



# Hyperthyroidism

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## Objectives:

- 1- Describe different classes of drugs used in hyperthyroidism and their mechanism of action.
- 2- Understand their pharmacological effects, clinical uses and adverse effects.
- 3- Recognize treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and thyroid storm.

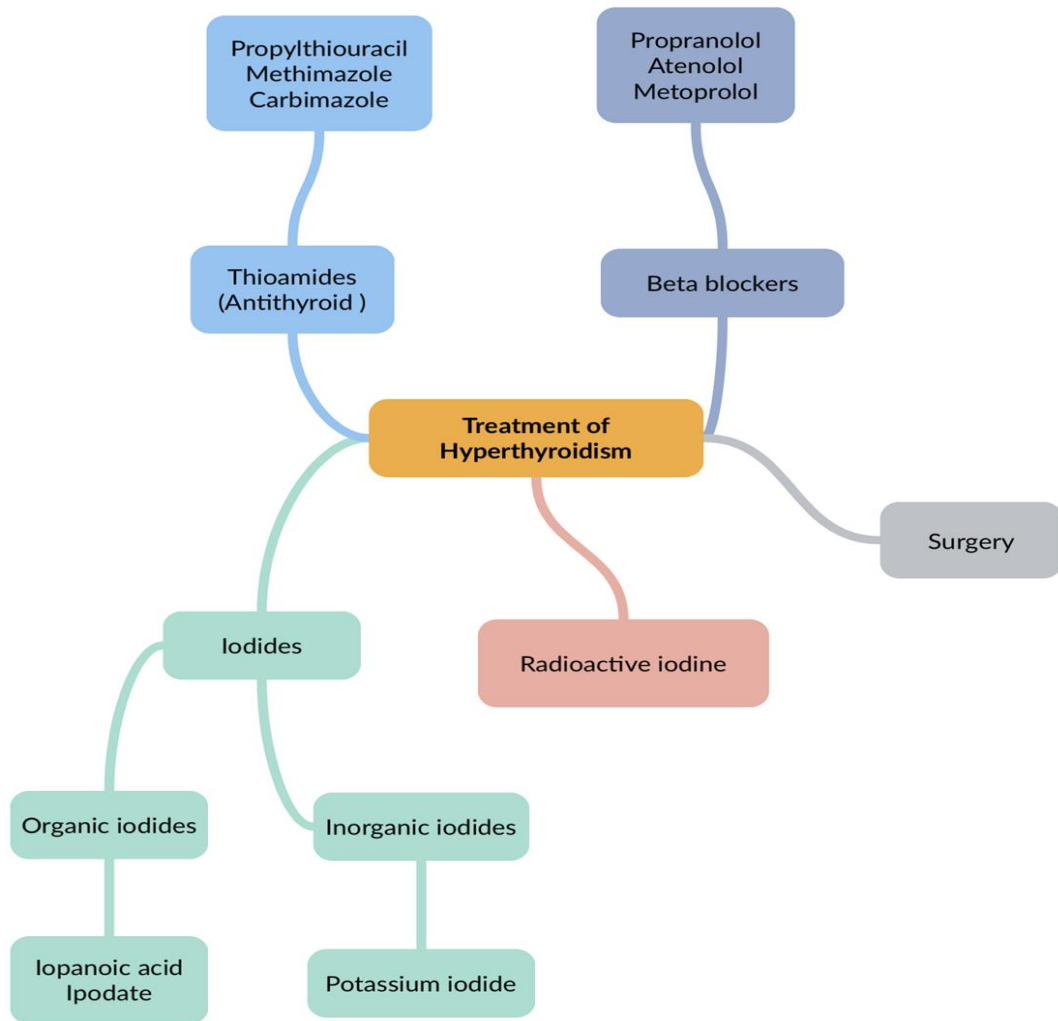
Color index:

Important

Note

Extra

# Mind Map



# Introduction

## Thyroid function

- Normal amount of thyroid hormones are essential for **normal growth and development** by maintaining the level of energy metabolism in the tissue.
- Either too little or too much thyroid hormones will bring disorders to the body.

### -Important functions are:

- Growth & development, especially in the embryo & brain
- Thermoregulation: increase basal metabolic rate (BMR)
- Helps maintain metabolic energy balance
- CVS: increase heart rate & cardiac output which increase oxygen demand

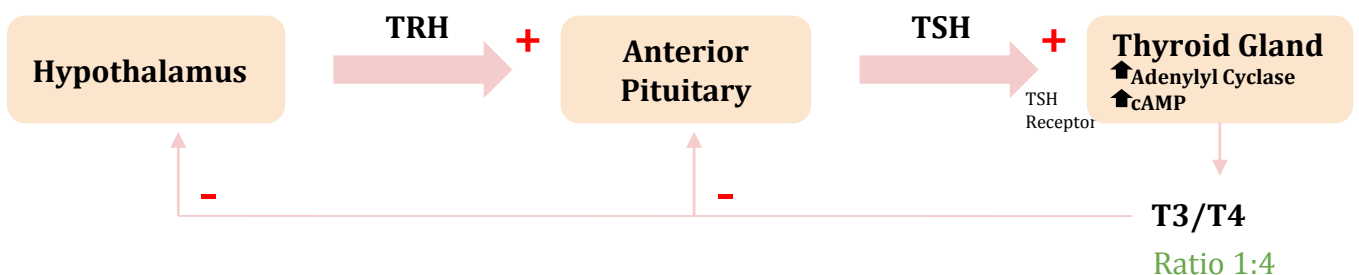
# Iodine Importance \ metabolism:

- Thyroid hormones are unique biological molecules in that they incorporate iodine in their structure
- Adequate iodine intake (diet, water) is required for normal thyroid hormone production
- Major sources of iodine:- iodized salt, iodized bread, dairy products, shellfish
- Minimum requirement: 75 micrograms/day
- Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys)
- Iodide taken up by the thyroid gland is **oxidized** by **peroxidase** in the lumen of the follicle:  

$$\text{I}^- \xrightarrow{\text{H}_2\text{O}_2} \text{I}_2$$
site of action of antithyroid drugs (h<sub>2</sub>o<sub>2</sub> = peroxidase)
- **Oxidized** iodine can then be used in production of thyroid hormones

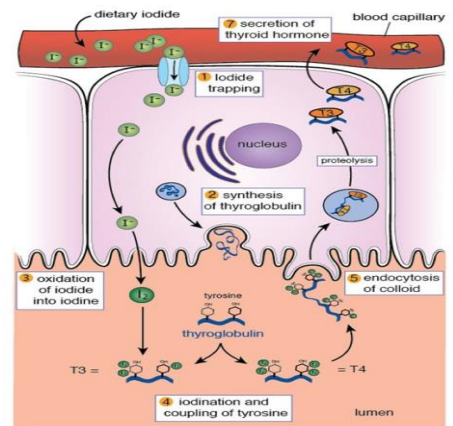
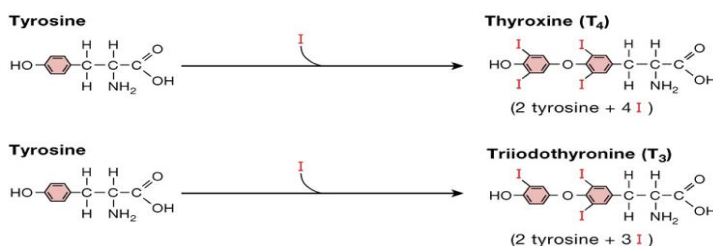
## Thyroid regulation

1. **Hypothalamus** secretes Thyrotropin- Releasing Hormone (**TRH**) which stimulates synthesis & release of thyrotropin (Thyroid Stimulating Hormone or (**TSH**) by the anterior pituitary.
2. TSH then stimulates the thyroid gland to uptake iodine, synthesize & release T<sub>4</sub> & T<sub>3</sub>, by increasing adenyl cyclase and cAMP.
3. T<sub>4</sub> & T<sub>3</sub> levels feedback to both hypothalamus & pituitary affecting the release of TRH & TSH.
4. Thyroid hormones exert negative feedback on TSH release at the level of the anterior pituitary:
  - Inhibition of TSH synthesis receptors.
  - Decrease in pituitary receptor for TRH.
5. TSH release is influenced by hypothalamic (TRH), and by thyroid hormones themselves.

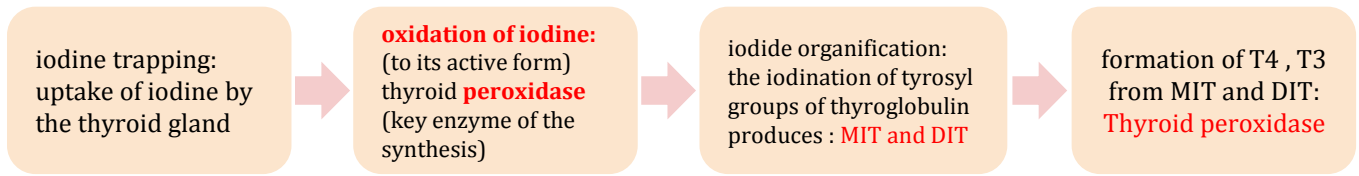


## Thyroid Hormones

- tetraiodothyronine (**T<sub>4</sub>**; thyroxine)
- triiodothyronine (**T<sub>3</sub>**)



# Thyroid Hormones Synthesis



# Thyroid Hormones Disorders

Goiter can be with hyper or hypothyroidism\*

## HYPOTHYROIDISM:

Refers to disorders in which the thyroid gland secretes decreased amounts of hormones

## Thyroid neoplasia:

Benign enlargement or malignancies of the gland

## THYROTOXICOSIS :

Is the term for all disorders with increased levels of circulating thyroid hormones

## HYPERTHYROIDISM :

Refers to disorders in which the thyroid gland secretes increased amounts of hormones

Differences are very important

THYROTOXICOSIS	HYPERTHYROIDISM
Hypermetabolic state caused by thyroid hormone excess at the tissue level	Increased thyroid hormones synthesis and secretion
<b>Not all patients with thyrotoxicosis have hyperthyroidism</b>	<b>All patients with hyperthyroidism have thyrotoxicosis</b>

# Causes of thyrotoxicosis

**RAIU:** radioactive iodine uptake

## With high RAIU

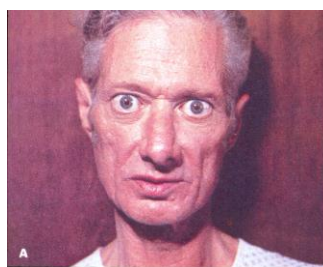
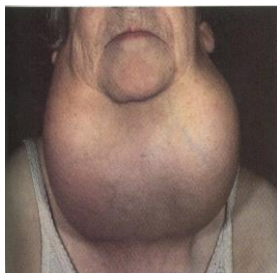
- Graves' disease (60-80%)
- Multinodular goitre (14%)
- Adenomas / carcinomas

## With low RAIU

- Thyroiditis
- Iodine-induced thyrotoxicosis:
  - drugs (e.g. amiodarone antiarrhythmic drug )
  - radiografic contrast media

# Features of Graves' Disease (Diffuse Toxic Goiter)

- ❖ Caused by thyroid stimulating immunoglobulins that stimulate TSH receptor resulting in sustained thyroid over activity.
- ❖ Mainly in young adults aged 20 to 50 , 5 times more frequent in women.
- ❖ Swelling and soft tissues of hands and feet- Clubbing of fingers and toes.
- ❖ Half of cases have Exophthalmos (not seen with other causes of hyperthyroidism)
- ❖ 5% have pretibial myxedema (thyroid dermatopathy)



51 year old male who presented with urinary retention and proved to have Graves Disease



Pretibial myxedema and "square toes" in the same patient

# Features of Toxic Multinodular Goiter

- ❖ Second most common cause of hyperthyroidism
- ❖ Most cases in women in 5th to 7th decades
- ❖ Often have long standing goiter
- ❖ Symptoms usually develop slowly

## THYROTOXICOSIS

Symptoms	Signs
Irritability Dysphoria Heat intolerance & sweating Palpitations Fatigue & weakness Weight loss Diarrhea	Arrhythmias Thyroid enlargement Warm, moist skin Exophthalmos Pretibial myxedema

# Treatment of Hyperthyroidism

Thioamides  
(antithyroid  
drugs)

Iodides

Radioactive  
iodine

Beta blockers

Surgery

## Thioamides

Drug	Propylthiouracil (PTU)	Methimazole & Carbimazole
<b>M.O.A</b>	<b>Inhibit synthesis of thyroid hormones by inhibiting the <u>peroxidase</u> enzyme that catalyzes the iodination of tyrosine residues.</b>	
	PTU ( <b>but</b> not methimazole) blocks the conversion of T4 to T3 in peripheral tissues.	Carbimazole is a <b>prodrug converted to the active metabolite methimazole</b> .
<b>Absorption</b>	Rapidly absorbed	Rapidly absorbed
<b>Protein binding</b>	80-90% <b>high</b>	Most of the drug is free <b>low</b>
<b>Accumulation</b>	in thyroid	in thyroid
<b>Excretion</b>	Kidneys as inactive metabolite within 24 hrs <b>faster</b>	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs <b>slower</b>
<b>Half life</b>	1.5 hrs (short)	6 hrs (long)
<b>Administration</b>	Every 6-8 hours	Every 8 hours
<b>Pregnancy</b>	Crosses placenta less. <b>Recommended in pregnancy</b> (Crossing placenta is less readily as it is highly protein bound)	Concentrated in Thyroid & crosses placenta.  Not recommended in pregnancy
<b>Breast feeding</b>	Less secreted in breast milk <b>Recommended</b>	Secreted Not recommended

# Thioamides cont.

Adverse Effect	Frequency	Comments
<b>Skin reactions</b>	4-6%	Urticarial or macular reactions
<b>Arthralgia</b>	1-5%	
<b>Polyarthritis</b>	1-2%	So-called anti-thyroid arthritis
<b>GIT effects</b>	1-5%	Gastric distress and nausea
<b>Immunoallergic hepatitis **</b>	0.1-0.5%	Almost exclusively in patients taking <b>propylthiouracil</b>
<b>Agranulocytosis</b> Both drugs due to chronic administration	0.1-0.5%	Seen in patients with Graves' disease; occurs within 90 days of treatment <b>precaution: frequent blood count should be done</b>
<b>ANCA-positive vasculitis</b> <i>(Anti-neutrophil cytoplasmic antibodies)**</i>	Rare	With <b>propylthiouracil</b>
<b>Abnormal sense of taste or smell**</b>	Rare	With <b>methimazole</b> only

## Warnings (male slides only)

- **Agranulocytosis:**

Patients on PTU or methimazole should be instructed to immediately report to their physicians any symptoms suggestive of agranulocytosis, such as fever or sore throat.

- **Congenital Malformations:**

Methimazole crosses the placental causing fetal harm, when administered in the first trimester of pregnancy.

# IODINE

## (Lugol's solution, potassium iodide)

<b>Drug</b>	<b>Organic iodides as : iopanoic acid or ipodate</b>	<b>Potassium iodide</b>
<b>M.O.A</b>	<ul style="list-style-type: none"> <li>• <b>Inhibit thyroid hormone synthesis and release</b></li> <li>• <b>Block the peripheral conversion of T4 to T3</b></li> </ul> <p>We give iodine in excess, and anything in excess will cause inh</p>	
<b>P.K</b>	The <u>effect is not sustained</u> ( produce a <b>temporary remission of symptoms</b> this is why we use it before surgery ) (rapid + temporary)	
<b>Uses</b>	<ul style="list-style-type: none"> <li>• <b>Prior to thyroid surgery</b> to decrease <b>vascularity &amp; size of the gland</b></li> <li>• Following radioactive iodine therapy</li> <li>• Thyrotoxicosis</li> </ul>	
<b>Precautions /toxicity</b>	<ul style="list-style-type: none"> <li>• Should not be used as a single therapy</li> <li>• Should <b>not</b> be used in <b>pregnancy</b></li> <li>• <b>May produce iodism</b> ( Rare, as iodine is not much used now)</li> </ul> <p><b>Iodism Symptoms:</b> (skin rash , <b>hypersalivation</b>, oral ulcers, <b>metallic taste</b>, <b>bad breath</b>).</p> <p>scenario : a patient with hyperthyroidism was treated with and then developed hypersalivation and bad breath. What drug was he treated with? <b>Iodine</b></p>	

# ADRENOCEPTOR BLOCKING AGENTS

<b>Drug</b>	<b>Propranolol</b>	<b>Atenolol</b>	<b>Metoprolol</b>
<b>M.O.A</b>	• Adjunctive therapy to relieve the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.		
<b>C.I</b>	• <b>Propranolol</b> is <b>contraindicated in asthmatic patients</b> because propranolol is not selective and will cause bronchoconstriction		



# RADIOACTIVE IODINE ( RAI )

<b>M.O.A</b>	<ul style="list-style-type: none"><li>● <b><math>^{131}\text{I}</math> isotope ( therapeutic effect due to emission of <math>\beta</math> rays )</b></li><li>● <b>Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.</b></li></ul>
<b>P.K</b>	<ul style="list-style-type: none"><li>● Clinical improvement may take <b>2-3 months</b>.</li><li>● Half -life 5 days.</li><li>● Cross placenta &amp; excreted in breast milk. → <b>contraindicated during pregnancy and breastfeeding</b></li><li>● Available as a solution or in capsules.</li></ul>
<b>Uses</b>	<ul style="list-style-type: none"><li>● Hyperthyroidism mainly in old patients (above 40)</li><li>● Graves, disease</li><li>● Patients with toxic nodular goiter</li><li>● <b>As a diagnostic</b></li></ul> <p>This drug is used both diagnosis and treatment.</p>
<b>Advantages</b>	<ul style="list-style-type: none"><li>● Easy to administer ,effective , painless and less expensive.</li></ul>
<b>Disadvantages</b>	<ul style="list-style-type: none"><li>● High incidence of delayed hypothyroidism</li><li>● Large doses have cytotoxic actions ( necrosis of the follicular cells followed by fibrosis )</li><li>● May cause genetic damage</li><li>● May cause leukemia &amp; neoplasia</li></ul>

## Thyrotoxicosis during pregnancy

- Better to start therapy before pregnancy with  $^{131}\text{I}$  or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
- **During pregnancy radioiodine is contraindicated.**
- **Propylthiouracil is the drug of choice during pregnancy.**

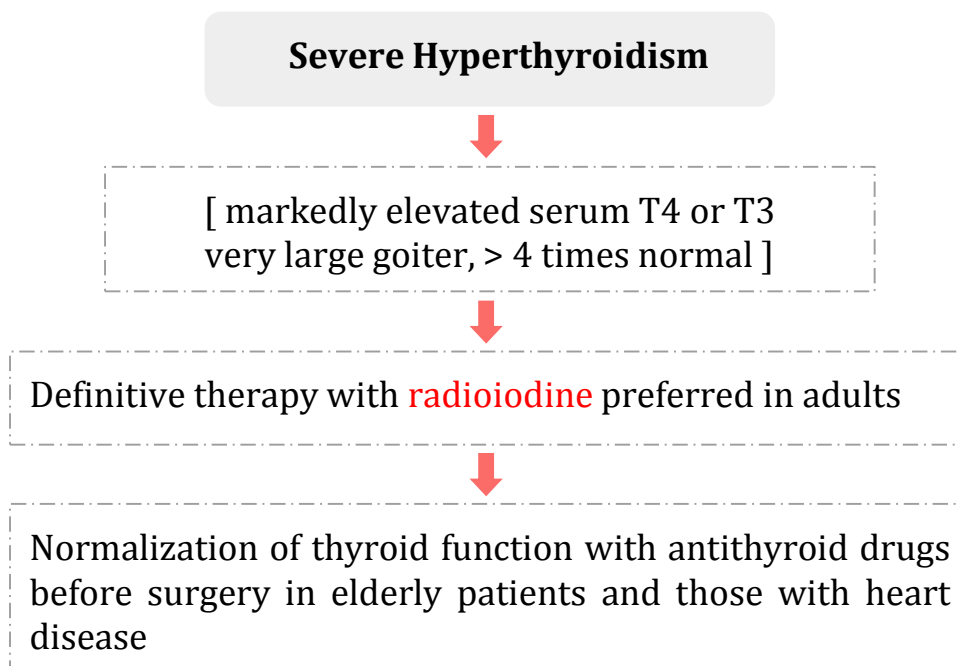
# Thyroid Storm

- A sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome.
- There is hypermetabolism, and excessive adrenergic activity, death may occur due to heart failure and shock.
- It is a medical emergency.

## Management of Thyroid Storm (IMP)\*\*

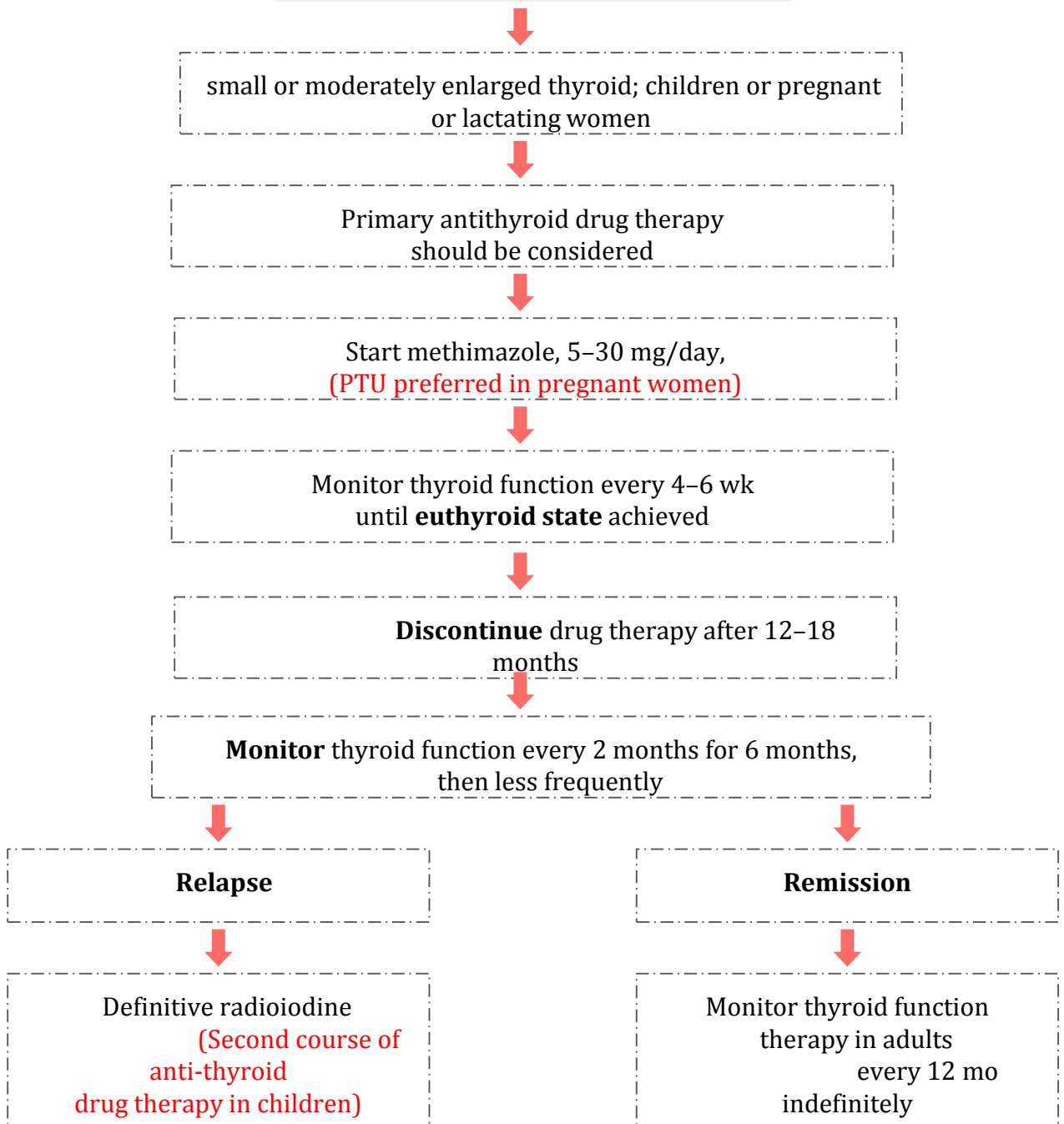
- Should be treated in an ICU for close monitoring of vital signs and for access to invasive monitoring and inotropic support
- Correct electrolyte abnormalities, Treat cardiac arrhythmia (if present) & Aggressively control hyperthermia by applying **ice packs**
- Promptly administer antiadrenergic drugs (e.g. **propranolol**) to minimize sympathomimetic symptoms **what is the life saving drug in thyroid storm? Propranolol \*\***
- **High-dose Propylthiouracil (PTU)** is preferred because of its early onset of action (**risk of severe liver injury and acute liver failure**)
- Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube
- **Hydrocortisone** 50 mg IV every 6 hours **to prevent shock.**
- Rarely, plasmapheresis has been used to treat thyroid storm

## Management of Hyperthyroidism due to Graves' disease



# Management of Hyperthyroidism due to Graves' disease

## Mild/Moderate hyperthyroidism



## Thyroidectomy

- Subtotal thyroidectomy is the treatment of choice in very large gland or multinodular goiter  
Why do we do subtotal thyroidectomy instead of removing the whole gland? To leave a portion that can secrete hormones

# MCQs

1- a 50 year old woman presented to the clinic complaining of weight loss, heat intolerance and excessive sweating. On examination she had an obvious goiter and bulging of her eyes.the doctor prescribed for her propylthiouracil. What is this drug's mechanism of action?

- a) inhibit peroxidase enzyme.
- b) Blocks conversion of T4 to T3 in peripheral tissues.
- c) Destroy the parenchymal cells of the thyroid.
- d) Both A&B

2-which of the following is the drug of choice in treating a pregnant woman with hyperthyroidism?

- a) methimazole
- b) Carbimazole
- c) Propylthiouracil
- d) Radioactive iodine

3- which of the following side effects is rare but exclusive to propylthiouracil?

- a) abnormal sense of taste and smell
- b) Urticaria
- c) Agranulocytosis
- d) Immunoallergic hepatitis

4- a patient with hyperthyroidism developed vasculitis. Tests were done and her serum was positive for anti neutrophil cytoplasmic antibodies.which of the following drugs was she most likely on ?

- a) propylthiouracil
- b) Methimazole
- c) Carbimazole
- d) Potassium iodide

5- a patient was scheduled for partial thyroidectomy , which of the following drugs is used prior to the surgery to reduce the vascularity and size of the gland ?

- a) Potassium iodide
- B) propylthiouracil
- c) methimazole
- d) radioactive iodine

6- a patient with hyperthyroidism developed hypersalivation and oral ulcers. Which drug was the patient most likely on ?

- a) Methimazole.
- b) Carbimazole.
- c) Potassium iodide.
- d) Propranolol.

7- an asthmatic patient with hyperthyroidism is suffering from tachycardia, tremors, and palpitation. All of the following can be used to relieve his symptoms except:

- a) Atenolol
- b) Metolol
- c) Propranolol
- d) bisoprolol

8- which of the following side effects is most likely to develop in a patient with Graves' disease after prolonged treatment with methimazole?

- a) Immunoallergic hepatitis
- b) Agranulocytosis.
- c) ANCA-positive vasculitis
- d) Hypersalivation.

9- what is the treatment of choice in multinodular goiter?

- a) Radioactive iodine.
- b) Propylthiouracil
- c) Sub-total thyroidectomy.
- d) Methimazole.

## SAQ

A patient with hyperthyroidism developed a sudden acute exacerbation of all of the symptoms of thyrotoxicosis, the doctor said that it is a case of "thyroid storm" and is life threatening if not managed properly. What is the line of treatment in this case?

- 1- correct electrolytes abnormalities, and control hyperthermia with ice packs.
- 2- administration of **anti-adrenergic** drugs.
- 3- High dose of **propylthiouracil** intravenously.
- 4- administer **iodine** compounds orally.
- 5- **Hydrocortisone** to prevent shock.

Mention 3 side effects of the antithyroid drug propylthiouracil.

- 1- polyarthrititis.
- 2- immunoallergic hepatitis.
- 3- ANCA- positive vasculitis.

MCQ answers:

- 1) D
- 2) C
- 3) D
- 4) A
- 5) A
- 6) C
- 7) C
- 8) B
- 9) C



## Team Leaders:

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## Thanks for those who worked on the lectures :

Noura ALOthaim  
Khulood ALWehaibi  
Rinad Alghoraiby  
Ghada ALQarni  
Dana ALKadi  
Dana ALRasheed  
Sara ALSultan  
Alanoud ALMufarrej  
Ghada ALMuhanna  
Munira ALHadlg  
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## References:

✓ Doctors' slides and notes



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