATDs are suggested in GD patients with the following conditions:

- a. Patients with high likelihood of remission (patients, especially females, with mild disease, small goiters, and negative or low-titer TRAb)
- b. Elderly or others with comorbidities increasing surgical risk or with limited life expectancy
- c. Individuals in nursing homes or other care facilities who may have limited longevity and are unable to follow radiation safety regulations
- d. Patients with previously operated or irradiated necks
- e. Moderate-to-severe active Graves' ophthalmopathy (GO)

Radioactive iodine therapy is highly favored in GD patients with the following clinical conditions:

- a. Females planning a pregnancy in the future (in more than 4–6 months following radioiodine therapy, provided thyroid hormone levels are normal),
- b. Individuals with comorbidities increasing surgical risk

- c. Patients with previously operated or externally irradiated necks, or lack of access to a high-volume thyroid surgeon
- d. Contraindications to ATDs use

Surgical procedures are recommended in patients with GD with the following conditions:

- a. Symptomatic compression or large goiters (≥ 80 g)
- b. Relatively low uptake of radioactive iodine
- c. When thyroid malignancy is documented or suspected (e.g., suspicious or indeterminate cytology);
- d. Large nonfunctioning, photopenic or hypofunctioning nodule
- e. Coexisting hyperparathyroidism requiring surgery
- f. Females planning a pregnancy in <4–6 months (i.e., before thyroid hormone levels would be normal if radioactive iodine were chosen as therapy), especially if TRAb levels are particularly high
- g. Patients with moderate-to-severe active GO

Contraindications to a particular modality as treatment for Graves' hyperthyroidism:

1. Radioactive iodine therapy: Definite contraindications include:
 - a. Pregnancy and lactation
 - b. Coexisting thyroid cancer or suspicion of thyroid cancer
 - c. Individuals unable to comply with radiation safety guidelines
 - d. Females planning a pregnancy within 4–6 months
 - e. Severe and active GO

2. ATDs

Definite contraindications to long-term ATD therapy include previous known major adverse reactions to ATDs

3. Surgery

Definite contraindications might include:

- a. Substantial comorbidity such as cardiopulmonary disease
- b. End-stage cancer
- c. Other debilitating disorders

1. Management of GD using ATDs

There are 2 classes of ATDs available: thiouracil (propylthiouracil (PTU)) and imidazoles (methimazole (MMI), carbimazole and thiamazole).

PTU is suggested as the preferred drug in the following conditions: during the first trimester of pregnancy; thyroid storm or thyroid crisis; and among those with history of allergy or intolerance to anti-thyroid drugs and who refuse to undergo radioactive iodine or surgical therapies.

Combination of ATDs with low-dosage L-thyroxine as hormone replacement therapy is generally not recommended.

The initial dose of PTU is high, starting with 100-200 mg three times daily, depending on the severity of the hyperthyroidism. As the clinical findings and thyroid function tests return to normal, reduction to a maintenance PTU dose of 50 mg two or three times daily, even once daily is usually possible as the maintenance dose.

As with PTU, at the start of MMI therapy, higher doses are advised (10–20 mg daily) to restore euthyroidism, following which the dose can be titrated to a maintenance level (generally 5–10 mg daily). MMI has the benefit of once-a-day administration and a reduced risk of major side effects compared to PTU.

An assessment of serum free T4 should be obtained about 4 weeks after initiation of therapy, until euthyroid levels are achieved with the minimal dose of medication. Once the patient is euthyroid, biochemical testing and clinical evaluation can be undertaken at intervals of 2–3 months.

Before initiating antithyroid drug therapy, requesting for baseline blood tests, primarily differential white blood cell count, bilirubin and transaminases may be considered.

2. Radioactive iodine therapy in GD

Patients with GD who are at increased risk for complications due to worsening of hyperthyroidism (i.e., those who are extremely symptomatic or have free T4 estimates 2–3 times the upper limit of normal) should be treated with beta-adrenergic blockade and/or ATDs prior to radioactive iodine therapy.

If given as pretreatment, MMI should be discontinued 3–5 days before the administration of radioactive iodine, restarted 3–7 days later, and generally tapered over 4–6 weeks as thyroid function normalizes.

A pregnancy test should be obtained within 48 hours prior to treatment in any female with childbearing potential who is to be treated with radioactive iodine. The treating physician should obtain this test and verify a negative result prior to administering radioactive iodine. Approximately 2 weeks after and prior to radioactive iodine therapy, high-iodine-containing foods such as seafoods and iodine-containing drugs are strictly prohibited. During 3 days following a radioactive iodine therapy, patients should be advised not to stay close (less than 5 meters in radius of distance) with children aged less than 13 years old and pregnant women. Patients are strictly prohibited to get pregnant in 6 months following radioactive iodine therapy; contraceptives are advisable during that period.

Follow-up within the first 1–3 months after radioactive iodine therapy for GD should include an assessment of free T4 and total T3. If after 3 months follow-up, the patient remains thyrotoxic, a second dose of radioactive iodine therapy shall be considered. Transient hypothyroidism following radioactive iodine therapy can rarely occur during 6 months following iodine therapy, with subsequent complete recovery of thyroid function. Therefore, hypothyroidism occurring during those first 6 months does not necessitate a thyroid hormone replacement therapy.

Thyroid hormone replacement therapy should be given accordingly for a lifetime basis. Every patient who undergo radioactive iodine therapy should be thoroughly explained regarding the occurrence of post therapy hypothyroidism and other substantial information related to radioactive iodine therapy.

3. Surgical management of patients with GD

Whenever possible, patients with GD undergoing thyroidectomy should be rendered euthyroid. In exceptional circumstances, when it is not possible to render a patient with GD euthyroid prior to thyroidectomy, the need for thyroidectomy is urgent, or when the patient is allergic to antithyroid medication, the patient should be adequately treated with beta-blockade and potassium iodide in the immediate preoperative period.

Surgical complications following thyroidectomy in GD patients are relatively scarce, i.e., hypoparathyroidism and vocal cord paralysis. Improved patient outcome, specifically complication rate, has been shown to be independently associated with high thyroidectomy surgeon volume.

Prognosis

GD prognosis is well-reflected with remission and relapse rates. Remission rates among adults are higher than children.

ATDs are able to induce permanent remission in 30-50% cases. If relapse occurs in GD patients treated with ATDs, then destructive therapy is more likely to be a more appropriate option. Following 12-18 months of ATDs administration, approximately more than 50% of patients will develop a relapse. Several studies reported that a high TSH-R Ab level prior to therapy discontinuation suspectedly related to high relapse rate.

T3/T4 ratio of more than 20 is related to more than 80% relapse risk. Low TSH level 4 weeks after ATDs discontinuation has been correlated with relapse occurrence in 70% cases. There is a correlation between thyroid volume and blood flow, in which this finding strengthened previous known correlation between large struma and high risk to recur. Superior thyroid artery

blood flow also has already been known as one of relapse risk predictors.

All patients shall be strictly-monitored for relapse occurrence after discontinuation of ATDs. Approximately 75% relapse events occurred in the first 3 months after discontinuation. If relapse does occur, further ATDs administration in a longer period shall be prescribed or destructive therapy is likely to be considered.

Hyperthyroidism in pregnancy

Patients with GD require prompt treatment with ATDs and should undergo frequent monitoring for signs of fetal and maternal hyper- and hypothyroidism. ATDs are now considered the mainstay of therapy for hyperthyroidism during pregnancy to help prevent perinatal complications.

Diagnosis

Clinical features that may indicate the presence of significant hyperthyroidism include failure to gain weight, heart intolerance, excessive sweating, and tachycardia, beyond that normally associated with pregnancy. Therefore clinical diagnosis indices such as Wayne's index is not appropriate to be used to diagnose hyperthyroidism in pregnancy.

We have to be aware of thyrotoxicosis in molar pregnancy when pulse rate > 100 bpm and/or when the fundus of uterus larger than 20 gestational weeks. (Bandung Study, 1992)

Biochemical evaluation

The diagnosis of hyperthyroidism in pregnancy should be made using serum TSH values, and either total T4 and T3 (with total T4 and T3 reference range adjusted at 1.5 times the nonpregnant range) or free T4 and free T3 estimations (with trimester-specific normal reference ranges).

In the first trimester serum TSH may be transiently suppressed (< 0.2 μ U/L), at time of peak hCG level and this must be considered in making diagnosis. Free T₄ is the parameter that has been most closely correlates with good fetal outcome. Serum TSH may still be suppressed in these patients and should not be used as the sole guide in treatment, although normalization of maternal TSH during ATDs therapy may indicate a need to reduce the dose of ATDs.

TRAb

GD as the cause of hyperthyroidism in pregnancy may be diagnosed from typical clinical findings, including the presence of GO and/or serum TRAb in hyperthyroid patients. TRAb levels should be measured when the etiology remains unclear.

TRAb measurement is indicated when the etiology could not be ascertained. Other indications are fetal tachycardia, fetal goiter on USG and intrauterine growth restriction.

Complications

Patients with this disorder should be treated at centers with specific expertise in this area. Maternal complications are miscarriage, pregnancy-induced hypertension, preterm delivery, congestive heart failure, thyroid storm and placenta abruption. Fetal complications are low birth weight, prematurity, small for gestational age, intrauterine growth restriction, stillbirth and thyroid dysfunction.

Management

Effective treatment of hyperthyroidism during pregnancy is necessary to prevent maternal, fetal, and neonatal complications. ATDs remain the treatment of choice for hyperthyroidism during pregnancy. The goal is to use the lowest possible dosage of antithyroid medication necessary to maintain the free T₄ in the upper one-third of the reference range or just above the normal range. Transient hCG-mediated thyrotropin suppression in early pregnancy should not be treated with antithyroid drug therapy.

Antithyroid drug therapy

Propylthiouracyl and methimazole should be used for hyperthyroidism due to GD that requires treatment during pregnancy. Propylthiouracil should be used when antithyroid drug therapy is started during the first trimester. Methimazole should be used when antithyroid drug therapy is started after the first trimester.

The initial recommended PTU dosage is 100 to 450 mg daily, depending on symptoms and results of thyroid function tests. The total dosage is divided into 3 daily doses. Methimazole can be initiated at 10 to 20 mg daily in 1 dose.

The dose of ATD should be kept as low as possible. Block-replacement therapy consisting of ATD plus levothyroxine should not be used in pregnancy. If a woman receiving such therapy becomes pregnant, therapy should be changed to an ATDs alone.

β -Adrenergic blockers, such as propranolol, 10 to 40 mg every 4 to 6 hours, or atenolol, 25 to 50 mg daily, are also recommended for treatment of hyperadrenergic symptoms present in hyperthyroidism, but should be discontinued once symptoms resolve or within the first few weeks of treatment.

Monitoring

At the initiation of therapy, women should be monitored every 2 weeks for titration of antithyroid drug dosage; the dosage should be decreased with the improvement of symptoms and signs (eg, weight gain and normalization of pulse rate) and free T₄. Once the free T₄ target is achieved, thyroid tests may be repeated every 2 to 4 weeks to keep the patient's free T₄ in the upper reference range with the lowest possible dosage of antithyroid drug. The presence

of detectable TSH is an indication to decrease the antithyroid drug dosage.

Patients who achieve euthyroidism with minimal dosages of ATDs and have a short duration of symptoms, undetectable or low TRAb titers, and small goiters may be able to discontinue ATDs during the last 4 to 8 weeks of pregnancy. Discontinuing medication before 32 weeks' gestation is not recommended because of the possibility that hyperthyroidism may recur.

Other management alternatives

Radioactive iodine therapy is contraindicated in pregnancy and lactation. A pregnancy test is mandatory for any woman of childbearing age who is receiving either diagnostic or therapeutic doses of radioactive iodine.

When thyroidectomy is necessary for the treatment of hyperthyroidism during pregnancy, the surgery should be performed if possible during the second trimester. Although it is the safest time, it is not without risk (4.5%-5.5% risk of preterm labor).

Breast feeding

MMI and PTU both appear in breast milk in small concentrations. However, because of potential to progress into hepatic necrosis in either mother or child from maternal PTU use, MMI is the preferred ATD in nursing mothers.

Patient counseling

Patients taking methimazole who decide to become pregnant should get a pregnancy test at the earliest suggestion of pregnancy and be switched to propylthiouracil as soon as possible in the first trimester and changed back to methimazole at the beginning of the second trimester. Similarly, we suggest that patients started on propylthiouracil during the first trimester be switched to methimazole at the beginning of the second trimester.

Prepregnancy counselling for all patients with hyperthyroidism or a history of hyperthyroidism is imperative. Before conception, a hyperthyroid patient may be offered ablative by iodine 131 (¹³¹I) or surgery or definitive treatment or medical therapy

Risks associated with both PTU and methimazole should be informed to patients. Close monitoring and follow-up throughout pregnancy with frequent blood tests and adjustment of ATDs are needed since reduction in drug dosages are commonly required.

Authors Disclosure

This review was written independently; no company or institution supported it financially. Authors declared no inherent conflicts of interest.

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