Thyroid Disease

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Outline

- Hypothyroidism
- Hyperthyroidism
- Thyroid Nodularity
- Thyroid and pregnancy

Case #1

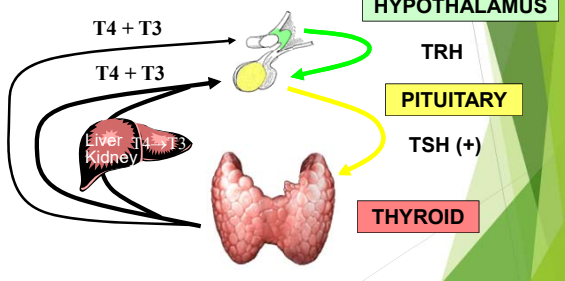
- 56 y/o F with goiter, and fatigue.
  - TSH = 46 (elevated)
  - Free T4 = 0.06 (low)
- Diagnosis?

Hypothyroidism

Hypothyroidism

- Symptoms
  - Fatigue
  - Cold intolerance
  - Weight gain
  - Difficulty with learning, depression
  - Constipation
  - Dry brittle hair & nails
  - Hoarse voice
  - Swelling & puffiness
  - Muscle & joint aches
  - Heavy menstrual flow
  - Miscarriages

Hypothyroidism



Original illustration created by Diane Abeloff, 2002.

Causes of Hypothyroidism

- Autoimmune thyrioditis
  - Hashimoto's
- Radioactive Iodine
- Spontaneous onset
- Surgical
- Subacute thyroiditis
- Medications
  - Lithium, Amiodarone
  - PTU, Tapazole
- Postpartum
- Congenital
- Pituitary

Hypothyroidism Diagnosis

- Classic:
  - Elevated TSH (usually >10)
  - Low T4
  - Symptomatic
- Subclinical Hypothyroidism:
  - Elevated TSH
  - Normal T4 & T3
  - Asymptomatic

When to treat hypothyroidism?

- Recommendations
  - TSH >10 mIU/mL, and low T4 or T3
  - Asymptomatic +TSH >10
    - +Risk factor for future hypothyroidism
      - Goiter, multinodular thyroid, +FH, + thyroid peroxidase (TPO) antibodies
- Arguments against treatment in subclinical disease.
  - Cost

How to treat hypothyroidism?

- Weight based calculation (status post thyroidectomy ,complete failure of thyroid)
  - 1.6 x weight in Kg
  - 75% weight in lbs
- If still have partial thyroid function, start around 50 mcg if they are small/older, 75-100mcg if they are heavier
- If miss a dose, can take 2 tabs the next day
- Don't take with calcium, iron, estrogens, or soy
  - All can bind LT4 in the gut, decreasing it's absorption
- Recheck TSH, Free T4 in 6-8 half lives (7 day half life)
- If patient changes brands, recheck TSH in 6-8 weeks
  - Pharmacy can now put them on generic without asking you…

Case #2

- 56 y/o F with goiter, and fatigue. (identical twin sister of Case #1)
  - TSH = <0.001 (very low)
  - Free T4 = 4.62 (very high)
- Diagnosis?

Hyperthyroidism

Hyperthyroidism Signs & Symptoms

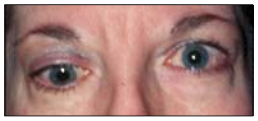
- Skin
  - Sweating & heat intolerance
  - Onchoclysis- loosening of nail beds
  - Hyperpigmentation
  - Thinning of hair
- Eyes
  - Lid lag & stare
  - Proptosis with Graves' opthalmopathy
  - Double vision, conjunctival irritation
- CV
  - Tachycardia, palpitations
  - Widened pulse pressure
  - A. Fib and CHF
- GI
  - Vomiting & abd pain
  - Elevated liver funct tests
- Neuromuscular
  - Tremor, weakness
- Psych
  - Apathetic hyperthyroidism in elderly
  - Fatigue

Lid lag vs lid retraction

Right lid lag on downgaze – von Graefe sign

Graves' Orbitopathy

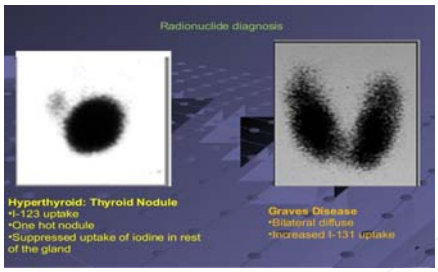
- Proptosis
  - Conjunctival injection
- Disconjugate gaze & diplopia



Diagnosis

- Low TSH & elevated T4/T3
  - Currently on Thyroid hormone?
  - Goiter?
    - Graves' vs hot nodule
    - Painful, or preceded by viral URI?
    - May be thyroiditis
- Next step is radioiodine uptake scan to make the diagnosis

Uptake scan



Hyperthyroidism Treatment

- Beta-Blockers for symptoms & refer to Endocrinologist
- Methimazole /Propylthiouracil (PTU) : Are actively transported into the thyroid gland where they inhibit both the organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodotyrosines
- Radioiodide ablation – watch out for Graves' Opthalmopathy
- Surgery
- Thyroiditis
  - Observation & symptomatic treatment, watch closely as can get subsequent hypothyroidism
- Risk of observation: Atrial fibrillation, CHF, osteoporosis, LFT's

Thyroid storm

- Thyroid storm is a rare, life-threatening condition characterized by severe clinical manifestations of thyrotoxicosis
- Incidence of thyroid storm was 0.57 - 0.76 per 100,000 persons per year (based on national survey data)
- Can be precipitated by an acute event : thyroid or nonthyroidal surgery, trauma, infection,acute iodine load, irregular use or discontinuation of antithyroid drugs.

Thyroid storm: Diagnostic criteria

Diagnostic Criteria for Thyroid Storm*†

Thermoregulatory dysfunction		**Cardiovascular dysfunction**	
Temperature		Tachycardia	
99–99.9	5	99–109	5
100–100.9	10	110–119	10
101–101.9	15	120–129	15
102–102.9	20	130–139	20
103–103.9	25	≥ 140	25
≥ 104.0	30		
Central nervous system effects		**Congestive heart failure**	
Mild	10	Mild	5
Agitation		Pedal edema	
Moderate		Moderate	
Delirium	20	Bibasilar rales	10
Psychosis		Severe	15
Extreme lethargy		Pulmonary edema	
Severe	30	Atrial fibrillation	10
Seizure			
Coma			
Gastrointestinal–hepatic dysfunction		**Precipitant history**	
Moderate	10	Negative	0
Diarrhea		Positive	10
Nausea/vomiting			
Abdominal pain			
Severe	20		
Unexplained jaundice			

* A score of 45 or more is highly suggestive of thyroid storm; a score of 25 to 44 supports the diagnosis; and a score below 25 makes thyroid storm unlikely.

† Adapted from Burch, HB, Wartofsky, L, Endocrinol Metab Clin North Am 1993; 22:263.

Treatment of thyroid storm

- Beta blockers : propranolol : 60 to 80 mg orally every 4-6 hrs hours, with appropriate adjustment for HR&BP.
- PTU 200 mg every 4 hrs or Methimazole (20 mg orally every 4-6 hrs). Block de novo thyroid hormone synthesis within 1-2 hours after administration.
- Lugol's solution-10 drops TID /SSKI -5 drops q 6hrs (iodine): blocks the release of T4 and T3 from the gland within hours .Given 1 hr after thionamides .
- Glucocorticoids reduce T4-to-T3 conversion. Hydrocortisone 100 mg q 8 hrs .

Thyroiditis: diverse group of disorders characterized by some form of thyroid inflammation

Subtype	Etiology	Neck pain	RAIU	TSH	T_4	Thyroid autoantibodies
Chronic lymphocytic (Hashimoto's disease)	Autoimmune	No	Variable	Variable	Variable	Present
Subacute granulomatous	Viral	Yes	Decreased	Decreased	Increased	Absent
Subacute lymphocytic	Autoimmune	No	Decreased	Decreased	Increased	Present
Microbial inflammatory	Bacterial, fungal, parasitic	Yes	Variable	Normal	Normal	Absent
Hashitoxicosis	Autoimmune	No	Decreased	Decreased	Increased	Present
Invasive fibrous	Unknown	No	Variable	Normal	Normal	Variable

RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone; T_4 = thyroxine.

American Family Physician Vol. 61/No. 4 (February 15, 2000)

Thyroiditis subtypes

Pain on exam?

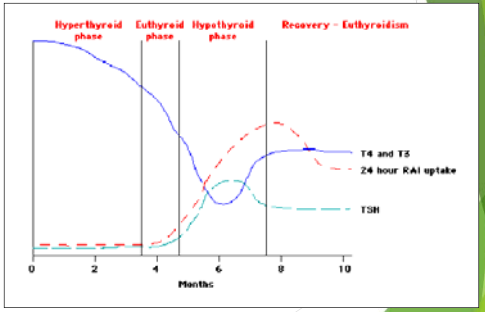
No

- Painless
  - 1-10% of all hyperthyroid, small goiter, symptoms for only 1-2 months, no opthalmopathy, ♀
    - Silent thyroiditis, subacute lymphocytic thyroiditis, and lymphocytic thyroiditis
- Post-partum
  - 6w-1yr following pregnancy, vs. Graves' dx, +Ab
- Drug-induced
  - IF-α, IL-2, Amiodarone, lithium
- Fibrous
  - Tightening of throat, dysphagia, hoarseness
  - Dx biopsy with fib, mono, & Eos
    - Riedel's thyroiditis or invasive thyroiditis

Yes

- Subacute
  - Tender diffuse goiter, bilateral, preceeding viral illness, -Ab
    - De Quervain's, subacute supperative/granulomatous
- Infectious
  - Usually imunocompromised or children, fevers, chills, unilateral
    - fistula from piriform sinus, hematogenous spread
    - Fungal, G-, G+, mycobact
- Radiation
- Palpation/trauma

Thyroiditis Timeline



Case #3

- You are at the state fair in Colorado, checking people's thyroid function studies for fun.
- 72y/o WM, feels fine, with…
  - TSH = 0.02 (low but not undetectable)
  - Free T4 = 1.2 (normal)
- What's the diagnosis?
  - Can you make it at this point? Another lab perhaps?
    - Total T3 = 140 (mid-upper normal)

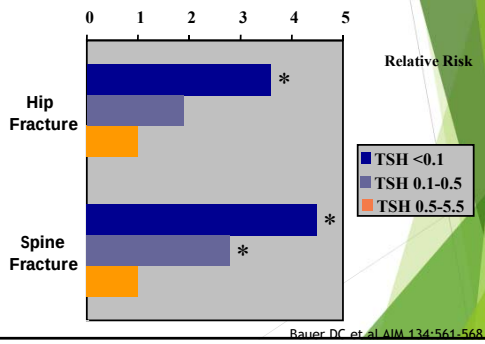
Subclinical Hyperthyroidism

- Labs show low TSH and normal T4/T3
- Higher risk for bone or cardiac complications
  - TSH < 0.1 µU/ml
    - Treat like is regular hyperthyroidism
  - TSH 0.1-0.5 µU/ml
    - Treat if uptake scan shows high uptake or if the bone DXA is low
    - Observation if uptake scan is normal, already on B-Blocker, or bone DXA is normal.
- Lower risk patients
  - TSH < 0.1 µU/ml
    - Treat if uptake scan shows high uptake or if the bone DXA is low
  - TSH 0.1-0.5 µU/ml, recheck in 6-8 weeks

Risks of Subclinical Hyperthyroidism

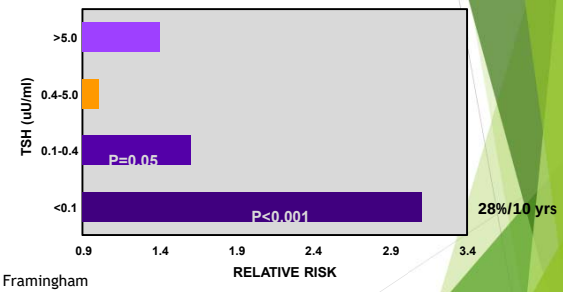
- Heart
  - Increased A.Fib
  - Increased contratility
  - Increased ventricular mass
- Bone
  - Decreased density & increased bone resorbtion
- Lab
  - Decrease LDL
  - Increase LFT's, CK, & SHBG
- Other
  - Less sleep & improved mood

Subclinical Hyperthyroidism and Fractures
The Study of Osteoporotic Fractures



Bauer DC et al AIM 134:561-568, 2001

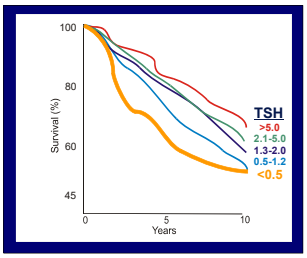
Subclinical Hyperthyroidism and Atrial Fibrillation



Framingham

Sawin, NEJM 331:1249-52, 1994

Survival vs Serum TSH
Age >60yrs



Parle J et al Lancet 358:861,2001

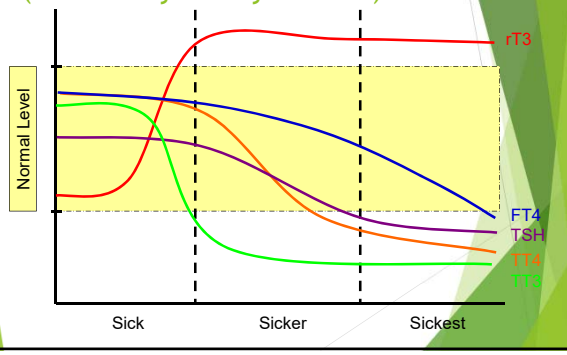
Case #4

- Pt is on their way home from their Endocrinologists appointment, where they had a complete panel of thyroid function studies performed that were normal, including a TSH of 2.21 and they wreck their car.
  - You are consulted on them later that day for their hyperthyroidism, checked in the ICU, with the patient on a ventilator and a TSH of 0.02
  - What's the diagnosis?

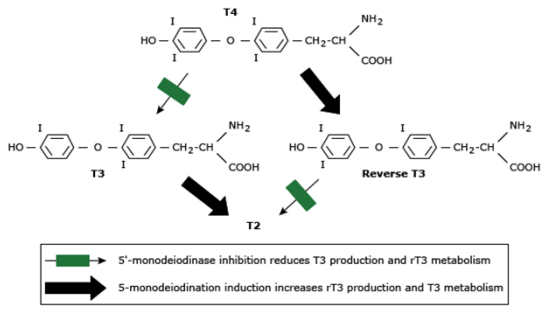
Sick Euthyroid syndrome

- Many hospitalized/ill patients have low or low-normal serum total T4, low T3 concentrations, and low, low-normal, or normal TSH .
- This pattern is similar to the pattern seen in patients with central hypothyroidism.
- ↑ Reverse T3
- It is possible that these changes in thyroid function during severe illness are protective in that they prevent excessive tissue catabolism

Nonthyroidal Illness (Sick euthyroid syndrome)



T4 metabolism in nonthyroidal illness



The inhibition of 5'-monodeiodinase in nonthyroidal illness leads to decreased conversion of T4 to T3 and reduced metabolism of rT3. The induction of 5-monodeiodinase (D3) leads to increased conversion of T4 to rT3 and the metabolism of T3.

T4: thyroxine; T3: triiodothyronine; T2: diiodothyronine; rT3: reverse triiodothyronine.

Nonthyroidal Illness (Sick euthyroid syndrome)

- Thyroid levels may be also abnormal due to medications

Drugs that cause hypothyroidism, hyperthyroidism, or changes in thyroid function tests

Drugs causing hypothyroidism
Inhibition of thyroid hormone synthesis and/or release – thionamides, lithium, perchlorate, aminoglutethimide, thalidomide, and iodine and iodine-containing drugs including amiodarone, radiographic agents, expectorants (eg, guaifenesin), kelp tablets, potassium iodine solutions (SSKI), Betadine douches, topical antiseptics
Decreased absorption of T4 – cholestyramine, colestipol, colesevelam, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole, and possibly other medications that impair acid secretion, sevelamer, lanthanum carbonate, and chromium; malabsorption syndromes can also diminish T4 absorption
Immune dysregulation – interferon alfa, interleukin-2, ipilimumab, alemtuzumab, pembrolizumab, nivolumab
Suppression of TSH – dopamine
Destructive thyroiditis – TKIs (eg, sunitinib, sorafenib); checkpoint inhibitors (eg, nivolumab, pembrolizumab, and ipilimumab)
Increased type 3 deiodination – TKIs (eg, sorafenib)
Increased T4 clearance and suppression of TSH – bexarotene
Drugs causing hyperthyroidism
Stimulation of thyroid hormone synthesis and/or release – iodine, amiodarone
Immune dysregulation – interferon alfa, interleukin-2, ipilimumab, alemtuzumab, pembrolizumab
Drugs causing abnormal thyroid function tests without thyroid dysfunction
Low serum TBG – androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), L-asparaginase
High serum TBG – estrogens, tamoxifen, raloxifene, methadone, 5-fluorouracil, clofibrate, heroin, mitotane
Decreased T4 binding to TBG – salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
Increased T4 clearance – phenytoin, carbamazepine, rifampin, phenobarbital
Suppression of TSH secretion – dobutamine, glucocorticoids, octreotide
Impaired conversion of T4 to T3 – amiodarone, glucocorticoids, contrast agents for oral cholecystography (eg, iopanoic acid), propylthiouracil, propanolol, nadolol

Nonthyroidal Illness (Sick euthyroid syndrome)

- Several disease states are associated with abnormal thyroid function tests including :
  - Acute hepatitis
  - Hepatoma
  - Acute intermittent porphyria
  - Acromegaly
  - Nephrotic syndrome
  - Cushing's syndrome
  - Acute psychosis
  - Depression

Treatment

- Thyroid function should not be assessed in seriously ill patients unless there is a strong suspicion of thyroid dysfunction, since there are many other factors in acutely or chronically ill euthyroid patients that influence thyroid function tests
- When thyroid dysfunction is suspected in critically ill patients, measurement of serum TSH alone is inadequate for the evaluation of thyroid function
- In critically ill patients with low free T4 and total T3 who do not appear to have an underlying primary thyroid disorder, we recommend not treating with thyroid hormone

Treatment

- Critically ill patients with suspected hypothyroidism and TSH ≥20 mU/L with low free T4 low should be treated with thyroid hormone replacement and reassessed after recovery. In the absence of suspected myxedema coma, repletion should be cautious, beginning with approximately half the expected full replacement dose of T4 .
- In critically ill patients with suspected hyperthyroidism (TSH usually <0.01 but can be as high as 0.05 mU/L, and normal or high-normal serum T4 and/or T3), we suggest antithyroid drug therapy

Case #5

- 68 y/o M presents with SOB & facial flushing every time he has to lift his hands above his head at work.
  - What's the name of this sign?

Pemberton's sign/maneuver

Goiter

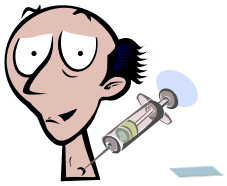
- Associated with iodine deficiency, hypo-, or hyperthyroidism
- When do we worry about it?
  - Impinges on wind-pipe
  - Dominant nodule/nodules involved (↑1.5 cm)
  - + Pemberton's sign
- Rarely causes swallowing difficulty before respiratory symptoms

Goiter

Case #6

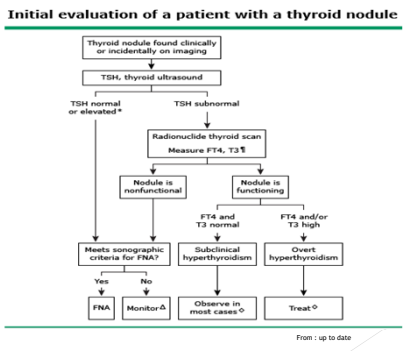
- 74 y/o M presents for evaluation of a lump in his neck he noticed while shaving.
- On exam a palpable nodule is felt
- What is the next step?

Thyroid Nodularity



- Noted on:
  - Self exam
  - Physician exam
  - Incidentally on imaging
- Higher risk
  - <30 or >60 yrs of age
  - Radiation history
  - Positive FH of PTC, MTC , MEN type 2
  - Male gender
  - Growth of nodule
  - Elevated TSH
  - Persistent dysphagia, dysphonia
  - Firm or hard consistency
  - Cervical adenopathy

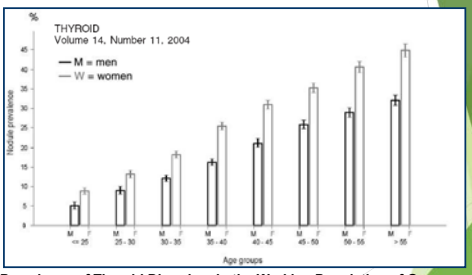
Thyroid nodularity



Thyroid Nodularity

- 5% of thyroid nodules are cancer, 95% benign
  - 50% of people at age 50 have thyroid nodules, 65% at age 80
  - 5-7% of people know they have a thyroid nodule

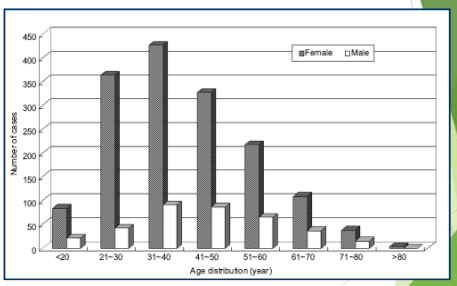
Nodule Prevalence



Prevalence of Thyroid Disorders in the Working Population of Germany: Ultrasonography Screening in 96,278 Unselected Employees

Thyroid. Nov 2004, Vol. 14, No. 11: 926-932

Papillary Thyroid CA Age and Gender Distribution



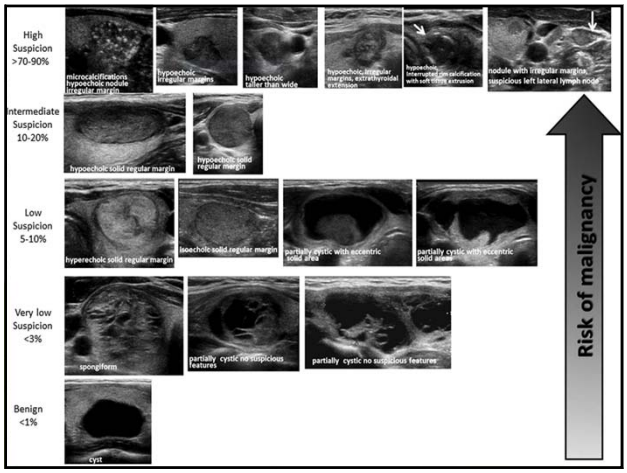
A 29-Year Retrospective Review of Papillary Thyroid Cancer in One Institution

Thyroid Jun 2007, Vol. 17, No. 6: 535-541.

Table 6. Sonographic Patterns, Estimated Risk of Malignancy, and Fine-Needle Aspiration Guidance for Thyroid Nodules

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule *with* one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins *without* microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, *without* microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules *without* any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).



Results

Diagnostic Category	Risk of Malignancy (%)	Usual Management*
Nondiagnostic	1-4	Repeat FNA usually
Benign	< 1%	Clinical follow-up 6-12 months
"Indeterminate follicular lesion, favor benign"	1-7%	Gene classifier or imaging follow up
Atypical Cells of Undetermined Significance (ACUS) "follicular lesion"	~ 5-10%**	Gene classifier or imaging follow up
Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy.
Suspicious for a Hürthle Cell Neoplasm	15-45	Surgical lobectomy.
Suspicious for Malignancy Papillary carcinoma Medullary carcinoma Other	60-75	Near total thyroidectomy or surgical lobectomy.***
Malignant	97-99	Near total thyroidectomy.***

Questions

Thyroid and pregnancy

- ↑ estrogen →increase thyroid binding globulin (TBG) →↑total T4 and T3. Levels of total T4 and T3 rise by approximately 50% during the first half of pregnancy, plateauing at approximately 20 weeks of gestation, at which time a new steady state is reached and the overall production rate of thyroid hormones returns to pre-pregnancy rates
- There is considerable homology between the beta subunits of hCG and TSH. As a result, hCG has weak thyroid-stimulating activity

Thyroid and pregnancy

- Serum hCG concentrations increase soon after fertilization and peak at 10 to 12 weeks.
- During this peak, total serum T4 and T3 concentrations increase.
- Serum free T4 and T3 concentrations increase slightly, usually within the normal range, and serum TSH concentrations are appropriately reduced
- This transient, usually subclinical, hyperthyroidism should be considered a normal physiologic finding.
- Later in pregnancy, as hCG secretion declines, serum free T4 and T3 concentrations decline and serum TSH concentrations rise slightly to or within the normal range.

Hyperthyroidism in pregnancy

- Diagnosis of true hyperthyroidism during pregnancy may be difficult because of the changes in thyroid function that occur during normal pregnancy.
- Commonest causes are Grave's disease (on exam will have goiter, or ophthalmopathy) and human chorionic gonadotropin (hCG)-mediated hyperthyroidism.
- TSI or TRAB will help confirm Graves disease

Hyperthyroidism in pregnancy

- Overt hyperthyroidism can lead to :
  - spontaneous abortion
  - Premature labor
  - Low birth weight
  - Stillbirth
  - Preeclampsia
  - Heart failure

Hyperthyroidism in pregnancy

- PTU is used in the 1st trimester and can be continued throughout (associated with more serious hepatotoxicity)
- At 2nd trimester switch to Methimazole (more potent than PTU, switching may increase the risk of maternal or fetal hypothyroidism)
- Both are teratogenic : Methimazole associated with more serious defects : aplasia cutis, a scalp defect. Other include : tracheoesophageal fistulas, patent vitellointestinal duct, choanal atresia, omphalocele, and omphalomesenteric duct anomaly.
- Beta blockers : Metoprolol/propranolol: neonatal growth restriction, hypoglycemia, respiratory depression, and bradycardia

Hyperthyroidism in pregnancy

- All fetuses of women with Graves' disease should be monitored for signs of fetal thyrotoxicosis (↑fetal HR, fetal goiter, advance bone age).
- Post partum Methimazole rather than PTU (due to associated hepatotoxicity) should be used for nursing mothers.
- Methimazole should be administered following a feeding in divided doses.
- When the maternal dose of methimazole is >20 mg daily, infants should have thyroid function tests assessed after one and three months.

Hypothyroidism and pregnancy

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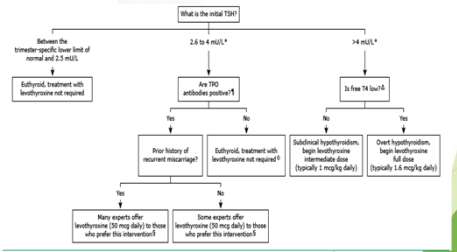
Management of pregnant women with or at risk for hypothyroidism



Hypothyroidism and pregnancy

- Complications of overt hypothyroidism include :
  - Preeclampsia and gestational hypertension
  - Placental abruption
  - Nonreassuring fetal heart rate tracing
  - Preterm delivery, including very preterm delivery (before 32 weeks)
  - Low birth weight
  - Increased rate of cesarean section
  - Postpartum hemorrhage
  - Perinatal morbidity and mortality
  - Neuropsychological and cognitive impairment in the child

Monitoring

- Serum TSH measured in 4 weeks.
- The goal is to maintain TSH in the lower half of the trimester-specific reference range. If not available, a goal TSH of <2.5 mU/L is reasonable.
- If the TSH remains above the normal trimester-specific reference range, the dose of T4 can be increased by 12 to 25 mcg/day.
- TSH should be measured every four weeks during the first half of pregnancy because dose adjustments are often required.
- TSH can be monitored less often (at least once each trimester) in the latter half of pregnancy, as long as the dose is unchanged

Questions

References

- Up to date
- American thyroid association guidelines
- AACE guidelines