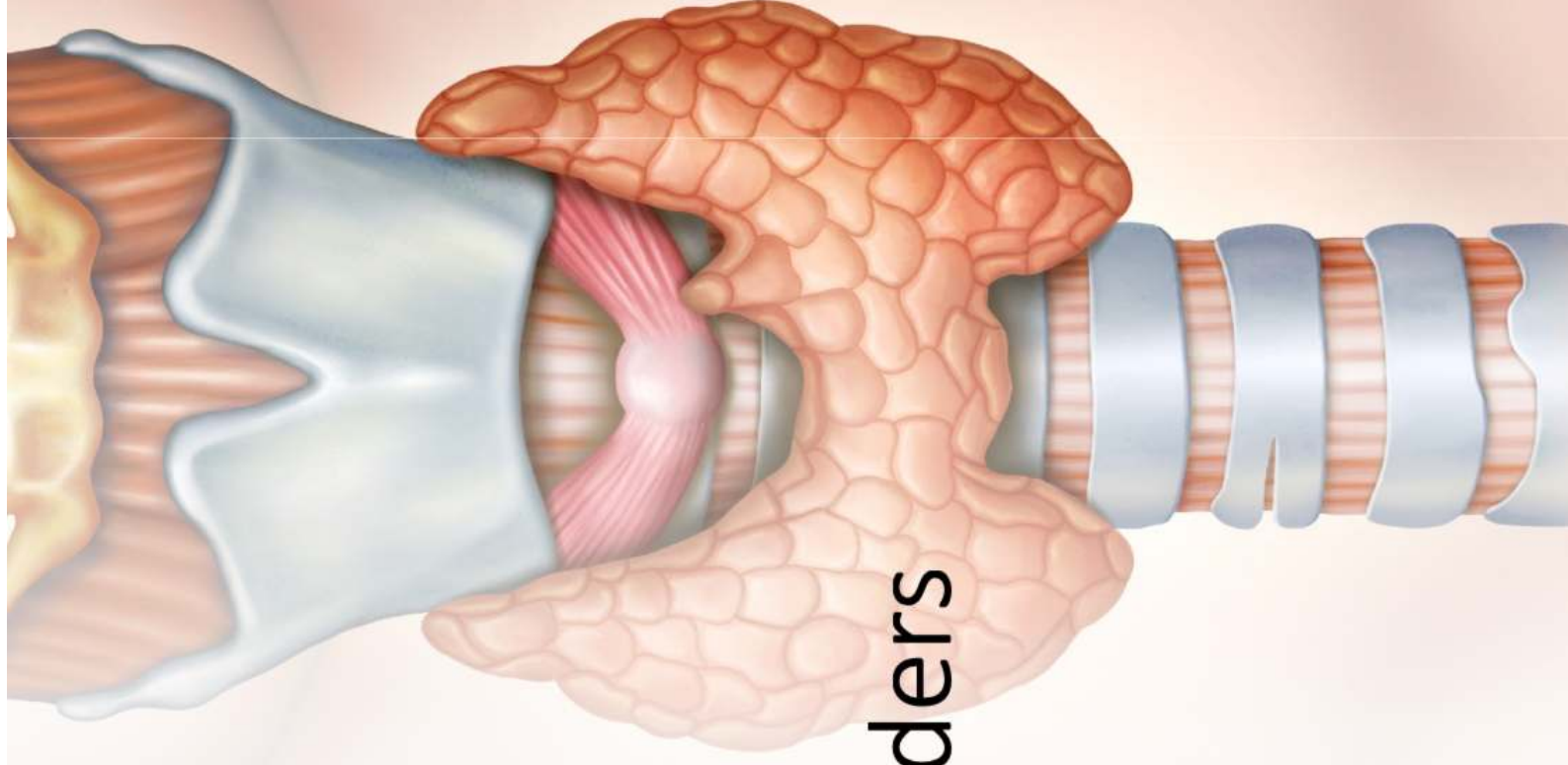




Thyroid gland disorders

Dr. Sara Awad MBBS MHPE FRCPC

Queen's University

December 9, 2021

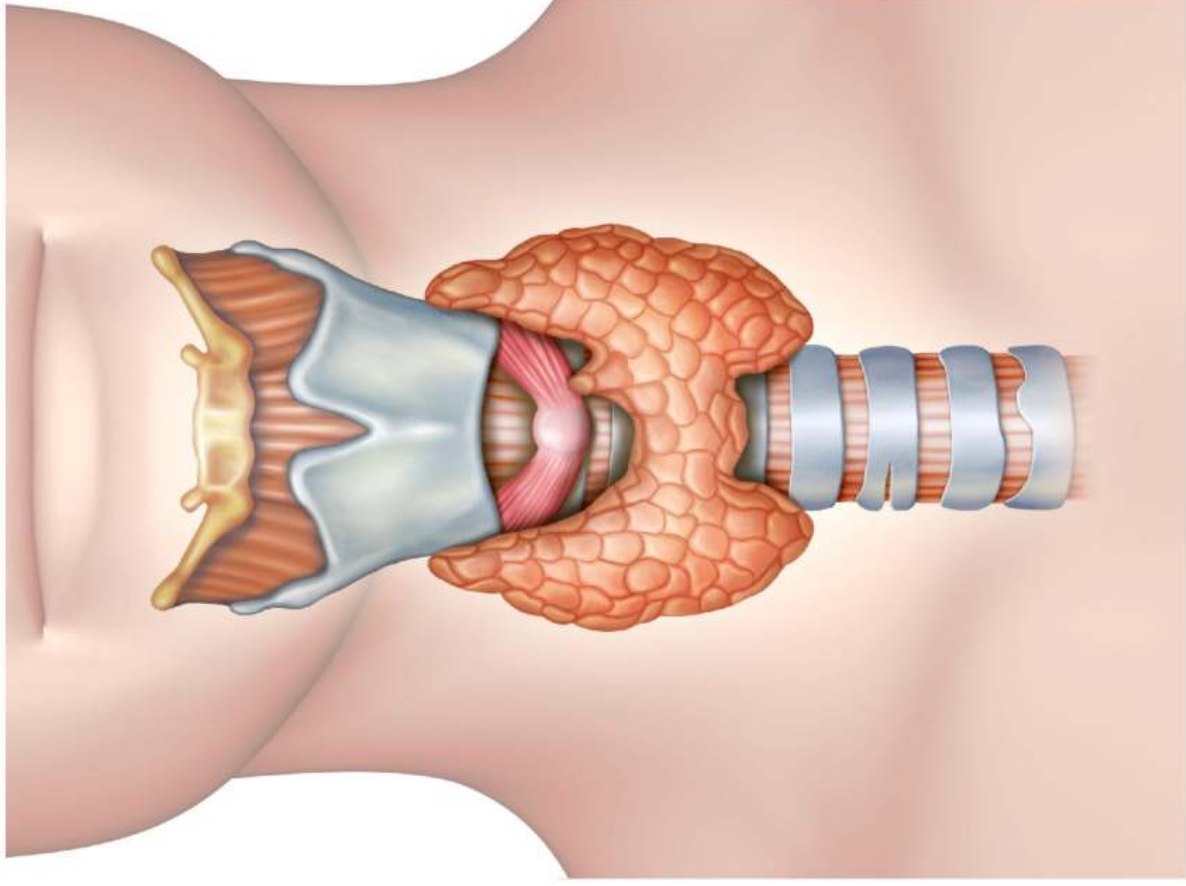
Objectives

- Review of thyroid gland anatomy and physiology
- Approach to assessment and management of hyperthyroidism
- Approach to assessment and management of hypothyroidism

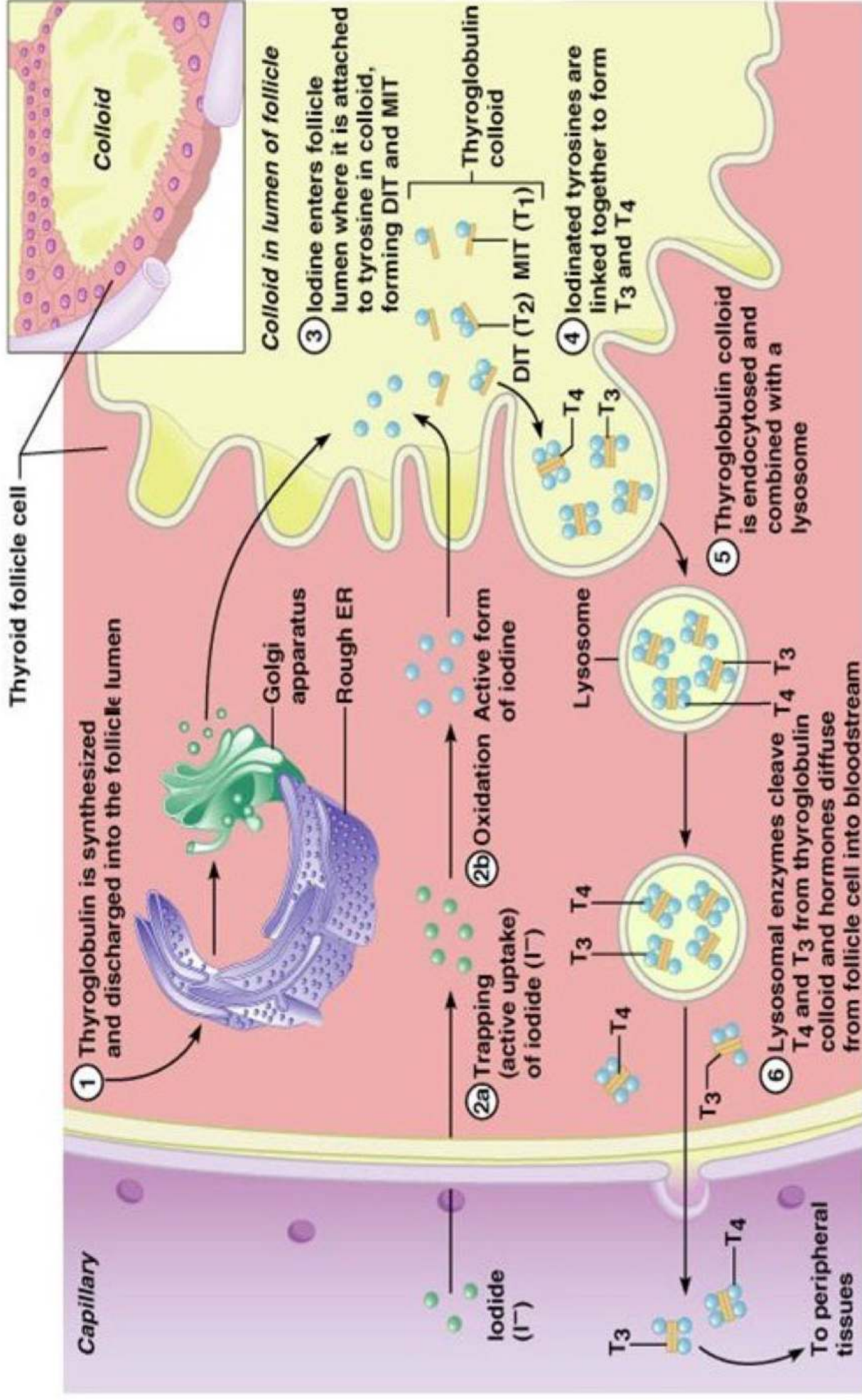
Objectives

- **Review of thyroid gland anatomy and physiology**
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Thyroid gland: Anatomy



Thyroid hormone synthesis



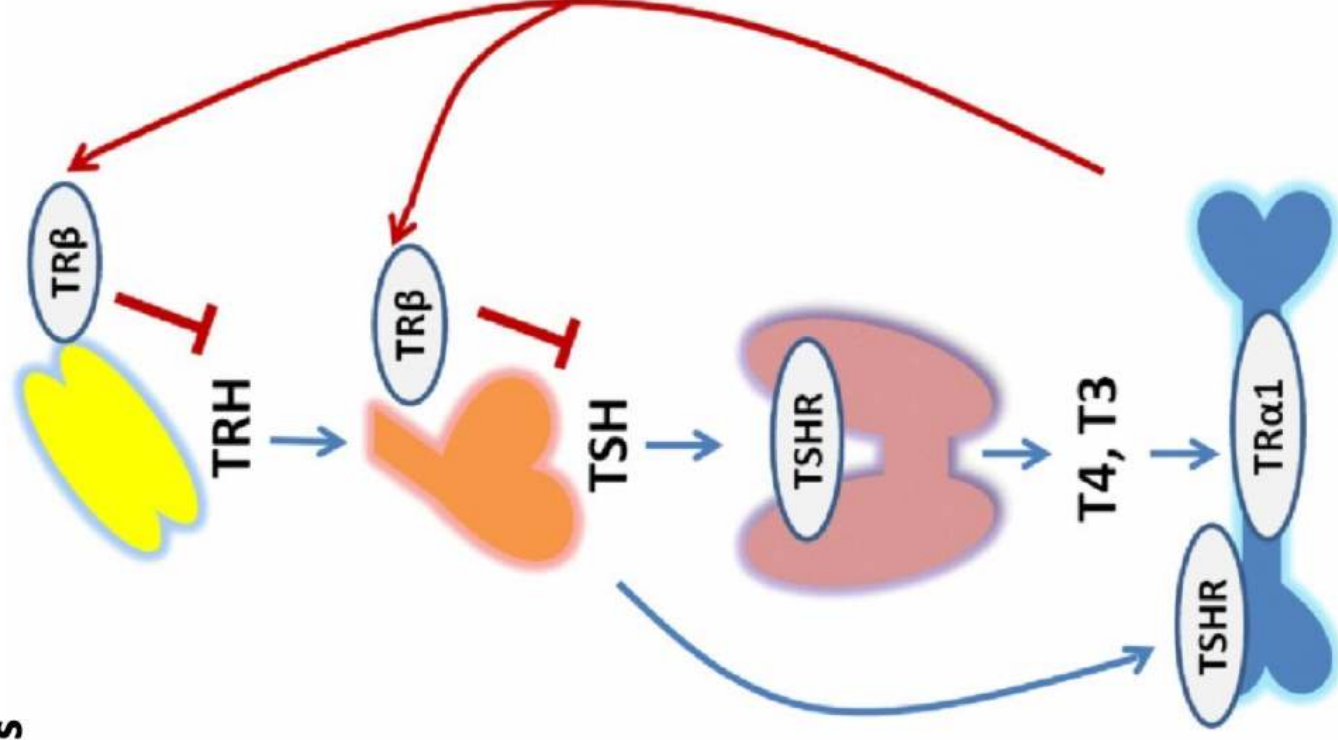
Hypothalamic-Pituitary-Thyroid Axis

Hypothalamus

Pituitary Gland

Thyroid

Bone



Thyroid hormone action

- Protein synthesis
- Carbohydrate metabolism (increase glucose)
- Lipid metabolism (decrease cholesterol)
- Increased metabolic rates
- Cardiac function (ionotropic and chronotropic)
- Increased sensitivity to catecholamines
- Stimulate GI motility
- Respiration
- Increased EPO secretion and thus RBC synthesis
- Fetal brain development
- Skeletal maturation
- Growth and development
- Thermal regulation
- Sexual function

Objectives

- Review of thyroid gland anatomy and physiology
- **Approach to assessment and management of hyperthyroidism**
- Approach to assessment and management of hypothyroidism

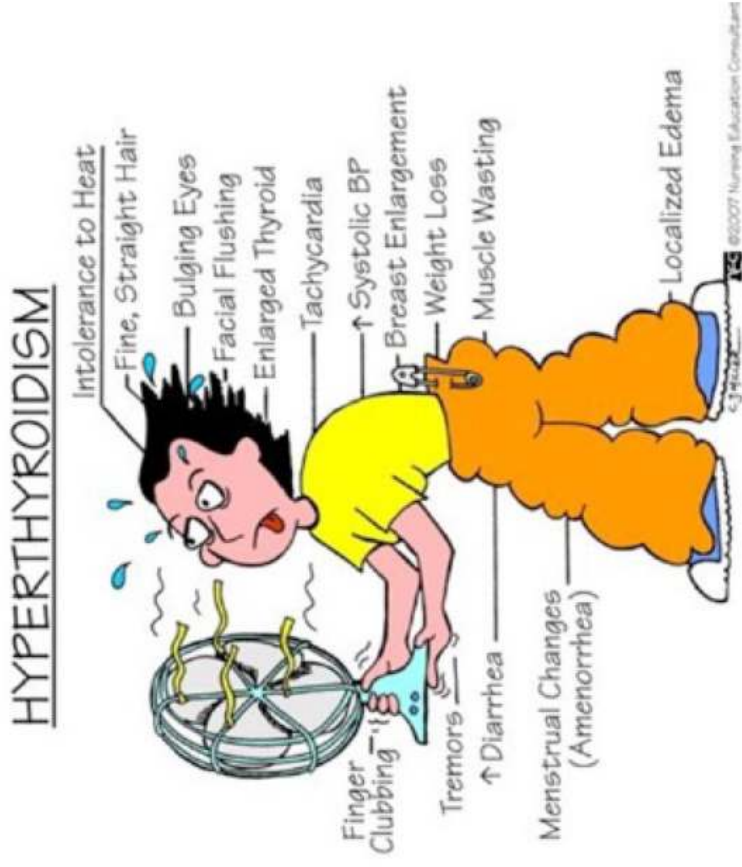
Approach to Hyperthyroidism

- Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland
- Thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source.

When to suspect?

Thyrotoxicosis symptoms:

- Heat intolerance
- Increased sweating
- Tremor
- Palpitations/Tachyarrhythmias
- Heart failure
- Insomnia
- Emotional lability/anxiety
- Unintentional weight loss despite increased appetite
- Increased bowel frequency
- Menstrual abnormalities



When to suspect?

Thyrotoxicosis signs:

- Fine tremors
- Soft, warm and sweaty skin (handshake)
- Tachycardia/atrial fibrillation
- Eyes (exophthalmos, lid lag, lid retraction)
- Increased cardiac output/wide pulse pressure
- Systolic hypertension
- Heart failure
- Hyperreflexia

Approach to differential diagnosis of thyrotoxicosis

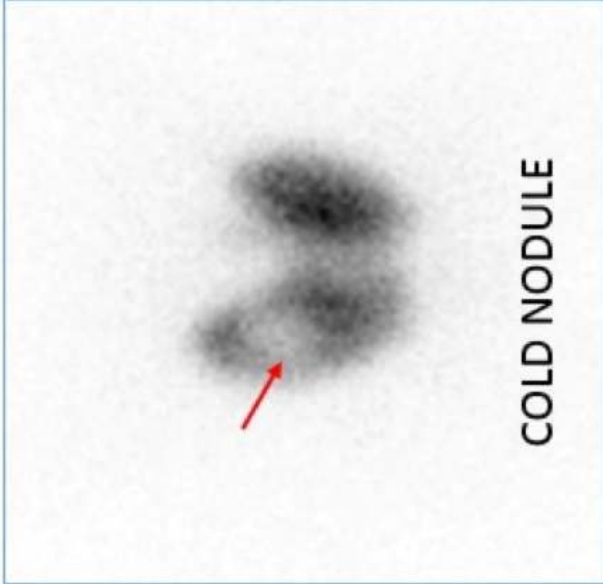
- Increased thyroid hormone production (hyperthyroidism):
 - Grave's disease
 - Toxic nodule/toxic multinodular goiter
 - TSH-secreting pituitary tumor (rare)
- Release of preformed thyroid hormones:
 - Thyroiditis (acute, subacute, postpartum, chronic, infectious)
- Exogenous use of thyroid hormones
- Medications: amiodarone
- Laboratory interference: Biotin
- Rare: struma ovarii, metastatic functional follicular thyroid cancer

Confirmation of Thyrotoxicosis

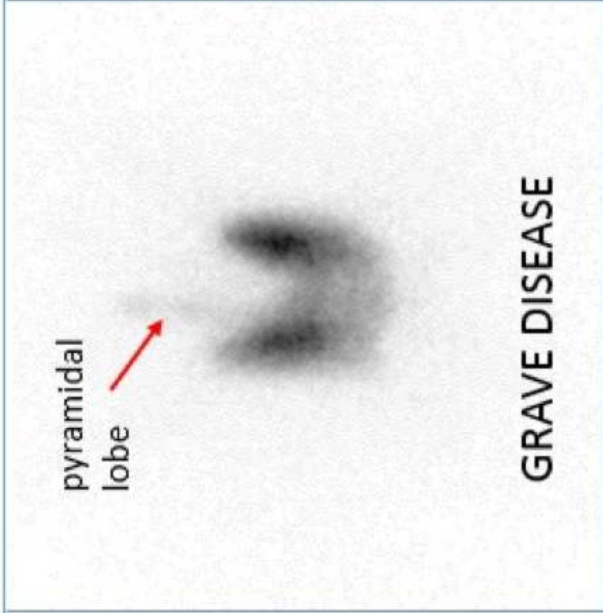
- **Case finding: TSH**
 - Low TSH
- **Confirmation:**
 - Repeat ↓TSH + ↑FT4 + ↑FT3

Role of Thyroid imaging

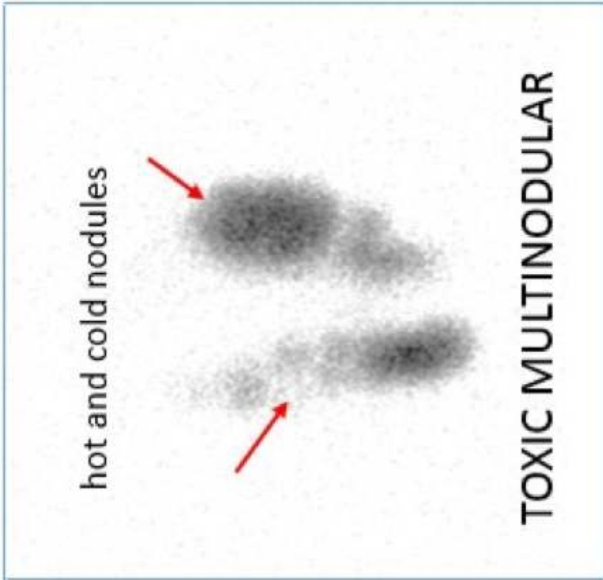
- Thyroid radioactive iodine uptake and scan
 - Increased I-131 uptake
 - Diffuse (Graves) vs. nodule uptake (toxic nodule/TMNG)
 - Decreased I-131 uptake
 - Thyroiditis, exogenous ingestion
- Thyroid Ultrasound
 - Can show goiter/increased vascularity (Grave's) vs. decreased vascularity/atrophy (thyroiditis)
 - Not sensitive nor specific or required for the diagnosis
 - Only for palpable nodule on thyroid exam



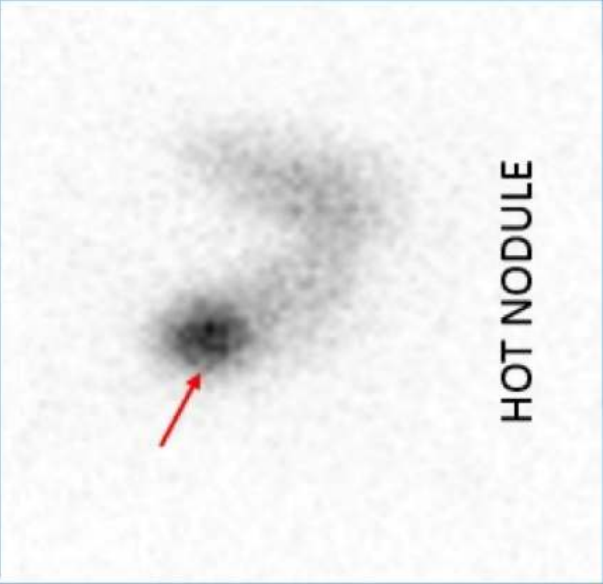
COLD NODULE



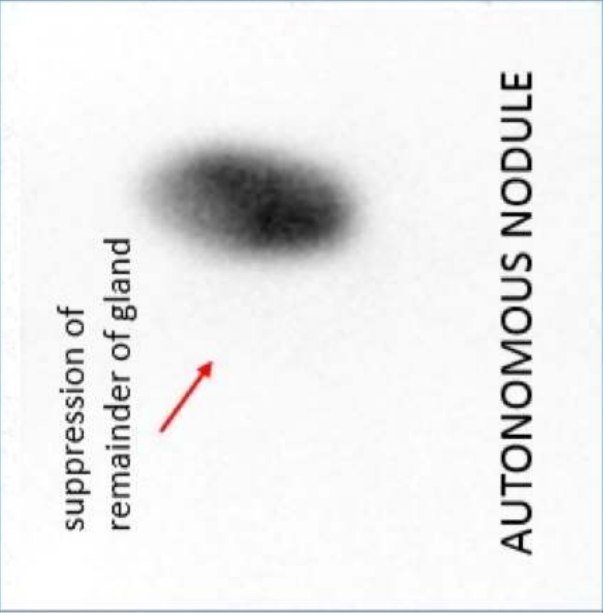
GRAVE DISEASE



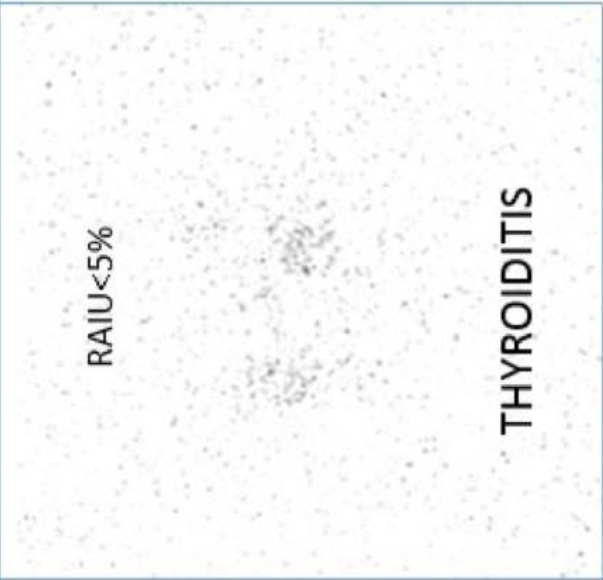
TOXIC MULTINODULAR



HOT NODULE



AUTONOMOUS NODULE



THYROIDITIS

RAIU < 5%

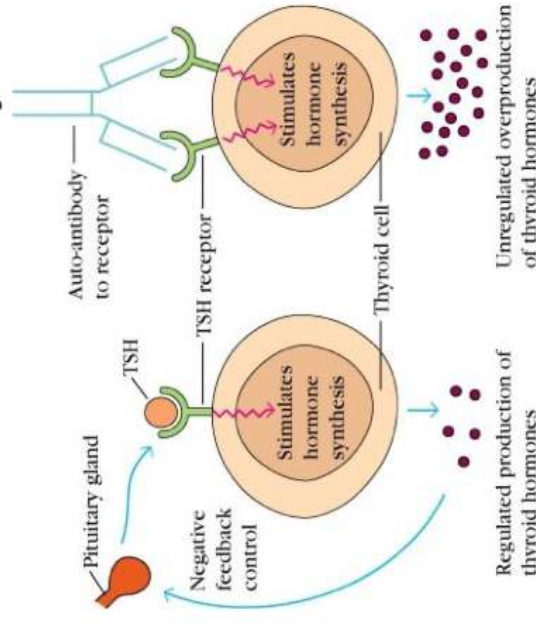
Initial treatment

- Until the diagnosis is clear, patients with thyrotoxicosis and hyperadrenergic symptoms should be started on beta-blockers (BB)
- Propranolol reduces $T4 \rightarrow T3$ conversion
 - (only at high doses)
- Any BB will work for symptom relief
 - Improves HR, SBP, muscle weakness, tremor, irritability, and exercise intolerance

Graves Disease



- Also known as toxic diffuse goiter
- Most common cause of hyperthyroidism
- Caused by an autoantibody against the thyroid-stimulating hormone (TSH) receptor
 - TSH-receptor antibody (TRAb)
- Unlike most autoantibodies, which are inhibitory, this autoantibody is stimulatory

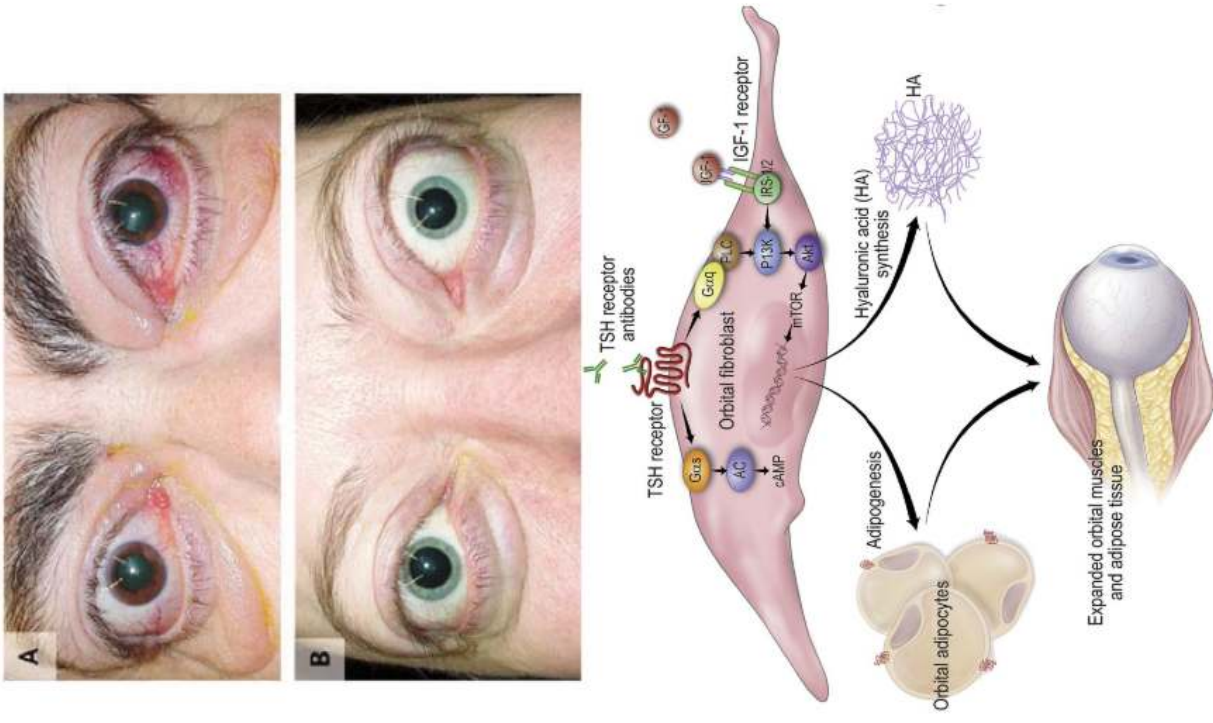


Graves Disease

- Risk factors: female, age ~ 30-50, personal or family history of autoimmune diseases, iodine load
- Symptoms: acute/subacute, thyrotoxic, goiter, bruits, Graves orbitopathy or dermopathy
- Signs: thyrotoxic, diffuse goiter, orbitopathy, dermopathy

Graves Orbitopathy

- Proptosis
- Periorbital edema
- Ophthalmoplegia/diplopia
- Chemosis
- Visual loss
 - Ocular emergency
- TRAb related



Graves Dermopathy

Pretibial myxedema



Biochemical diagnosis

- Consider pretest probability of Graves
- ↓TSH ↑fT3 ↑fT4
- fT3:fT4 ratio >0.3
- TRAb +
 - 97% sensitive, 98% specific
 - Not covered by OHIP

Graves Disease: Treatment

- Antithyroid medications (Thionamides): methimazole (MMZ) and propylthiouracil (PTU)
- First line: Methimazole OD or BID
 - fT4 1-1.5x ULN: 5-10 mg
 - fT4 1.5-2x ULN: 10-20 mg
 - fT4 2-3x ULN: 20-40 mg
- Second line: PTU
 - Higher rate of hepatotoxicity
 - Preferred 1st T pregnancy due to fewer birth defects

Graves Disease: Treatment

- Antithyroid Drugs (ATD)
 - Thyroid function is assessed every 6 - 8 weeks
 - The dose is reduced as thyroid hormone levels normalize (follow fT3 and fT4, TSH takes longer to recover)
 - 50-70% will go into **remission**. Predictors are:
 - females, non-smokers
 - mild disease, small goiter
 - low-titer or negative TRAb
- Recurrences may occur in up to 30%
- Lifelong or second-line therapy is needed in some

Side effects of Thionamides

- Common
 - Rash, pruritis, metallic taste, nausea, dyspepsia
- Hematologic
 - Agranulocytosis 0.1-0.5% risk
 - More likely in first 3 months
 - Controversy about CBC monitoring, not about case finding
- Hepatotoxicity
 - PTU –very rarely Hepatic Failure and death
 - MMI –cholestatic; lower risk of liver failure
- Vasculitis
 - ANCA + Vasculitis -Rare PTU +/-methimazole; Blood test may be positive with no clinical vasculitis
- Pancreatitis
 - Methimazole 6 case reports
- Baseline CBC/differential, LFTs, and q 4-6 weeks in the first 3 months and as needed if symptoms
 - Counsel the patient when to seek medical attention

Radioactive Iodine treatment

- Safe and cost-effective
- Single oral dose, outpatient procedure
- Success rate 75-90%
- Goal is Euthyroidism, gland shrinkage
 - 60-70% develop hypothyroidism
- Check labs q4-6 wks
 - Levothyroxine replacement therapy is started when low fT4/high TSH



Radioactive Iodine treatment

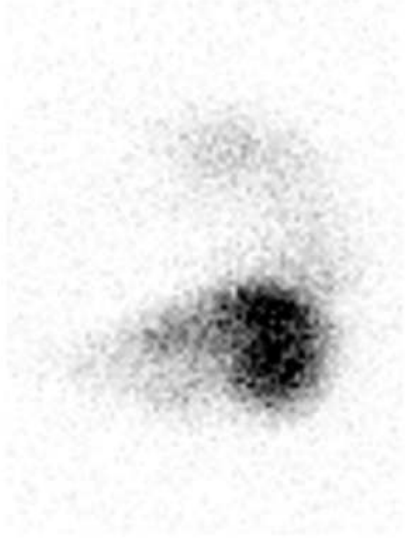
- Indications:
 - Contraindication or intolerance of ATD
 - No remission on ATD
 - Previous neck surgery/radiation
 - Patient preference
- Contraindications:
 - Planning pregnancy in <6-12 months
 - Pregnancy and breast feeding
 - Moderate to severe active Graves orbitopathy
 - Cannot follow radiation safety guidelines
 - Thyroid storm
 - Thyroid cancer or suspicion for thyroid cancer.

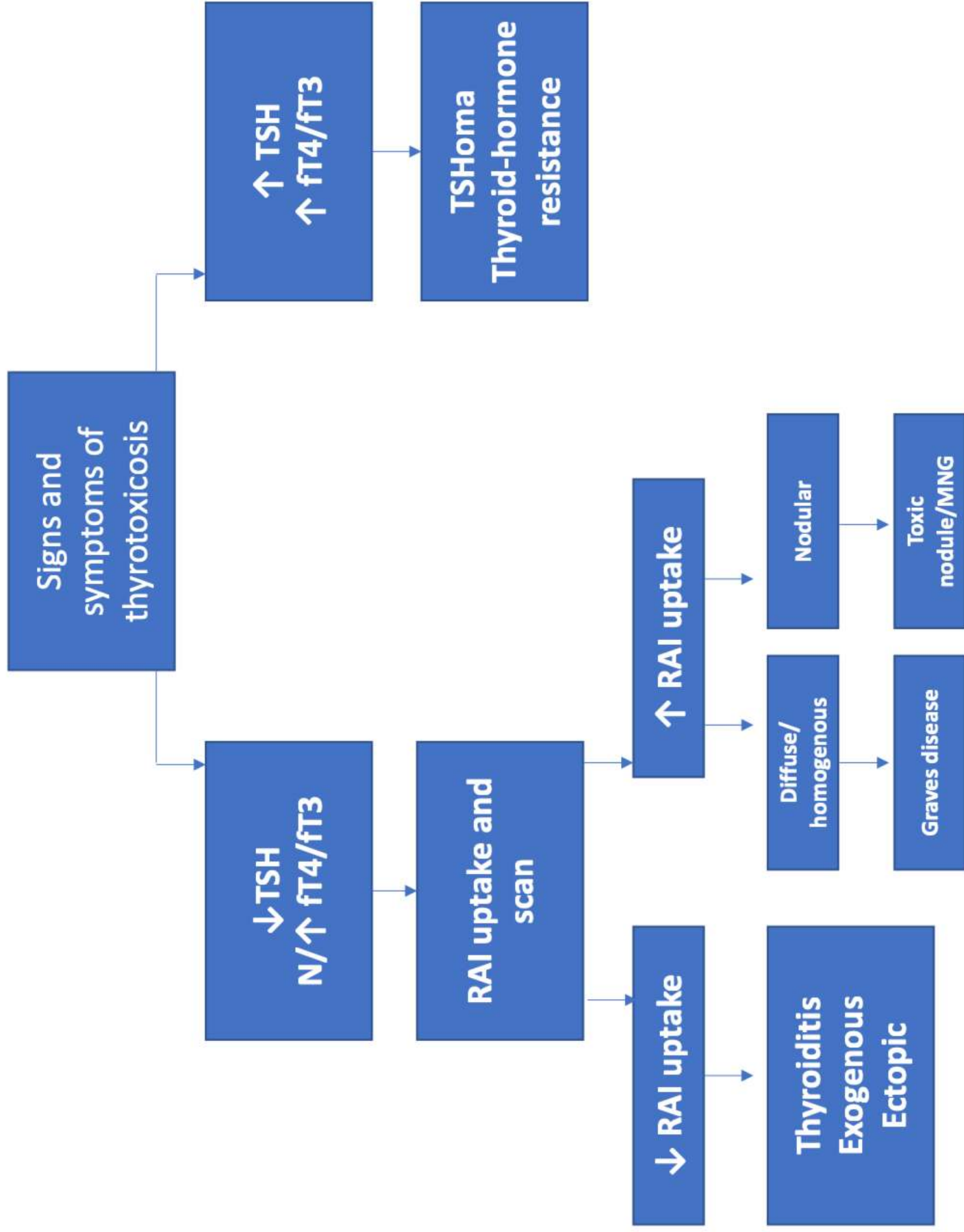
Surgery: Total Thyroidectomy

- Pre-treat with ATDs
- Consider potassium iodide pre-op to reduce blood flow
- Risks: Hypoparathyroid, RLN, bleeding
- Surgery recommended
 - Symptomatic or very large goiters
 - Suspected thyroid cancer/ worrisome nodules
 - Moderate to severe active Graves' orbitopathy and desire for definitive therapy
- Surgery discouraged
 - High risk for surgery
 - Pregnancy
 - If responsive to ATDs, if necessary, surgery in 2nd trimester is best time.

Other causes of thyrotoxicosis

- Toxic nodule or toxic MNG
 - RAI treatment, ATD or surgery
- Thyroiditis
 - Monitor
 - Treat if permanent hypothyroidism





Isolated low TSH?

- Subclinical hyperthyroidism
 - Graves disease, toxic nodule/TMNG, thyroiditis
- Recent treatment for hyperthyroidism (ATDs, RAI)
- Drugs (steroids)
- Non-thyroidal illness
- Laboratory errors
 - Assay interference (heterophile antibodies, rheumatoid factor, macroTSH), false positive
- Overtreatment with Synthroid
- hCG mediated (gestational, hyperemesis gravidarum, trophoblastic germ cell tumors)



Progression to over hyperthyroidism

- Conflicting data
 - Rates all over the place
- More likely TSH <0.1
- Spontaneous recovery
 - Sometimes happen
- Increased bone resorption and fracture risk,
increased risk of CAD/CHF/arrhythmias and mortality
(elderly)

SC Hyperthyroidism: Treatment

- Treat if TSH <0.1 and any of the following
 - CVD or high cardiac risk
 - Osteoporosis or high fracture risk
 - Age >65 years
- Don't treat if >0.1 , no risk factors for complications and age <65 years
- Otherwise, unclear
 - Favor treatment
 - Symptoms, autonomous nodule, or CVD, osteoporosis and TSH >0.1
 - Favor observation if age > 65 years and TSH >0.1 and none of the above

Objectives

- Review of thyroid gland anatomy and physiology
- Approach to assessment and management of hyperthyroidism
- **Approach to assessment and management of hypothyroidism**

Hypothyroidism

- Poor Thyroid production
- Differential diagnosis:
 - Iodine deficiency
 - Autoimmune / Hashimoto's
 - Thyroidectomy or iodine ablation
 - Post Thyroiditis
 - Drugs (eg. lithium, amiodarone, TKI)
 - Congenital absence of gland

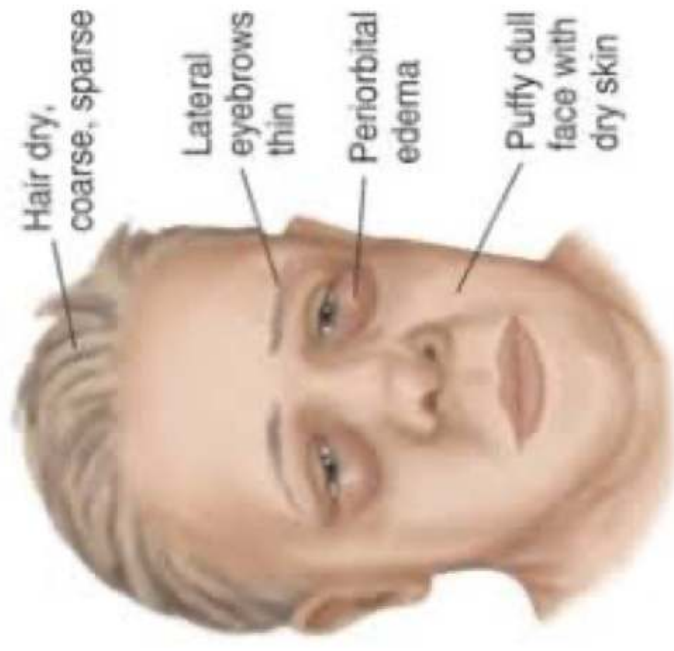
When to suspect? Hypothyroidism symptoms

- Fatigue
 - Dry skin
 - Hair loss
 - Cold intolerance
 - Weight gain despite decreased appetite
 - Constipation
 - Menorrhagia
 - Memory impairment
 - Poor concentrating
 - Muscle ache
- Elderly Patients:
Fewer symptoms, subtle and vague
- Confusion, memory change
 - Anorexia
 - weight loss
 - Falling, decreased mobility
 - Incontinence
 - Arthralgias
 - Constipation
 - Heart failure
 - Bradycardia

When to suspect?

Hypothyroidism signs

- Puffy face
- Nonpitting edema (myxedema)
- Dry, coarse skin, hair
- Hair loss
- Hoarse voice
- Carotinemia
- macroglossia
- Bradycardia
- Diastolic hypertension
- Delayed reflex relaxation phase
- Carpal tunnel syndrome
- Pleural and pericardial effusions



Confirmation of hypothyroidism

- **Case finding: ↑TSH**
- ↑TSH + ↓fT4
- Do not order fT3
- Anti-TPO and Anti-thyroglobulin
 - Available
 - Sensitive for autoimmune hypothyroidism but less specific
 - Almost (never?) influence clinical decisions in overt hypothyroidism
 - US thyroid or radioactive iodine
 - Characteristic features in Autoimmune but not sensitive nor specific or required for the diagnosis
 - Only if palpable thyroid nodule on physical exam

Hypothyroidism: Treatment

- Thyroid hormone: levothyroxine (L-T4)
 - Brand names: Synthroid, Eltroxin
- Converted to T3 peripherally by deiodinase enzymes
- Half-life of 7 days
- Given 30-60 min before breakfast with water
- Alternate: At bedtime 3 hours after last meal
- Full replacement dose $\sim 1.6 \mu\text{g/kg}$ of IBW
 - Start low in subclinical hypothyroidism and elderly
- Wait 6-8 weeks after a change in the dosage to see the effect in the TSH
- Target normalization of TSH level
- When target TSH obtained, monitor TSH every 6-12 m

Hypothyroidism: Treatment

- Use of a consistent preparation to minimize variability
- Absorption impaired:
 - Iron, calcium, aluminum, soy, sucralfate, cholestyramine
 - Take these 4 hrs before or after the levothyroxine
 - Ask about multivitamins
 - Malabsorptive states, eg. Celiac disease (IgA, anti-TTG antibodies)
- Increased metabolism:
 - Eg. Phenytoin, carbamazepine

Isolated high TSH

- Subclinical hypothyroidism
 - Autoimmune/Hashimoto's
- Poor adherence to LT4
- Malabsorption of LT4
- Drugs (amiodarone, lithium)
- Non-thyroidal illness recovery
- Laboratory errors
 - Assay interference (heterophile antibodies, rheumatoid factor, macroTSH), false positive
- TSH resistance



SC Hypothyroidism: Treatment

- TSH >10 mIU/L
- Therapeutic trial for possible hypothyroidism symptoms
- Age <40-65
- ?Infertility, Ovulatory dysfunction
- ?DLP, CKD, CVD

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SPECIAL ARTICLE

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

Erik K. Alexander,^{1,*} Elizabeth N. Pearce,^{2,*} Gregory A. Brent,³ Rosalind S. Brown,⁴ Herbert Chen,⁵
Chrysoula Dosiou,⁶ William A. Grobman,⁷ Peter Laurberg,^{8,†} John H. Lazarus,⁹ Susan J. Mandel,¹⁰
Robin P. Peeters,¹¹ and Scott Sullivan¹²

Pregnancy specific reference ranges

TABLE 4. REFERENCE RANGES FOR THYROTROPIN AND FREE THYROXINE DURING EARLY PREGNANCY WORLDWIDE

Author, country (reference) (analyzing method)	N	Gestation (week)	TSH, mU/L		FT4, pmol/L (ng/dL)		Population characteristics			
			Median	2.5th– 97.5th	Median	2.5th– 97.5th	(Median, 2.5th–97.5th)	Iodine insufficiency	Mean BMI	Ethnicities
Bestwick <i>et al.</i> , Italy (24) (AutoDELFIA)	5505	<16	1.07	0.04–3.19	9.3	7.4–12.2	(0.73, 0.58–0.95)	Moderate-mild ^a	NR	NR
Bestwick <i>et al.</i> , UK (24) (Advia Centaur)	16,334	<16	1.11	0.06–3.50	13.9	10.9–17.9	(1.08, 0.85–1.40)	Moderate-mild ^a	NR	
Bocos-Terraz <i>et al.</i> , Spain (264) (Architect)	481	<14	0.94	0.41–2.63	13.9	10.8–17.8	(1.08, 0.84–1.38)	Mild	NR	
Gilbert <i>et al.</i> , Australia (271) ^b (Architect)	1817	9–13	0.74	0.02–2.15	13.5	10.4–17.8	(1.05, 0.81–1.39)	Borderline	NR	Australian
Shift the lower limit of normal down by 0.4 (TSH ~ 0.1) Shift the upper limit of normal down by 0.5 (TSH ~ 3.5-4)										
Pearce <i>et al.</i> , USA (142) (Advia Centaur)	585	<14	1.1	0.04–3.60	2.1 ^b	1.5–2.9 ^g	—	Borderline	NR	Turkish (8%), Moroccan (6%) White (77%) and African American (10%)
Quinn <i>et al.</i> , Russia (272) (Abbott AxSYM)	380 549	T1 T2	1.66 2.00	0.09–4.67 0.20–4.68	—	—	—	Moderate	NR	Russian (presumed)
Springer <i>et al.</i> , Czech Republic (268) ^b (ADVIA Centaur)	4337	9–11	1.21	0.06–3.67	—	—	—	Mild	NR	Caucasian (99%)
Stricker <i>et al.</i> , Switzerland (262) (Architect i2000SR)	575 528	6–12 T2	0.95 1.02	0.07–2.82 0.20–2.79	13.9 12.2	10.5–18.5 9.5–15.7	(1.08, 0.82–1.44) (0.95, 0.74–1.22)	Sufficient	NR	Swiss (presumed)
Vaidya <i>et al.</i> , UK (Modular E 170) (274)	1089	<12	1.08	0.14–3.19	14.6	10.7–19.4	(1.12, 0.83–1.59)	Mild-moderate	NR	Caucasian (91) and South Asian (4)

Screen and Treat SC Hypo/Anti-TPO

- Does it decrease pregnancy loss and complications?
 - Negro et al. 2006 RCT LT4 vs placebo in euthyroid, anti-TPO positive JCEM
 - Small study. Reduced pregnancy loss. LT4 started late.
 - Negro et al. 2010 Universal screening vs case finding. JCEM
 - Larger study. No difference between groups.

Screen and Treat SC Hypo/Anti-TPO

- Does it improve neurocognitive outcomes in offspring?
 - Observational studies show association between thyroid abnormalities and poorer cognitive outcomes in pregnancy
- Lazarus et al. 2012. Antenatal screening and child cognitive fx. NEJM (CATS trial)
 - RCT; No benefit.
- Casey BM et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. NEJM 2017
 - RCT; No Benefit.

SC Hypothyroidism is pregnancy

ATA Recommendations

- Universal screen with TSH in early pregnancy—
Insufficient Evidence
- Preconception screening with TSH –Insufficient
evidence
 - Exceptions –Seeking assisted reproduction or known
anti-TPO +
- Screen with FT4 –Not recommended

SC Hypothyroidism is pregnancy

Case Finding – ATA Recommended

- History of or signs/symptoms of thyroid dysfunctions
- Positive TPO+ antibody known
- Goitre
- Head and neck radiation or thyroid surgery
- Age > 30
- Type 1 diabetes or other autoimmune disorder
- Family history of thyroid dysfunction
- BMI>40
- Amiodarone, lithium or recent radiocontrast
- Iodine deficient area

SCH Pregnancy: Treatment

- Strong evidence to start treatment is TSH >10
- I would treat if TSH 4-10
- Consider treatment if TSH 2.5-4.0
 - Check anti-TPO?
 - Previous miscarriage?
 - Other risk factors for pregnancy loss?
 - Assisted reproductive technology?
 - Risk vs. benefits?
 - Very low on both sides

Objectives

- Review of thyroid gland anatomy and physiology
- Approach to assessment and management of hyperthyroidism
- Approach to assessment and management of hypothyroidism

Thank you
Questions?

