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DIAGNOSIS AND MANAGEMENT OF THYROID HORMONES DISORDERS

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TOPICS

- Physiologic of Thyroid Hormones.
- Thyroid Hormones Disorders.
- Hypothyroidism: Subclinical and Overt.
  - Hashimoto Thyroiditis.
- Hyperthyroidism: Subclinical and Overt.
  - Graves' Disease.

PHYSIOLOGIC OF THYROID HORMONES

Bowers J et al. Endocrine Rev 2013; 34: 556-589

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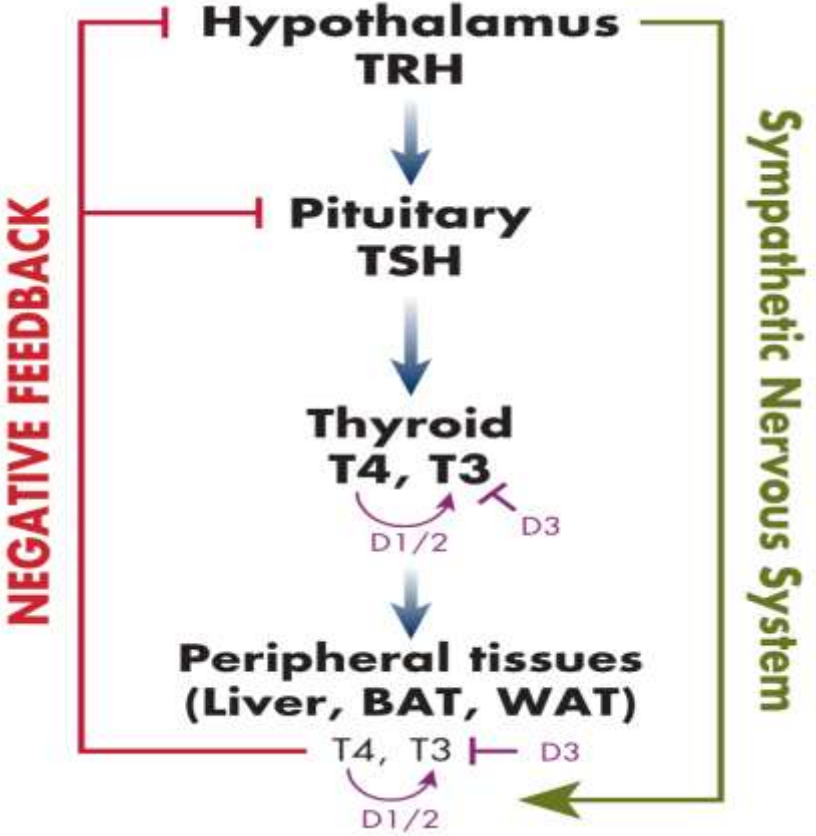
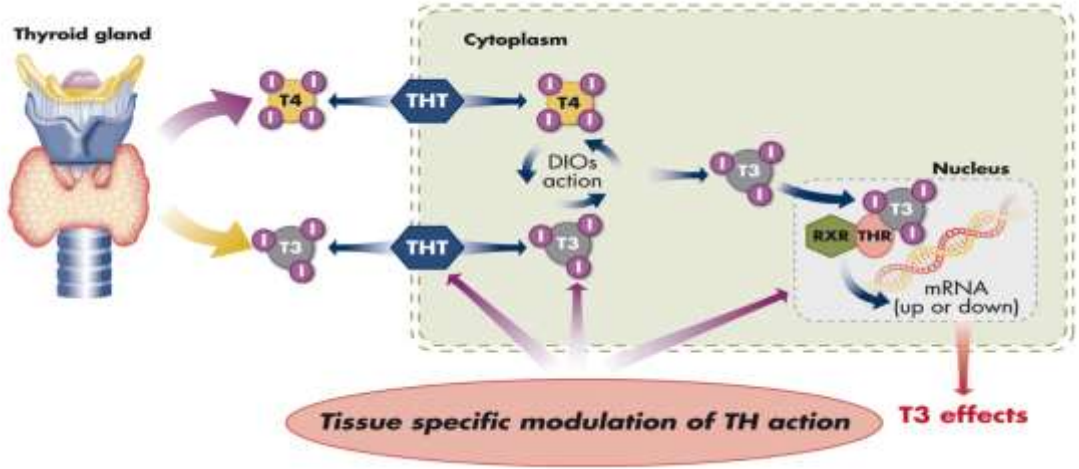


SIMPLIFIED OVERVIEW OF THE HPT AXIS

- Stimulation of the hypothalamus results in TRH release, which increases TSH secretion from the pituitary.
- TSH acts to increase TH production and secretion from the thyroid gland. Hypothalamic signals can also directly influence peripheral tissues via the SNS.
- THs are secreted into the circulation, and they enter target tissues such as liver, BAT, and white adipose tissue (WAT).
- The main form released into the blood is T4, which in turn can be locally activated into T3 by deiodinases D1 and 2.

PHYSIOLOGIC EFFECTS OF THYROID HORMONES



- Fetal development
- Oxygen consumption, heat production & free radical formation
- Cardiovascular effects
- Sympathetic effects
- Pulmonary effects
- Hematopoietic effects
- Gastrointestinal effects
- Skeletal effects
- Neuromuscular effects
- Effects on lipid & carbohydrate metabolism
- Endocrine effects

Cooper DS and Ladenson PW. 2018. The Thyroid Gland. In Greenspan's Basic and Clinical Endocrinology. Gardner DG and Shoback D (Eds.). 10th Edition, 2018
Bowers J et al. Endocrine Rev 2013; 34: 556-589

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THYROID HORMONES DISORDERS

WORK-UP:
STRUCTURE, FUNCTION, AND ETIOLOGY

- **Clinical features.**
- **Lab studies:**
  - **Screening: TSHs.**
  - Next step: FT4.
  - Further lab testing: thyroid antibodies (TRAb, Anti TPO), thyroglobulin, calcitonin (at high risk for medullary carcinoma of thyroid).
- **Imaging studies:**
  - Ultrasound.
  - CT scan or MRI.
  - Radionuclide uptake and radionuclide scan.

Graves disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety

CLASSIFICATION OF THYROID DYSFUNCTION: BIOCHEMICAL DEFINITION

TSH LEVEL, BY CONDITION	THYROID HORMONES	COMMENTS
Overt hyperthyroidism: <0.1 mIU/L or undetectable.	Elevated thyroxine or triiodothyronine.	-
Overt hypothyroidism: >4.5 mIU/L.	Low thyroxine.	-
Subclinical hyperthyroidism: <0.1 mIU/L.	Normal thyroxine and triiodothyronine.	Clearly low serum TSH.
0.1–0.4 mIU/L.	Normal thyroxine and triiodothyronine.	Low but detectable.
Subclinical hypothyroidism: 4.5–10.0 mIU/L.	Normal thyroxine.	Mildly elevated TSH.
>10 mIU/L.	Normal thyroxine.	Markedly elevated TSH.

Rugge JB et al. Screening and Treatment of Thyroid Dysfunction: An Evidence Review for the U.S. Preventive Services Task Force. Ann Intern Med 2015; 162: 35-45. doi:10.7326/M14-1456.

HYPOTHYROIDISM: SUBCLINICAL AND OVERT

IMPORTANT CAUSES OF HYPOTHYROIDISM

Primary:

- **Hashimoto's thyroiditis.**
- Radioactive iodine therapy.
- Thyroidectomy.
- Excessive iodide intake (kelp, radiocontrast dyes).
- Subacute thyroiditis (usually transient).
- Iodide deficiency.
- Inborn errors of thyroid hormone synthesis.
- Drugs: lithium, IF-alpha, amiodarone.

Secondary:

- Pituitary adenoma, pituitary ablative therapy, pituitary destruction.

Tertiary:

- Hypothalamic dysfunction (rare).

Peripheral resistance to the action of thyroid hormone.

PRESENTING FEATURES OF HYPOTHYROIDISM

- Exhaustion.
- Somnolence.
- Slow cognition.
- Intolerance to cold.
- Constipation.
- Depression.
- Weight gain.
- Calf stiffness.
- Menstrual disturbance.
- Carpal tunnel syndrome.
- Hearing impairment.
- Dry, thin and pale skin.

- Puffiness below the eyes.
- Bradycardia.
- Slow relaxing tendon reflexes.
- Coarsening of facial features.
- Pleural effusion.
- Pericardial effusion.
- Ascites.
- Non-pitting edema of lower leg.
- Hyponatraemia.
- Hypercholesterolaemia.
- Impaired consciousness (myxoedema coma).

DIAGNOSIS OF HYPOTHYROIDISM

- **History and physical examination.**
- **Laboratory examination:**
  - ↑TSHs.
  - ↓FT4, FT3.
- **Autoantibodies:**
  - TPO antibody (+).
  - Thyroglobulin antibody (+).
- **Radiography.**
- **Biopsy.**

ALGORITHM FOR PRAGMATIC MANAGEMENT OF PRIMARY HYPOTHYROIDISM IN NON-PREGNANT

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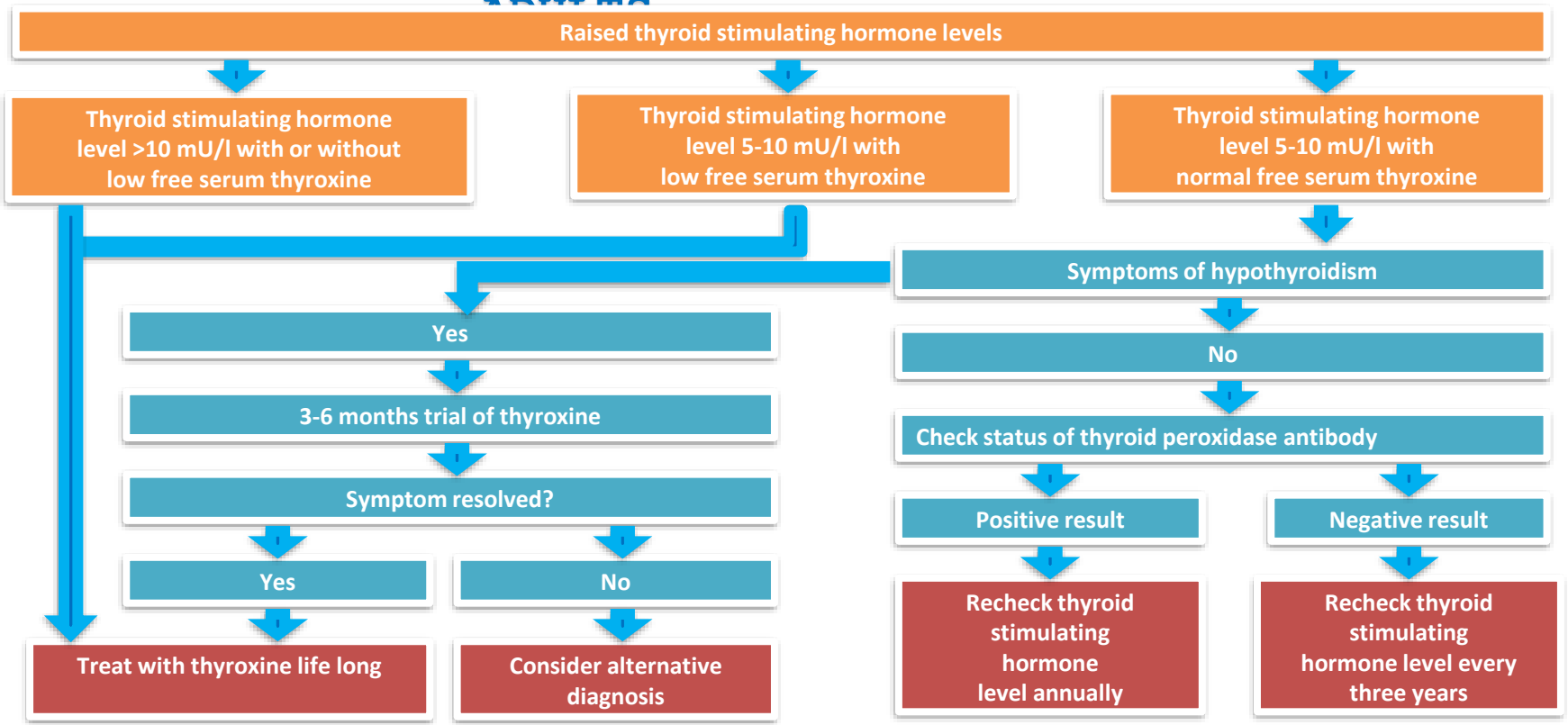

Vaidya B and Peacrce SHS. BMJ 2008; 337: 284-289

FACTORS FAVORING

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LEVOTHYROXINE THERAPY IN PATIENTS WITH A TSH LEVEL OF 5 TO 10 MIU/L AND NORMAL FT4 (SUBCLINICAL

- Pregnancy or intention of pregnancy.
- Goiter.
- Therapeutic trial for possible hypothyroid symptoms.
- Patient preference.
- Childhood and adolescence.
- 2 TSH levels >8 mIU/L.
- Bipolar disorder, depression.
- Infertility.
- Presence of antithyroid antibodies.
- Progressive TSH increase.
- Ovulatory dysfunction.
- Young age of the patient.
- Hyperlipidemia?

THYROXINE THERAPY

- Initial dose: 50-75 mg/day.
- Patients with CAD: 12.5-25 mg/day.
- Dose can be increased.
- TSH should be measured 4-6 weeks after therapy begun then annually once the levels become stable.

HASHIMOTO THYROIDITIS

HASHIMOTO THYROIDITIS DEFINITION & DIAGNOSIS

- HT: chronic inflammation of the thyroid **the most common autoimmune disease**, the most common endocrine disorder, as well as the most **common cause of hypothyroidism**.
- Based on the etiology, HT can be classified into primary and secondary forms.
- Established by a combination of clinical features, presence of serum antibodies against thyroid antigens (mainly to **thyroperoxidase and thyroglobulin**), and appearance on thyroid sonogram.
- Thyroid uptake of radioactive iodine and cytological examination of thyroid aspirate are used more rarely.
- Clinical features:
  - Local manifestations originate from compression of the cervical structures that are anatomically close to the thyroid gland, and include dysphonia (from involvement of the recurrent laryngeal nerve), dyspnea (from restriction of the trachea), and dysphagia (from impingement upon the esophagus).
  - Systemic manifestations originate from loss of function of the thyroid gland and subsequent primary hypothyroidism.

P. Caturegli et al. Autoimmunity Reviews 13 (2014) 391–397

HASHIMOTO THYROIDITIS MANAGEMENT

- HT is mainly a **medical disease**.
- Thyroidectomy is nowadays performed when there are signs and symptoms of severe cervical compression, upon patient's request for cosmetic reasons, or, more commonly, when the patient has a thyroid nodule with a cytology "suspicious" for malignancy and the clinician does not know whether the patient has just HT (where no surgery would be required) or HT and thyroid cancer (where instead surgery is indicated).
- **The therapy** of the primary and permanent hypothyroidism seen in many forms of HT consists in the daily, lifelong, oral administration of synthetic **levo-thyroxine** (L-T4), which is given at doses of 1.6- 1.8 μg per kg of body weight.

P. Caturegli et al. Autoimmunity Reviews 13 (2014) 391–397

HYPERTHYROIDISM: SUBCLINICAL AND OVERT

CAUSES OF HYPERTHYROIDISM

Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists

Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck:

- Grave's disease.
- Toxic adenoma or Toxic multinodular goiter.
- Trophoblastic disease.
- TSH-producing pituitary adenomas.
- Resistance to thyroid hormone (T3 receptor mutation).

Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck:

- Painless (silent) thyroiditis.
- Amiodarone-induced thyroiditis.
- Subacute (granulomatous, de Quervain's) thyroiditis.
- Iatrogenic thyrotoxicosis.
- Factitious ingestion of thyroid hormone.
- Struma ovarii.
- Acute thyroiditis.
- Extensive metastases from follicular thyroid cancer.

Bahn RS et al. Thyroid 2011; 21: 593-646

MANIFESTATIONS OF HYPERTHYROIDISM

SYMPTOMS

- Hyperactivity, irritability, altered mood, insomnia.
- Heat intolerance, increased sweating.
- Palpitations.
- Fatigue, weakness.
- Dyspnea.
- Weight loss with increased appetite (weight gain in 10 percent of patients).
- Pruritus.
- Increased stool frequency.
- Thirst and polyuria.
- Oligomenorrhea or amenorrhea, loss of libido.

SIGNS

- Sinus tachycardia, atrial fibrillation.
- Fine tremor, hyperkinesis, hyperreflexia.
- Warm, moist skin.
- Palmar erythema, onycholysis.
- Hair loss.
- Muscle weakness and wasting.
- Congestive (high-output) heart failure, chorea, periodic paralysis (primarily in Asian men), psychosis*

Weetman AP. NEJM 2000; 343: 1236-1248

GRAVES' DISEASE

MANIFESTATIONS OF GRAVES' DISEASE

- **Diffuse goiter.**
- **Ophthalmopathy.**
  - A feeling of grittiness and discomfort in the eye.
  - Retrobulbar pressure or pain.
  - Eyelid lag or retraction.
  - Periorbital edema, chemosis, scleral injection.
  - Exophthalmos (proptosis).
  - Extraocular-muscle dysfunction.
  - Exposure keratitis.
  - Optic neuropathy.
- **Localized dermopathy.**
- Lymphoid hyperplasia.
- Thyroid acropachy.

Bartalena L and Tanda ML. NEJM 2009; 360: 994-1001

Weetman AP. NEJM 2000; 343: 1236-1248

Fatourechi V et al. JCEM 2002; 87: 5435-5441

Schwartz KM et al. JCEM 2002; 87: 438-446

ALGORITHM FOR THE MANAGEMENT OF A PATIENT WITH GRAVES' HYPERTHYROIDISM (ETA, 2018)

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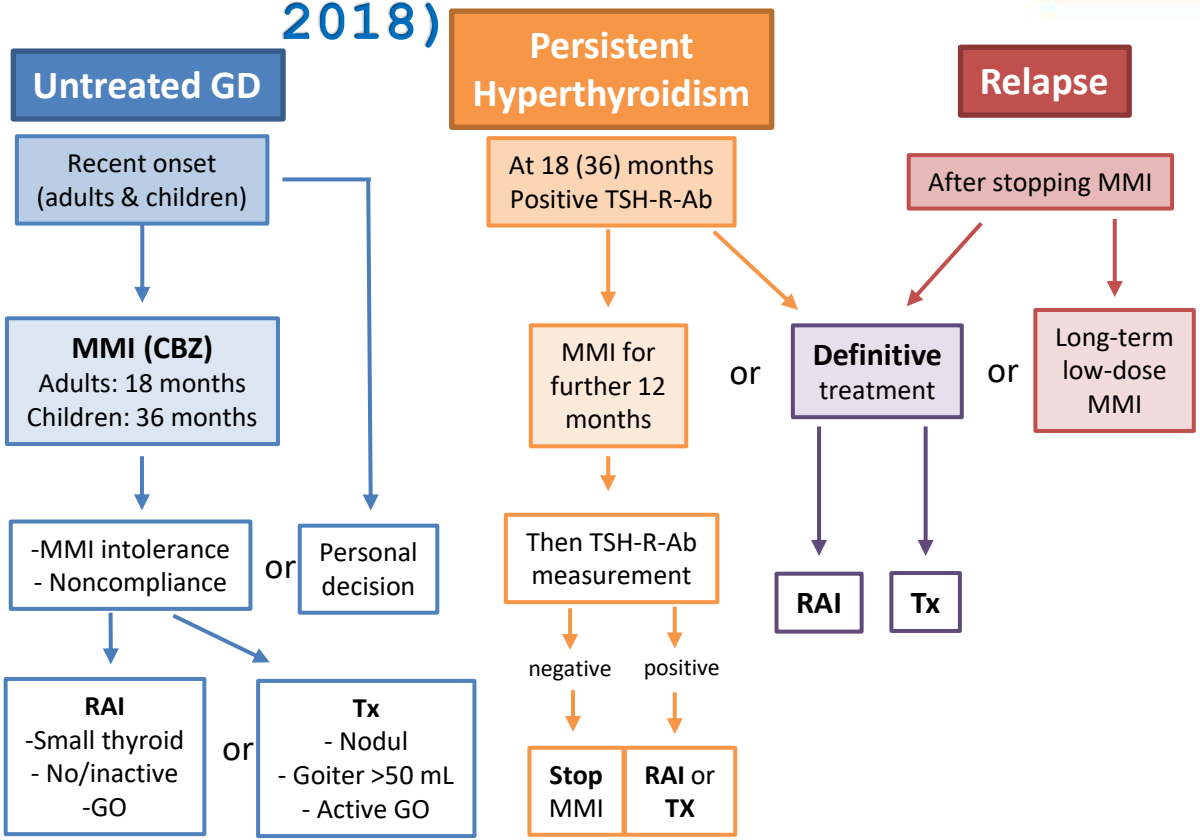

Kahaly GJ et al. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 2018;7:167–186

ADVERSE EVENTS OF ANTITHYROID DRUGS

Common (1.0–5.0%)

- Skin rash.
- Urticaria.
- Arthralgia, polyarthritis.
- Fever.
- Transient mild leukopenia.

Rare (0.2–1.0%)

- Gastrointestinal.
- Abnormalities of taste and smell.
- Agranulocytosis.

Very rare (<0.1%)

- Aplastic anemia (PTU, CBZ).
- Thrombocytopenia (PTU, CBZ).
- Vasculitis, lupus-like, ANCA+ (PTU).
- Hepatitis (PTU).
- Hypoglycemia (anti-insulin Abs; PTU).
- Cholestatic jaundice (CBZ/MMI).

ANCA, antineutrophil cytoplasmic antibody.

Kahaly GJ et al. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 2018;7:167–186

BETA-ADRENERGIC RECEPTOR BLOCKADE IN THE TREATMENT OF THYROTOXICOSIS

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2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Drug	Dosage	Frequency	Considerations
Propanolol	10–40 mg	3–4 times per day	Nonselective β-adrenergic receptor blockade Longest experience May block T_4 to T_3 conversion at high doses Preferred agent for nursing and pregnant mothers
Atenolol	25-100 mg	1–2 times per day	Relative β-1 selectivity Increased compliance Avoid during pregnancy
Metoprolol	25-50 mg	2–3 times per day	Relative β-1 selectivity
Nadolol	40-160 mg	1 times per day	Nonselective b-adrenergic receptor blockade Once daily Least experience to date May block T_4 to T_3 conversion at high doses
Esmolol	IV pump 50–100 lg/kg/min		In intensive care unit setting of severe thyrotoxicosis or storm

Ross DS et al. THYROID Volume 26, Number 10, 2016. DOI: 10.1089/thy.2016.0229

THE RECOMMENDED FREQUENCY OF THYROID FUNCTION TESTING FOR PATIENTS RECEIVING DIFFERENT ANTI- THYROID TREATMENTS

Anti-thyroid Treatment	Recommended Frequency Of Thyroid Function Testing	
	Frequency of testing	**Period during which thyroid function is tested**
Carbimazole	Every 4–6 weeks	From starting carbimazole until euthyroidism has been established on a maintenance dose of 5–15 mg daily
	Every 3 months	From establishing euthyroidism on a maintenance dose until 1 year after stopping carbimazole
	Annually	If euthyroidism persists 1 year after stopping carbimazole
Radioiodine and Thyroidectomy	Initial test	Check thyroid function 4–8 weeks after treatment
	Every 3 months	From 4 to 8 weeks after treatment until 1 year after treatment
	Annually	If euthyroidism persists 1 year after treatment

Grayston F. InnovAiT, Vol. 4, No. 12, pp. 698–705, 2011

THERAPY OF HYPERTHRYROIDISM IN PREGNANCY

2017 Guideline of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

- PTU is recommended through 16 weeks of pregnancy.
- Receiving MMI is switched to PTU as early as possible.
- When shifting from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g., MMI 5mg/d = PTU 50 mg twice daily).
- FT4/ TT4 and TSH should be monitored every 4 weeks.
- The lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at the upper limit or moderately above the reference range.

Alexander EK et al. THYROID 27, 3, 2017. DOI: 10.1089/thy.2016.0457

SUMMARY

- Thyroid hormones disorders are the second frequent diseases in endocrinology after diabetes mellitus.
- Thyroid hormones disorders included hypothyroidism and hyperthyroidism.
- Most common causes of hypothyroidism: hashimoto thyroiditis, total thyroidectomy and radioactive iodine ablation.
- Most common cause of hyperthyroidism: graves disease.
- Prompt treatment with levothyroxine is required for hypothyroidism and anti thyroid drugs, radioactive iodine ablation or thyroidectomy for hyperthyroidism.


thank
you