Special Considerations for Women and Thyroid Disease

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Purpose

Efforts must be made to improve care for women with thyroid disease who often lack access to trained providers. Inappropriate diagnosis or inappropriate dosing of hormone therapy may raise several issues for women including increased risk of miscarriages or premature labor. Supraphysiologic and infraphysiologic dosing of thyroid hormones can result in osteoporosis, arrythmias, dyslipidemias and poor quality of life.

Outcome Objectives

- Upon successful completion of the activity, participants should be able to:
- Identify and differentiate the sign and symptoms between menopause and hyperthyroidism.
- Diagnose and manage thyroid pathology in pregnancy and postpartum women.
- Incorporate lifestyle modifications for their patients to help manage thyroid function.

Introduction

- Pregnancy is associated with physiological changes in the thyroid gland, leading to hormonal and metabolic variations in relation to pregnancy.
- Autoimmune thyroid dysfunctions remain a common cause of hyperthyroidism and hypothyroidism in pregnant women.
- Graves' disease accounts for 85% of all cases of hyperthyroid, whereas Hashimoto thyroiditis is the most common cause of hypothyroidism.

Introduction

Thyroid disorders are the second most common endocrinologic disorders found in pregnancy:

- Overt hypothyroidism is estimated to occur in 0.3-0.5% of pregnancies.
- Subclinical hypothyroidism appears to occur in 2-3%.
- Hyperthyroidism is present in 0.1-0.4%.

Introduction

- The clinical manifestations of hyperthyroidism are largely independent of its cause.
- Most patients with overt hyperthyroidism have a dramatic constellation of symptoms.
- The classic symptoms of hyperthyroidism include heat intolerance, tremor, palpitations, anxiety, weight loss despite a normal or increased appetite, increased frequency of bowel movements, and shortness of breath.

Introduction

The menopausal transition, or perimenopause, begins on average four years before the final menstrual period (FMP) and includes a number of physiologic changes that may affect a woman's quality of life.

It is characterized by irregular menstrual cycles and marked hormonal fluctuations, often accompanied by hot flashes, sleep disturbances, mood symptoms, and vaginal dryness (1-6).

Signs/Symptoms of Hyperthyroidism

Signs/Symptoms of Hyperthyroidism

Skin:

- Skin is warm in hyperthyroidism due to increased blood flow; also smooth because of a decrease in the keratin layer (7).
- Onycholysis (loosening of the nails from the nail bed, Plummer's nails) and softening of the nails.
- Hyperpigmentation (8).
- Pruritus and hives (9).
- Vitiligo and alopecia areata, which can occur in association with autoimmune disorders.
- Thinning of the hair.

Signs/Symptoms of Hyperthyroidism

Eyes:

- Stare and lid lag occur in all patients with hyperthyroidism (10). Lid lag is evaluated by having the patient follow the examiner's finger as it is moved up and down. The patient has lid lag if sclera can be seen above the iris as the patient looks downward.
- Ophthalmopathy is characterized by inflammation of the extraocular muscles and orbital fat and connective tissue, which results in proptosis (exophthalmos), impairment of eye muscle function, and periorbital and conjunctival edema. Ophthalmopathy is more common in patients who smoke cigarettes.

Signs/Symptoms of Hyperthyroidism

Cardiovascular:

- Patients with hyperthyroidism have increase in cardiac output, due both to increased peripheral oxygen needs and increased cardiac contractility.
- Heart rate increased, pulse pressure widened, and peripheral vascular resistance decreased (12). Systolic hypertension is common (11).
- Atrial fibrillation occurs in 10 to 20 percent of patients with hyperthyroidism, and it is more common in older patients (13).
- Other abnormalities, including mitral valve prolapse, mitral regurgitation, and an increase in left ventricular mass index have also been reported.

Signs/Symptoms of Hyperthyroidism

Bone:

- Thyroid hormone stimulates bone resorption, resulting in increased porosity of cortical bone and reduced volume of trabecular bone (14).
- Patients are at higher risk of osteoporosis and there is an increased fracture risk in patients with chronic hyperthyroidism (15).

Serum Lipids:

- Patients with hyperthyroidism tend to have low serum total and high-density lipoprotein (HDL) cholesterol concentrations and a low total cholesterol/HDL cholesterol ratio (16).

Signs/Symptoms of Hyperthyroidism

Gastrointestinal:

- Weight loss due primarily to increased metabolic rate (hypermetabolism) and secondarily to increased gut motility and the associated hyperdefecation and malabsorption.
- Most patients have hyperphagia, but an occasional patient with mild hyperthyroidism may have sufficient appetite stimulation that weight is gained (more commonly in younger patients) (17).
- Anorexia may be prominent in older hyperthyroid patients (18).
- Other changes that may occur include abnormalities in liver function tests, particularly high serum alkaline phosphatase concentrations. In one study of 1514 hyperthyroid patients, 39 percent had an abnormal liver function test within six months of diagnosis

Signs/Symptoms of Hyperthyroidism

Genitourinary:

- In women, serum sex hormone-binding globulin (SHBG) concentrations are high, which results in high serum estradiol concentrations and low-normal serum free (unbound) estradiol concentrations, high serum luteinizing hormone (LH) concentrations, a reduced mid-cycle surge in LH secretion, oligomenorrhea, and anovulatory infertility (20,21); amenorrhea can occur in women with severe hyperthyroidism.

Signs/Symptoms of Hyperthyroidism

Neuropsychiatric:

- Patients with thyrotoxicosis may experience behavioral and personality changes, such as psychosis, agitation, and depression.
- Less overt manifestations that are more common in less severe thyrotoxicosis include anxiety, restlessness, irritability, and emotional lability (22); insomnia is also common.
- These behavioral manifestations are accompanied by cognitive impairments, particularly impaired concentration, confusion, poor orientation and immediate recall, amnesia, and constructional difficulties.

Signs/Symptoms of Menopause

Signs/Symptoms of Menopause

The hallmark symptom of the menopausal transition/perimenopause and early postmenopausal years is the hot flash. Women may experience a number of other symptoms whose association with the menopausal transition is well established, including vaginal dryness, sleep disturbances, and new-onset depression (23).

Signs/Symptoms of Menopause

Hot flashes:

- Most common symptom during menopausal transition and menopause are hot flashes (also referred to as vasomotor symptoms or hot flushes), which occur in up to 80 percent of women in some cultures (24-27). When hot flashes occur at night, women typically describe them as "night sweats.“
- Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face that rapidly becomes generalized. The sensation of heat lasts from two to four minutes, is often associated with profuse perspiration and occasionally palpitations, and is sometimes followed by chills and shivering, and a feeling of anxiety.
- Hot flashes usually occur several times per day, although the range may be from only one or two each day to as many as one per hour during the day and night.

Signs/Symptoms of Menopause

Vaginal Dryness:

- The epithelial lining of the vagina and urethra are estrogen-dependent tissues, and estrogen deficiency leads to thinning of the vaginal epithelium.
- This results in vaginal atrophy (atrophic vaginitis), causing symptoms of vaginal dryness, itching, and often dyspareunia (25-27).
- Symptoms of vaginal atrophy are usually progressive and worsen as time passes and hypoestrogenism continues.

Signs/Symptoms of Menopause

Neuropsychiatric:

- Sleep disturbance: A distressing feature of hot flashes is that they are more common at night than during the day and are associated with arousal from sleep. However, women experience sleep disturbances even in the absence of hot flashes.
- Anxiety and depression symptoms may also contribute to sleep disturbances; In addition, perimenopausal women with hot flashes are more likely to be depressed (28,29).
- Depression: A number of reports indicate that there is a significant increased risk of new-onset depression in women during the menopausal transition compared with their premenopausal years (30-36).
- Cognitive changes: Women often describe problems with memory loss and difficulty concentrating during the menopausal transition and menopause, and substantial biologic evidence supports the importance of estrogen to cognitive function.

Signs/Symptoms of Menopause

Cardiovascular:

- The risk of cardiovascular disease increases after menopause, thought to be at least in part due to estrogen deficiency.
- This may be mediated in part by changes in cardiovascular risk factors such as lipid profiles that begin to change during perimenopause onset (37).

Signs/Symptoms of Menopause

Serum Lipids:

- After adjusting for subject age, there was a small increase in serum low-density lipoprotein (LDL) during the menopausal transition (a 6 percent increase in mean LDL from 116 mg/dL in the premenopausal years to 123 mg/dL in the early postmenopausal years). There was no change in serum high-density lipoprotein (HDL) (38).

Signs/Symptoms of Menopause

Bone:

- Bone loss begins during the menopausal transition. The annual rates of bone mineral density loss appear to be highest during the one year before the FMP through two years after. This leads to postmenopausal osteoporosis.

Skin:

- Collagen content of the skin and bones is reduced by estrogen deficiency. Decreased cutaneous collagen may lead to increased aging and wrinkling of the skin.

Hyperthyroidism and Menopause Main Differences

Hyperthyroidism	Menopause
Skin	
Warm, smooth skin	Aged and wrinkled skin
Eyes	
Lid lag, ophtalmopathy	No changes
Cardiovascular	
Increase in cardiac output, increased HR, Atrial Fibrillation	Increased CV disease (ischemic)
Bone	
Higher risk of osteoporosis	Higher risk of osteoporosis

Hyperthyroidism and Menopause Main Differences

Hyperthyroidism	Menopause
Serum Lipids	
Low serum total and high-density lipoprotein (HDL) cholesterol concentrations, low total cholesterol/HDL cholesterol ratio	Small increase in serum low-density lipoprotein (LDL), no change in serum high-density lipoprotein (HDL)
Gastrointestinal	
Weight loss, hyperdefecation and malabsorption; hyperphagia, abnormalities in liver function tests	No changes

Hyperthyroidism and Menopause Main Differences

Hyperthyroidism	Menopause
Genitourinary	
High serum sex hormone-binding globulin (SHBG) concentrations are high, high serum estradiol concentrations and low-normal serum free (unbound) estradiol concentrations, high serum luteinizing hormone (LH) concentrations, a reduced mid-cycle surge in LH secretion, oligomenorrhea, and anovulatory infertility, amenorrhea	High FSH and LH concentrations, low estrogen and progesterone concentrations, amenorrhea, vaginal dryness

Hyperthyroidism and Menopause Main Differences

Hyperthyroidism	Menopause
Neuropsychiatric	
Psychosis, agitation, and depression, anxiety, restlessness, irritability, and emotional lability Insomnia is also common. Cognitive impairments, particularly impaired concentration, confusion, poor orientation and immediate recall, amnesia, and constructional difficulties	Sleep disturbance, anxiety and depression symptoms, depression. Cognitive changes: memory loss and difficulty concentrating.

Thyroid Disease and Pregnancy

Thyroid Disease and Pregnancy

- The diagnosis of thyroid disease during pregnancy requires an understanding of the changes in thyroid physiology and thyroid function tests that accompany normal pregnancy (39).
- To meet the increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests (40).
- The major changes in thyroid function during pregnancy are an increase in serum thyroxine-binding globulin (TBG) concentrations and stimulation of the thyrotropin (thyroid-stimulating hormone [TSH]) receptor by human chorionic gonadotropin (hCG) (41).

Thyroid Disease and Pregnancy

- Together, these changes lead to an increase in both serum total thyroxine (T4) and triiodothyronine (T3) concentrations and a reduction in serum TSH (42).
- Because of the changes in thyroid physiology during normal pregnancy, thyroid function tests should, whenever possible, be interpreted using population and trimester-specific TSH and T4 reference ranges for pregnant women.
- If the laboratory does not provide trimester-specific reference ranges for TSH (mU/L), a TSH reference range of approximately 0.1 to 4 mU/L can be used.
- Total T4 and total T3 levels during pregnancy are 1.5-fold higher than in nonpregnant women (43).

Thyroid Disease and Pregnancy

- When evaluating thyroid tests during pregnancy, some authors measure TSH and free T4 (if there is a trimester-specific reference range), and/or total T4 (39).
- In such settings where free T4 measurements appear discordant with TSH measurements, total T4 should also be measured.
- Hyperthyroidism from any cause can complicate pregnancy, but Graves' hyperthyroidism is the most common cause of overt hyperthyroidism (39,44).
- hCG-mediated hyperthyroidism is a common cause of subclinical hyperthyroidism. It may occur transiently in the first half of gestation and is typically less severe than Graves' disease (39,45).

Thyroid Disease and Pregnancy

- The diagnosis of hyperthyroidism during pregnancy should be based primarily upon a suppressed (‹0.1 mU/L) or undetectable (‹0.01 mU/L) serum TSH value and also a serum free T4 and/or free T3 (or total T4 and/or total T3) measurement that exceeds the normal range during pregnancy (43).
- When iodine nutrition is adequate (as in the United States), the most common cause of hypothyroidism during pregnancy is chronic autoimmune (Hashimoto's) thyroiditis (46).
- In iodine-deficient areas, iodine deficiency itself is associated with hypothyroidism and goiter (47).

Thyroid Disease and Pregnancy

- The diagnosis of overt primary hypothyroidism during pregnancy is based upon the finding of a decreased free T4 concentration (below assay normal using reference range for pregnant women) and an elevated population and trimester-specific serum TSH (43).
- Subclinical hypothyroidism is defined as an elevated population and trimester-specific serum TSH concentration with a normal free T4 concentration.
- An increased rate of fetal loss and premature delivery has been reported in euthyroid women with high serum antithyroid peroxidase (TPO) antibody concentrations (48).
- In view of conflicting data regarding the efficacy of levothyroxine (T4) for reducing the risk of miscarriage, there is not a consensus approach to the management of euthyroid (TSH ≤4 mU/L), TPO-positive women.

Thyroid Disease and Pregnancy

- Euthyroid women with high serum TPO antibody concentrations are at risk for developing hypothyroidism (49).
- In antibody-positive, euthyroid pregnant women who are not treated with thyroid hormone, TSH should be measured every four weeks during the first trimester and, if stable, once during the second and third trimesters to monitor for the development of hypothyroidism (39).
- Postpartum thyroiditis occurs in 5 to 10 percent of women in the United States (49,50).
- It may occur after pregnancy loss (miscarriage, abortion, ectopic pregnancy), as well as after normal delivery (51).

Lifestyle Modifications

Lifestyle Modifications

- **Iodine requirements** — Iodine requirements are higher in pregnant than in nonpregnant women due both to the increase in maternal T4 production required to maintain maternal euthyroidism and an increase in renal iodine clearance (39).
- Severe maternal iodine deficiency during pregnancy results in a reduction in maternal T4 production, inadequate placental transfer of maternal T4, and impairment of fetal neurologic development. However, markedly excessive iodine intake may also be harmful as it can lead to fetal hypothyroidism and goiter (39).
- The World Health Organization (WHO) recommends 250 mcg of iodine daily during pregnancy and lactation (52).

Lifestyle Modifications

- The National Academy of Medicine (formerly the Institute of Medicine) recommends daily iodine intake of 220 mcg during pregnancy and 290 mcg during lactation (53).
- For women in the United States to achieve this level of daily intake, the ATA recommends supplementation with 150 mcg of iodine daily during pregnancy and lactation, which is the dose included in the majority of prenatal vitamins marketed in the United States, though pregnant women should verify the iodine content in their own prenatal vitamin (54).

Lifestyle Modifications

- Selenium supplementation may decrease inflammatory activity in pregnant women with autoimmune hypothyroidism (55).
- It may also reduce the risk of postpartum thyroiditis in women who are positive for thyroid peroxidase (TPO) antibodies.
- This was illustrated in a trial of 151 TPO-positive women randomly assigned to receive selenium (200 mcg daily) or placebo (beginning at approximately the 12th week of gestation).
- The prevalence of postpartum thyroiditis was significantly lower in the selenium group (22 of 77 women [29 percent] versus 36 of 74 [49 percent]) (56).

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