HYPERTHYROID STATE

Background

1. Definition: Hypermetabolic state caused by excess thyroid hormone

Pathophysiology[1]

1. Pathology of Disease: Clinical symptoms due to thyroid hormone causing increased catabolic activity and enhancement of catecholamine sensitivity
2. Cause of elevated thyroid hormone depends on etiology:
    - Graves' Disease (60-80% of cases): autoimmune-based antibody (Thyroid Stimulating Immunoglobulin/TSI) activation of Thyroid Stimulating Hormone (TSH) receptor resulting in increased thyroid hormone production
        - Familial
        - Autoimmune
    - Toxic Multinodular Goiter (MNG) (5% of cases):
        - Focal or diffuse hyperplasia of follicular cells whose function is independent of TSH regulation
        - 10X more common in areas where iodine intake low
        - Prevalence increases with age
    - Thyroiditis[2,3] (10%)
        - Painless - inflammatory mediated release of thyroid hormone
            - Hashimoto's (Chronic Lymphocytic or Chronic Autoimmune) Thyroiditis
                - Lymphocyte infiltration and formation of Hurthle cells
                - Most common inflammatory thyroid disorder
                - Female to male ratio 7:1
                - Usually 40-60 years of age
                - 90% symmetric, diffuse thyroid enlargement
                - Thyroid Peroxidase antibodies (TPOab) positive in 90-95%
                - RAIU (radioactive iodine uptake) low, normal or high (not necessary for diagnosis)
            - Postpartum
                - 5-7 % incidence after delivery
                - 50% have a family history of autoimmune thyroid disease
                - Painless, non-tender goiter 2-6 months after delivery
                - Can present with hypothyroidism or hyperthyroidism
                - 80% elevated TPOab levels, ESR normal
                - 80% have normal thyroid function at one year postpartum
                    - 30-50% develop permanent hypothyroidism within 9 years
                    - Predictive factors for development of permanent disease within 9 years:
                        - Hypothyroidism during acute phase
                        - High level of TPOab
                        - Hypoechogenic US pattern

        - If TPOab positive have 70% chance of recurrence with subsequent pregnancy
    - Subacute Lymphocytic
        - Similar to Postpartum but in the absence of pregnancy
        - Lymphocytic infiltrate similar to Hashimoto's with absence of fibrosis, Hurthle cells and lymphoid follicle formation
        - 4:1 Female to male ratio
        - Risk increased in areas of iodine deficiency
        - 50% present with small goiter
        - 5-20% present with hyperthyroidism then progress to hypothyroid and euthyroid states, respectively
        - Distinguished from Subacute Thyroiditis by absence of pain and tenderness
        - Low RAIU
    - Lithium
    - Interferon-alpha or Interleukin treatment
    - De Quervain thyroiditis
- Painful
    - Subacute, (de Quervain's, Giant Cell) Thyroiditis
        - Most common cause of thyroid pain
        - 4:1 female to male ratio
        - Usually 40-50 years of age at onset
        - Prodromal myalgias, pharyngitis, fever, fatigue followed by tender, diffuse goiter and neck pain
        - Pain often radiates to ears, jaw or throat
        - Possibly virus mediated (summer peak)
        - ESR, CRP elevated; mild anemia common
        - RAIU low (elevated in Graves' Dz)
        - Ultrasound - heterogeneous, decreased or normal blood flow (Graves' Dz enhanced flow)
    - Suppurative[2]
        - Rare, predominantly Streptococcal species infection
        - Can be fungal, mycobacterial or parasitic
        - Predisposing factors
            - Congenital abnormalities
            - Immunosuppression
        - Patients present with acute, unilateral anterior neck pain with overlying erythema with tenderness on exam
            - Fever, dysphagia, dysphonia also present
        - ESR, White blood cell count elevated (+ left shift)
    - Radiation-Induced
        - 1% of patients receiving radioactive iodine therapy or radiation therapy for head/neck malignancies
        - Usually presents 5-10 days post treatment
        - Presents with pain and tenderness
        - Risk Factors:

        - High dose irradiation
        - Younger age
        - Female
        - Pre-existing hypothyroidism
    - Post thyroid trauma
- Toxic Adenoma: similar pathophysiology to Toxic MNG
- Treatment Induced[3]:
    - Amiodarone (37% iodine component)
        - Iodine-induced increase in thyroid hormone production
        - Up to 5-10% of treated patients; months to years after initiation
        - Check thyroid function tests at baseline, 1, 3 months after initiation, 3-6 month intervals thereafter
        - Distinguish Type 1 (iodine-induced) from Type 2 (thyroiditis)
            - Type 1 - underlying thyroid autonomy in nodular goiter; RAIU may be measurable; MMI therapy
            - Type 2 - direct destructive effect; RAIU undetectable; Corticosteroid therapy
    - Lithium - painless thyroiditis; onset often > 1 year after initiation
    - Radiographic contrast which contain iodine; weeks to months after therapy
    - Interferon and Interleukin-2 – painless thyroiditis; months after initiation
- Factitious: intentional ingestion of excess thyroid hormone
- Tumors (rare): metastatic thyroid cancer; thyroid hormone producing ovarian tumors; trophoblastic tumors producing human chorionic gonadotrophin which activates TSH receptors; TSH-secreting pituitary tumors
- Subclinical[4,5]
    - Release of excess thyroid hormone; etiologies similar to overt hyperthyroidism
    - Exclude other causes of low TSH
        - Dopamine, Glucocorticoid use
        - Euthyroid Sick Syndrome
        - Pituitary source (TSH deficiency)
        - Hypothalamic source (Thyrotropin-releasing hormone deficiency)
        - Psychiatric affective disorders (generally low T4 and T3 levels vs. mid to high reference range in subclinical)
    - Treatment indicated if serum TSH is < 0.1 mIU/mL

3. Prevalence
    - 1.2 % (0.5 % overt; 0.7 % subclinical)[3]
    - 2 percent of women; 0.5 percent of men in community-based studies[1]
    - 15% prevalence of subclinical hyperthyroidism in patients over 70 years old in iodine-deficient regions[4]
4. Risk Factors: Varies by the cause:
    - Graves' Disease: female, genetic predisposition, co-morbid diabetes mellitus, smoking
    - Toxic Multinodular Goiter: living in an iodine deficient area, smoking
    - Thyroiditis: preceding viral illness

- Toxic Adenoma: radiation exposure, younger age, living in an iodine deficient area.

5. Morbidity / Mortality:
    - Most significant issues: cardiovascular disease, atrial fibrillation, embolic events, cardiovascular collapse, weight loss, osteoporosis, hip fractures

Diagnostics

1. History[1,5,6]
    - Heat intolerance
    - Hyperactivity
    - Increased appetite
    - Increased sweating
    - Diarrhea
    - Hand tremor
    - Palpitations
    - Dyspnea/exertional dyspnea
    - Chest pain
    - Emotional lability
    - Anxiety/nervousness/irritability
    - Cognitive complaints
    - Headaches
    - Weight loss
    - Musculoskeletal pain
    - Oligomenorrhea/menstrual irregularities
    - Sleep disturbance
2. Physical Examination[5]
    - Weight loss
    - Tachycardia
    - Irregular heart rhythm
    - Elevated blood pressure
    - Enlarged or nodular thyroid gland
    - Proximal muscle weakness
    - Tremor
    - Exophthalmos
    - Pretibial myxedema
    - Hyperreflexia
    - Thyroid bruit
    - Acropachy (swelling of fingers)
    - Gynecomastia
    - Hair loss
    - Lid lag
    - Proptosis
    - Palmar erythema
3. Laboratory evaluation:
    - TSH/Free T4 – accuracy of diagnosis improves when both ordered simultaneously; TSH highest sensitivity/specificity of any single test

- Blatant hyperthyroidism - Free T4 / Free T3 both elevated and TSH undetectable
- Milder hyperthyroidism – Serum T4 and Free T4 can be normal with only serum T3 elevated in conjunction with TSH < 0.01 mum
- Nonstandardization of Free T3 assays makes Total T3 preferred in practice
- Subclinical Hyperthyroidism = normal Free T4, normal Free or Total T3 and TSH below lower limit of normal
- Normal TSH rules out hyperthyroid unless TSH- producing pituitary adenoma (pituitary lesion on MRI) or thyroid hormone resistance (family history and genetic testing of T-3 receptor alteration)
- If free thyroid hormone elevated in face of normal TSH (euthyroid hyperthyroxinemia), further investigation warranted. Possibilities include:
    - Thyroid hormone binding protein disorders
        - Increased T4 binding globulin (TBG)
            - Hereditary X-linked
            - Acquired: pregnancy, estrogen admin, hepatitis, acute intermittent porphyuria, 5-FU, Perphenazine, some narcotics,
        - Increased trans-thyretin (TTR)
        - Familial hyperthyroxinemic dysalbuminemia
        - Thyroid hormone binding immunoglobulin excess
        - Drugs preventing conversion of T4 to T3 – amiodarone, high dose propranolol, acute psychosis, high altitude, amphetamine abuse
- Subacute Thyroiditis
    - Low TSH, NL Free T4 and Total T3
    - Repeat in 3-6 months to verify persistent state
    - Etiology should be elucidated if possible (most common - Toxic Multinodular Goiter, Graves' Dz or Toxic Adenoma)
- Diagnosis in Pregnancy
    - Most common cause = Graves' Disease; can be caused by human chorionic gonadotropin (hCG)-producing molar pregnancy or choriocarcinoma
        - Graves' Dz confirmed by presence of Graves' Ophthalmopathy and TRAb (TSH Receptor Antibodies)
            - 5% TRAb negative (usually milder disease)
        - Distinguish GD from hCG-producing disease by the absence of eye signs or TRAb in hCG-producing disease
        - TRAb levels should be used when etiology unclear (sensitivity 95%; specificity 99% for Graves' Ds)
        - Patients treated with Radioactive Iodine (I^{131}) or thyroidectomy prior to pregnancy should have TRAb levels measured at 22-26 weeks or initially in 1^{st} trimester and then repeated at 22-26 weeks if elevated
            - TRAb can cross the placenta and affect fetal thyroid function
            - Measurement not necessary if intact thyroid present (i.e. no I^{131} or thyroidectomy)

        - Early pregnancy experiences physiologic thyroid changes which mimic hyperthyroidism biochemically (requires no treatment)
            - TSH below nonpregnant reference range in first half of normal pregnancy (hCG stimulation effect)
            - Lower limit of normal TSH reference ranges can be used during 2nd half of pregnancy
            - Repeat abnormalities in 1st trimester at 3-4 week intervals to ensure the absence of subclinical disease
        - Serum Total T4 and T3 increase in early pregnancy; beginning late 1st trimester 1.5 times upper limit of reference range is normal
        - Method specific reference ranges for each trimester should be used by the manufacturer
    - Post-partum diagnosis - occurs after 10% of U.S. deliveries
        - Need to distinguish between postpartum thyroiditis vs. postpartum Graves' Dz
            - Goiter more pronounced in Graves' Ds
            - While TRAb may be measurable in thyroiditis, high levels more associated with Graves' Dz
            - If Thyroid Uptake scan needed - I^{123} should be used in breastfeeding due to more rapid clearance
            - Total T3 to T4 ratios are generally (> 20) in Graves' Ds patients while lower in Thyroiditis patients
        - Postpartum Thyroiditis
            - Smoking and Bottle feeding increase risk
    - Spurious increased levels of Free T4 can occur with heparin
    - Further testing should be based on clinical suspicion / epidemiologic data
        - Tests may include:
            - Antithyroid antibodies
            - CBC (anemia, granulocytosis, lymphocytosis)
            - Electrolytes (hypercalcemia)
            - Liver function tests (transaminase elevation, alkaline phosphatase elevation)
    - NOTE: If moderate to severe hyperthyroidism, new onset ophthalmopathy plus symmetrical enlargement of thyroid is present, no need for further workup - diagnostic of Graves' Disease
4. Diagnostic imaging:
    - Radionucleotide uptake (RAIU) scan when clinical signs/symptoms do not support diagnosis of Graves' Disease
        - Distinguishes elevated or normal intake from near zero uptake etiologies
        - Diagnostic patterns of uptake
            - Graves' Disease - elevated uptake
            - Toxic Nodular Goiter - normal or high uptake (unless recent exposure to iodine)
            - Subacute Thyroiditis - low uptake
    - If RAIU contraindicated (pregnancy) the following tests may help differentiate Graves' Dz from MNG or other autoimmune disorder:

        - Thyroid Peroxidase antibodies (TPOab)
        - TSH receptor antibodies (TRAb)
        - Thyroglobulin
    - If TSH, T4 and T3 elevated - MRI of pituitary region (TSH-secreting pituitary adenoma)

Differential Diagnosis

1. Key Differential Diagnoses: Graves' Disease, Thyroiditis, Toxic Multinodular Goiter, Toxic Adenomas, Treatment-Induced
2. Extensive Differential Diagnoses: Pituitary Lesions, Pregnancy, Iodine Exposure, Anxiety, Essential Tremor, Substance-Induced (Caffeine, cocaine, amphetamine, or other sympathomimetic)

Therapeutics

1. Acute Treatment[3]
    - Beta blockers should be considered in all symptomatic patients;
        - Reduces heart rate, blood pressure, muscle weakness, tremor, irritability, emotional lability and improves exercise tolerance
        - Propanolol, 10-40 mg TID-QID (nonselective, most commonly used; available once daily preparation)
            - Preferred agent in lactation
        - Atenolol, 25-100 mg qD or BID (relative beta-1 selectivity)
        - Metoprolol, 25-50mg QID (relative beta-1 selectivity; available once daily preparation)
        - Nadolol, 40-160 mg QD (non-selective)
        - Esmolol, 50-100 ug/kg/min (ICU setting, severe disease)
        - Contraindicated in bronchospastic asthma
            - If asthma well relatively inactive and heart rate control imperative (or in mild obstructive airway disease), non-selective B-blocker may be used with close monitoring (ex. nadolol)
    - Calcium channel blockers can be used for those who cannot tolerate beta blocker:
        - Diltiazem, Verapamil
    - Iodine (Radio contrast agents) may be used to block peripheral conversion of T4 to T3
    - Thyroid Storm (rare)[3]
        - Multimodal Treatment - B-blockers, anti-thyroid drugs, inorganic iodide, corticosteroids, aggressive cooling, volume resuscitation, ventilatory support and ICU monitoring
        - Criteria include tachycardia, dysrrhthmias, hypotension, heart failure, fever, agitation, delerium, psychosis, coma, gastrointestinal symptoms and hepatic failure
        - Pharmacotherapy
            - PTU 500-1000mg load, then 250mg q 4 hours
            - MMI 60-80mg/day
            - Propranolol 60-80mg q 4 hours
            - Iodine (saturated solution of K+ iodide) 250mg q 6 hours

- Hydrocortisone 300mg IV load, then 100mg q 8 hours

2. Further Management (24 hrs)
    - Care should be taken to avoid a hypothyroid state
3. Long-Term Care[1,3]
    - Graves' Disease - Three modalities:
        - Radioactive Iodine (I^{131}) - most preferred in US
            - Optimum candidates:
                - Females desiring pregnancy (at least 4-6 months post treatment)
                - Increased surgical risk
                - Elderly patients with cardiovascular risk
                - Prior irradiation or surgery to neck
                - Contraindications to antithyroid medications
                - Lack of access to high-volume thyroid surgeons
            - CONTRAINDICATIONS: Pregnancy, lactation, thyroid cancer, inability to comply with safety guidelines, females planning pregnancy within 4-6 months
            - Treat with B-blockers prior to ^{131}I therapy as necessary to control symptoms
            - Can consider use of methimizole prior to therapy in patients at risk for complications (not unanimously recommended)
                - Discontinue 3-5 days prior to therapy; restart 3-7 days post treatment; taper over 4-6 weeks
            - Co-morbidities should be stabilized prior to treatment
            - Excess iodine intake should be stopped 7 days prior to treatment
            - Propylthiouracil (PTU) increases thyroid resistance to ^{131}I
            - COMPLICATIONS: Thyroid Storm (rare); temporary decreased Testosterone in men (3-4 months)
        - Antithyroid Medications
            - Goal to produce euthyroid state as quickly and safely
            - Cohort to consider medication therapy:
                - High probability of remission (mild disease, small goiters, low-titer TRAb)
                - Elderly with limited life expectancy
                - Prior irradiation or surgery to neck
                - Lack of access to high-volume thyroid surgeons
                - Moderate to severe Graves' Ophthalmopathy
                - CONTRAINDICATIONS TO ANTITHYROID MEDS: absolute neutrophil count (ANC) < 500 or tranaminases > 5 fold upper limit of normal
            - Methimazole (MMI) should be used in all Graves' Dz patients who choose medication except in the following cases:
                - First trimester of pregnancy (Propylthiouracil preferred), thyroid storm or if adverse reactions to methimazole
                - Baseline CBC and liver profile recommended

    - Higher doses advised initially (10-20 mg daily); taper to maintenance dose (5-10 mg daily)
    - Advantages over PTU - once daily dosage; decreased risk of major side effects
    - Major toxicity: cholestatic hepatotoxicity; aplasia cutis of scalp found in babies to mothers on MMI in first trimester (associated with MMI embryopathy including choanal/exophageal atresia; arthropathy/lupus-like syndrome rare
- Propylthiouracil (PTU)
    - Shorter duration of action; dosing bid to tid
    - Start 50-150 mg tid; as thyroid function tests normalize, reduction to 50 mg bid-tid usual for maintenance
    - Major toxicities: agranulocytosis; ANCA-positive small vessel vasculitis (increased risk with time); fulminant hepatic necrosis; arthropathy/lupus-like syndrome rare
    - PTU should be discontinued if transaminase levels increase by 3 fold the upper limit of normal and fail to improve within one week of initial recognition of significant elevation
    - MMI can be used to control thyrotoxicosis in the face of PTU-induced mild to moderate hepatotoxicity
- Monitoring
    - Baseline Free T4 and TSH
    - TSH may remain suppressed for months after initiation of meds (suboptimal monitoring value early in course)
    - Free T4 four weeks after initiation; T3 levels can be monitored as Free T4 levels will normalize with consistent elevation of T3 levels
    - Monitor q 4-8 wks until euthyroid state reached; then q 2-3 months
    - White Blood Cell Count w/ Differential should be obtained during febrile illness and onset of pharyngitis for all patients taking antithyroid meds (routine monitoring of WBC count is not necessary); If agranulocytosis present, do not switch to the other antithyroid medication due to cross-reactivity
    - Liver profile should be assessed in patients taking PTU who develop pruritic rash, jaundice, light colored stools or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea or fatigue
    - Routine monitoring of liver profiles has not been proven to prevent severe hepatotoxicity; discontinue medication if elevations of 3 times upper limit of normal due not normalize within one week; REFER TO GI IF

TRANSAMINASES DO NOT RETURN TO NORMAL LEVELS DURING WEEKLY SURVEILLENCE
        - Minor skin reactions (5% incidence for either medication) can be treated with concurrent antihistamines w/o stopping medication; persistent minor side effects should prompt discontinuation of medication and consideration for ablation vs. surgery unless contraindicated;
        - If severe allergic reactions develop, do not switch to alternative medication
    - Duration of Therapy in Graves' Disease
        - MMI - continue for 12-18 months, then taper or discontinue if TSH normal (SOR:B) [JFP 2011]
        - TRAb levels prior to discontinuation assists in predicting which patients can be weaned (normal levels confer greater chance for remission)
        - If Graves' patient becomes hyperthyroid after finishing therapy with MMI, consider I^{131} treatment or thyroidectomy
        - Considered in remission if normal TSH, FT4 and T3 for 12 months after finishing ATD (~ 20-30% remission rate after 12-18 months)
        - Reduced remission rate in patients with goiter's > 80 grams, men and smokers
        - Elevated TRAb and increased thyroid blood flow have higher relapse rates
- Thyroidectomy
    - Indications:
        - Symptomatic compression
        - Large goiter (> 80 grams)
        - Low uptake radioactive iodine uptake scan
        - Suspected malignancy
        - Large nonfunctioning/hypofunctioning nodule
        - Co-existing hyperparathyroidism mandating surgery
        - Females desiring pregnancy (within 6 months post treatment)
        - Moderate to severe Graves' Ophthalmopathy
    - Contraindications:
        - Co-morbidities increasing surgical risk,
        - Pregnancy (relative - only use if rapid control of symptoms needed and medications contraindicated; best avoided in 1^{st} and 3^{rd} trimester; optimum time end of 2^{nd} trimester; still ~5% risk of preterm labor)
    - Complications:
        - Hypocalcemia
            - Graves' Dz

- OK to discharge if asymptomatic and serum Ca++ > 7.8 and not decreasing
- Low i-PTH immediately postoperatively predicts low calcium and should prompt calcium and calcitriol treatment
- Persistently low Ca++ postoperatively - check magnesium level (replace if low)

▪ Prophylactic Ca++ supplementation
- Calcium Carbonate 1250-2500mg QID
- Taper by 500mg q 2 days or 1000mg q 4 days

▪ Calcitriol - 0.5mcg qD for 1-2 weeks
- Taper based on Ca++ and/or i-PTH levels

o Superior Laryngeal nerve injury

- Graves' Dz:
  - o High-Volume Surgeon recommended (>30 good; > 100 best)
  - o Total (~ 0% recurrence at 5 yrs) or Near-total (8% persistence/recurrence) thyroidectomy procedure of choice
  - o MMI to make euthyroid prior to surgery (taper prior to surgery)
  - o Potassium Iodide just prior to surgery (reduces thyroid blood flow, vascularity and intraoperative blood loss)
  - o Pretreat with Beta-blocker and Potassium Iodide if unable to use MMI
    - ▪ Wean Beta-blocker post-operatively
  - o Thyroid Replacement
    - ▪ L-thyroxine 1.7 mcg/kg
    - ▪ Check TSH 6-8 weeks postoperatively

▪ Pediatric Treatment
- MMI (first line in most children - 0.2-0.5 mg/kg daily)
  - o Baseline labs recommended: CBC, Liver profile
  - o Stop immediately if pruritic rash, jaundice, light colored stools, dark urine, arthralgias, GI symptoms, fever or pharyngitis
  - o Monitor Free T4, Total T3 and TSH monthly initially then q 2-4 months
  - o Treat for 1-2 years then stop or reduce dosage depending on response
  - o I^{131} if not in remission after MMI therapy
- I^{131} (contraindicated < 5 years of age due to cancer risk)
- Thyroidectomy (higher complication rate than adults)

o Toxic Multinodular Goiter / Toxic Adenoma

▪ I^{131} favored in advanced age, patients with severe co-morbidities, prior anterior neck surgery, small goiter size, lack of access to high volume surgeon (SOR:A)[5]

        - Pretreatment with beta-blockers (+/- MMI) prior to I^{131} if increased risk of worsening thyrotoxic symptoms (age > 60, heart disease or severe thyroid disease)
        - If hyperthyroid state remains 6 months after therapy, repeat I^{131} recommended
    - Thyroidectomy/lobectomy/isthmusectomy favored in patients with compressive symptoms, concern for cancer, coexisting hyperparathyroidism, goiter > 80 grams, sub or retrosternal extension, need for rapid correction of elevated thyroid state
        - Same preoperative/postoperative care recommended above with the exception of no concern for hypocalcemia in lobectomy patients
- Subacute Thyroiditis[2,3]
    - Treat if TSH persistently < 0.1 mIU/mL and if > 65, postmenopausal women not taking estrogens or bisphosphonates, patients with heart disease, cardiac risk factors or osteoporosis and symptomatic patients
    - Treat if TSH below lower limit of normal but > 0.1 in patients over 65 years of age, those with heart disease or symptomatic
    - Treatment should be based on etiologic agent
        - Beta-blockers
        - Non-steroidal anti-inflammatory medications (NSAIDs)
        - Corticosteroids if persistent pain after several days of high dose NSAIDs
            - Prednisone 40 mg / day for 1-2 weeks followed by gradual taper over 2-4 weeks
        - Patients treated with steroids had quicker resolution of pain (median of 48 hours)
    - Levothyroxine during hypothyroid stage
        - Usually withdrawn within 3-6 months after verification of normal thyroid function
    - Recurrent in 2% of patients
- Painless Thyroiditis
    - Beta-blockers
    - Antithyroid drugs SHOULD NOT be used (new thyroid hormone synthesis already low)
    - Corticosteroids for extremely severe cases (rare)
- Pregnant Patient
    - If treatment required - PTU in 1st trimester; MMI thereafter
    - Antithyroid Drugs and TRAb cross the placenta; T4 and T3 cross the placenta in very small amounts
    - PTU - associated with fatal hepatotoxicity; hence only in 1st trimester
        - 0.1-0.5 percent of patient may develop agranulocytosis
    - MMI - well studied evidence of teratogenicity (aplasia cutis, choanal/esophageal atresia); hence use after 1st trimester

        - Female patients taking MMI should obtain pregnancy confirmation test at first suggestion of pregnancy; switch to PTU if in 1st trimester; switch back to MMI at onset of 2nd trimester
            - Potency ratio of 20-30:1 (MMI to PTU) be used when switching meds [example: 300mg PTU = 10-15 mg MMI)
            - Alternative is to remain on PTU and have liver function tests drawn every 4 weeks in concert with thyroid function tests
        - MMI (15-30 mg/day) or PTU (100 mg TID starting dose with 100-200 mg daily maintenance dose thereafter)
        - Goal of therapy: Keep Total T4 and T3 values above lower limit of normal; Free T4 should be kept at or just above upper limit of normal nonpregnant reference range
            - TSH should not be used as sole therapy guidance and may remain suppressed as long as above goals are reached
            - Free T4 is the marker which correlates best with good fetal outcome
        - Thyroidectomy - indicated when aggressive medical management has failed to control disease or if anti-thyroid medications cannot be used
            - If thyroidectomy necessary, late 2nd trimester targeted for execution
                - High-risk obstetrical counseling advised prior to surgery
                    - ~5% risk of preterm labor
                - 10-14 days of preoperative iodine, along with anti-thyroid meds and beta-blockers may be used to control symptoms
    - PostPartum Thyrotoxicosis
        - Postpartum Thyroiditis
            - Beta-blockers to control symptoms recommended
                - Propranolol has lowest breast milk excretion
                - Metoprolol can be used
            - Levothyroxine for those with symptomatic hypothyroidism or TSH levels over 10 mIU/mL
        - Lactating Patient
            - MMI and PTU cross into breast milk (small amounts) but no evidence of abnormal infant thyroid function or development
            - MMI preferred in lactation due to PTU associated hepatic toxicity
    - Subclinical Disease
        - There is conflicting evidence regarding the benefit of treating subclinical hyperthyroidism in adults older than 60-65 years of age who have cardiovascular risk factors (SOR:C)[4]
    - Graves' Ophthalmopathy (GO)[3]
        - Most common in patients with current or history of Graves' Dz
            - Risk Factors
                - Radiodine therapy
                - Smoking
                - High pretreatment T3 levels (> 325 mg/dL or > 5 nmol/L)
                - High pretreatment TRAb levels

        - Hypothyroidism following radioiodine therapy
    - ~ 50% of Graves' Dz patients have signs or symptoms of GO
    - Active phase of GO disease best characterized by GO Clinical Activity Score (CAS)[3]
    - Severity and activity of GO disease must be considered in all treatment decisions of hyperthyroidism
        - Graves Dz + Mild GO - I^{131} , MMI and thyroidectomy acceptable
        - Graves Dz + Mild GO (smoker) - concurrent steroids if I^{131} therapy chosen (SOR:A)[5]
        - Graves Dz + moderate to severe GO - MMI or thyroidectomy
            - I^{131} less desirable
    - Prevention:
        - Quick achievement/maintenance of euthyroid levels in hyperthyroid patients with GO or risk factors for developing GO
        - All patients with Graves' Dz should be advised to stop smoking and advised of the negative impact of second hand smoking
- TSH-secreting Pituitary Tumors
    - Surgical resection preceded by octreotide or bromocriptine
- Other treatment modalities: surgery, thyroid artery embolization, percutaneous toxic thyroid nodule ethanol injection, and nutritional supplementation with L-carnatine (2-4 g/day)[6].

Follow-Up

1. Patients treated for hyperthyroid disease have increased all-cause mortality risk and increased risk of death from thyroid, cardiovascular, cerebrovascular disease as well as hip fractures
    - Those treated for hyperthyroidism have increased incidence of insulin resistance and obesity[1]
2. Return to Office[1]
    - Close observation when initiating treatment,
    - Post-treatment follow-up frequent during first three months.
    - Annual follow-up once patients stable
    - Educate patients for signs/symptoms of failed treatment or hypothyroidism
    - Subclinical hyperthyroidism: recheck levels every 2-4 months[5]
3. Refer to Specialist
    - Radioiodine Therapy, Amiodarone Induced, Graves' Opthalmopathy: Endocrinologist, Cardiologist or Ophthalmologist as appropriate
    - Cosmesis/Obstruction/Failed Medical Therapy: Surgeon
4. Admit to Hospital
    - Severe cardiovascular symptoms such as CHF, atrial fibrillation, or angina.
    - Thyroid storm characterized by delirium, severe tachycardia, fever, vomiting, diarrhea, and dehydration.
5. Following Therapy
    - After MMI completed, thyroid labs q 1-3 months for 6-12 months

Prognosis[7]

1. Untreated hyperthyroidism may result in:
    - Severe cardiomyopathy (6% prevalence)
    - Atrial fibrillation/flutter found in 8.3% of hyperthyroid patients within 30 days of diagnosis
    - Pulmonary Hypertension[5]
    - Ischemic Stroke (age 18-44 years)[5]
    - Decreased bone mineral density, hip fracture
    - Neuropsychiatric problems
    - Some ocular, cardiac, and psychologic symptoms may not be reversible even with adequate treatment
2. Graves' Dz: absence of or small goiter better outcomes than medium or large goiter patients; most multi-nodular goiter patients had relapse within 1 year of medication cessation
3. Subclinical Hyperthyroidism:
    - Women over 60 and TSH between 0.1 - 0.4 mIU/mL have 1% risk of progression to overt hyperthyroidism per year[4]
    - Women over 65 and TSH under 0.1 mIU/mL have a 27% progression to overt hyperthyroidism over 2 years[4]
    - Graves' Dz- variable progression vs. remission over 41 months[4]
    - Multinodular Goiter - stable thyroid function over 41 months[4]
    - 41% higher risk of all cause mortality compared to euthyroid controls
    - Cardiovascular effects[4]
        - Increased average heart rate
        - Increased risk of atrial dysrrythmias; age and risk factor adjusted risk is 2.8 compared to euthyroid control patients
        - Increased left ventricle mass
        - Reduced heart rate variability and suspected subsequent increase in cardiovascular events
    - Bone and Mineral Metabolism
        - Reduced Bone Mineral Density; questionable increased fracture risk
        - Most significant in postmenopausal women (vs. premenopausal women or men)
        - Limited-quality evidence regarding benefit of treating decreased bone mineral density in subclinically hyperthyroid patients (SORT B)[5]
    - Quality of Life[7]
        - Higher prevalence of palpitations, nervousness, tremor, heat intolerance, sweating, lower functional health and well-being
        - ? casual relationship between subclinical hyperthyroidism and cognitive decline

Prevention

1. The U.S Preventive Services Task Force currently concluded that there is insufficient evidence to recommend for or against routine screening for thyroid disease in adults. **I recommendation** (SOR:C)[4]

2. The American Thyroid Association, the American Association of Clinical Endocrinologists, and The Endocrine Society recommend against routine screening for subclinical thyroid disease (SOR:C)[4]
3. TSH should be measured in any patient older than 60 years of age who presents with fatigue, atrial fibrillations, weight loss, and shortness of breath (SOR:B)[5]

Patient Education

1. Hyperthyroid Information from FamilyDoctor.org: http://familydoctor.org/online/famdocen/home/common/hormone/869.html
2. Hyperthyroid Information from Endocrineweb.com: http://www.endocrineweb.com/conditions/hyperthyroidism/hyperthyroidism-overactivity-thyroid-gland-0

References

3. Reid JR, Wheeler SF. Hyperthyroidism: Diagnosis and Treatment. *Am Fam Physician* 2005;72:623-30, 635-6.
4. Bindra A, Braunstein GD. Thyroiditis. *Am Fam Physician* 2006;73:1769-763.
5. Bahn, RS, et al. Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* 2011;17(No. 3):457-520.
4. Donangelo, I, Braunstein, GD. Update on Subclinical Hyperthyroidism. *Am Fam Physician* 2011;83(8):933-38.
5. Ghandour, A, Reust C. Hyperthyroidism: A Stepwise Approach to Management. Journal Fam Prac 2011;60(7):388-95.
6. Benvenga et al. Usefulness of L-Carnitine, A Naturally Occurring Peripheral Antagonist of Thyroid Hormone Action, in Iatrogenic Hyperthyroidism: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *The Journal of Clinical Endocrinology & Metabolism* 2001;86(8):3579–3594.
7. Nygaard, B. Clinical Evidence Concise: Hyperthyroidism. *Am Fam Physician* 2007;76(7):1014-1016.

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