Hypothyroidism

2

Jad G. Sfeir and Hossein Gharib

Introduction

Hypothyroidism is the clinical state which results from either inadequate production of thyroid hormone or impaired action of thyroid hormone at the tissue level. It is defined by the laboratory parameters of a low free thyroxine (FT4), associated with an elevated thyroid-stimulating hormone (TSH) in primary hypothyroidism or, less commonly, a low to low-normal TSH in central hypothyroidism.

Primary hypothyroidism, where the defect is at the level of the thyroid gland itself, accounts for over 95% of cases of overt hypothyroidism. The remaining 5% are caused by secondary or tertiary hypothyroidism (defect at the level of the pituitary gland or the hypothalamus) or thyroid hormone resistance.

Subclinical hypothyroidism (SCH), defined as an elevation in TSH but with a corresponding normal FT4 level, assumes that there is an intact hypothalamic-pituitary-thyroid axis and an absence of intercurrent illness. The values should also be reproducible over a 4–6-week period.

Given vague symptomatology that overlaps with other endocrine and non-endocrine disorders, hypothyroidism is commonly tested in clinical practice. It thus becomes important to differentiate overt hypothyroidism that thyroid hormone replacement, from non-thyroidal cause of such symptoms as fatigue, weight gain, or impaired cognitive function.

J. G. Sfeir
Division of Endocrinology, Metabolism, Diabetes and Nutrition, Mayo Clinic College of Medicine, Rochester, MN, USA
e-mail: sfeir.jad@mayo.edu

H. Gharib (✉)
Division of Endocrinology, Mayo Clinic College of Medicine, Rochester, MN, USA
e-mail: gharib.hossein@mayo.edu

Epidemiology

The prevalence of overt hypothyroidism in the United States has been reported to range between 0.3% and 0.8% and in Europe between 0.2% and 5.3% [1–3]. Worldwide, its prevalence is between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 men [4]. The variation in reported prevalence is due to both differences in case detection and availability of dietary iodine, whereby a lower prevalence is seen in areas of iodine deficiency [5]. Subclinical hypothyroidism is more prevalent with an estimation of 0.7–13% in US adults [1].

There are significant ethnic and sex differences in thyroid disease prevalence. It is ten times more common in women than men, and its incidence rises with age [6]. White and Mexican Americans are at approximately three times higher risk compared to Black Americans [1]. Pregnant women also seem to be at higher risk, with gestational hypothyroidism, defined as both overt and subclinical hypothyroidism, reported at 15.5% based on large laboratory-based datasets [7].

Clinical Presentation and Physical Examination

Common clinical presentation of hypothyroidism is generally related to decrease in metabolism and consequent symptoms of fatigue, weight gain, cold intolerance, constipation, and less commonly in extreme situations myxedema and hypothermia. Other symptoms include decline in cognitive function, dry skin, and muscle weakness. However all of these symptoms are nonspecific to thyroid disease and overlap with other endocrine diseases such as abnormal glucose metabolism or pituitary or adrenal dysfunction.

Associated biochemical and laboratory abnormalities include dyslipidemia, elevation in creatinine phosphokinase, prolactinemia, hyponatremia, and mild anemia.

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Table 2.1 Common physical examination findings in hypothyroidism

Skin	Puffiness of the periorbital tissues, hands, and feet and supraclavicular fossae secondary to myxedema; pallor from anemia; dry, coarse skin secondary to reduced sebaceous gland secretions; easy bruising; dry brittle hair and nails
Cardiovascular	Narrow pulse pressure; reduction in cutaneous blood flow leading to cool, pale skin; distant heart sounds (if pericardial effusion is present)
Gastrointestinal	Weight gain from fluid retention, abdominal gaseous distension (myxedema ileus)
Nervous system	Slowing of higher mental function including speech, slowing of the relaxation phase of tendon reflexes
Muscular	Slightly increased muscle mass due to interstitial myxedema, myoclonus

Physical signs of hypothyroidism are notoriously nonspecific and vary according to the severity of the disorder. The use of sensitive thyroid assays has largely superseded the value of physical examination findings in making the diagnosis of thyroid dysfunction (Table 2.1).

A firm, moderate-sized goiter that moves freely on swallowing is the most common physical feature of Hashimoto's thyroiditis. A large goiter can also be found in patients with severe iodine deficiency. Rarely, an atrophic gland is present, the end result of autoimmune destruction of the gland. The natural history of the untreated goiter is a slow enlargement over many years. When there is rapid, painful enlargement of the gland, thyroid lymphoma should be suspected, and an expedient work-up performed.

Etiology

Primary Hypothyroidism

Primary hypothyroidism has several causes, all resulting in a decreased output of thyroid hormone from the thyroid gland. The most common cause in the United States and other iodine-sufficient areas is chronic autoimmune thyroiditis, known as Hashimoto's thyroiditis. The hallmark of the disease is the presence of circulating antithyroid peroxidase (TPO) antibodies. Histopathologic examination of the thyroid gland, if performed, reveals diffuse lymphocytic infiltration, follicular destruction, and Hürthle cells. There is a polygenic susceptibility, with a known association between Hashimoto's thyroiditis and HLA-DR3 [8]. Other factors such as pregnancy, radiation exposure, and, as evidenced by animal studies, viral infections can also predispose to developing the condition [9].

Worldwide, the most common cause of primary hypothyroidism is iodine deficiency with approximately two billion people at risk, particularly those living in mountainous areas due to persistent glacial runoff depleting iodine stores. Large geographic areas of Africa and Asia also remain iodine-deficient. Consumption of cassava which contains compounds metabolized to thiocyanate enhances the iodine-deficient state by inhibiting thyroid iodine transport. Iodine is required for thyroid hormone production and an essential mineral component of the hormone. The World Health Organization recommends a daily iodine intake of 150 μg for the general adult population and 200 μg for pregnant or lactating women.

Other forms of thyroiditis may also cause primary hypothyroidism. Subacute or granulomatous thyroiditis that initially presents with neck pain and biochemical hyperthyroidism may progress to transient or permanent hypothyroidism. In one study, about 10% of patients developed permanent hypothyroidism, defined as an elevation in TSH lasting beyond 1 year [10]. Postpartum thyroiditis (PPT) may present with hyperthyroidism followed by transient hypothyroidism, hyperthyroidism alone, or hypothyroidism alone in about 50% of cases, usually within 2–6 months after delivery. It is more common in women with elevated titers of TPO antibodies, which confers up to a 50% chance of developing PPT [11]. Most patients are euthyroid within the first postpartum year, although permanent hypothyroidism is more likely to develop in women with higher TSH values and higher antibody titers [12].

Iatrogenic hypothyroidism includes surgical thyroidectomy and post-ablative hypothyroidism. Hypothyroidism occurs up to 4 weeks following total thyroidectomy owing to thyroxine's half-life of 7 days. Data from patients undergoing radioactive iodine therapy for Graves' disease indicate that the rate of subsequent hypothyroidism is largely dependent on the dose of radioiodine used; in the United States, most patients are hypothyroid within the first year of treatment [13]. External beam radiation which exceeds 25 Gy also causes hypothyroidism, which may be gradual in onset.

Infiltrative processes including hemochromatosis, lymphoma, amyloidosis, and sarcoidosis are rare causes of primary hypothyroidism. They tend to present as progressive, painless bilateral enlargement of the thyroid gland and are usually part of more widespread systemic involvement of the underlying condition. Infection of the thyroid is rare as the gland is encapsulated and has good blood flow and a high iodine content. However *Pneumocystis jiroveci* infection in immune-compromised patients has been reported to cause enough destruction of the thyroid gland leading to inadequate thyroid hormone production [14].

Consumptive hypothyroidism is a rare disorder that was initially identified in infants with visceral hemangiomas. There is a marked elevation in deiodinase type 3 enzyme activity which results in the conversion of T4 to reverse T3 and conversion of T3 to T2. The condition is treatable medically with glucocorticoids and interferon-α.

Congenital hypothyroidism affects 1:2000 to 1:4000 live births internationally. In the United States, data from the National Newborn Screening and Global Resource Center (NNSGRC) reveals an incidence of 0.04% [15]. It is more frequent in iodine-deficient regions; the prevalence of elevated TSH can be greater than 40 percent in severely iodine-deficient regions but less than 3 percent in iodine-sufficient populations [16]. Infants with the disorder have little to no clinical features of hypothyroidism, and they are detected largely through universal newborn screening programs in place since the 1970s. Thyroid dysgenesis is responsible for 85% of these cases, with the remaining being caused by defects in thyroid hormone production at every level. Worldwide, the commonest cause is thyroid ectopy which accounts for about two-thirds of patients with thyroid dysgenesis. Central congenital hypothyroidism is much rarer and may be missed by screening programs that utilize TSH only. These infants usually have other pituitary hormone deficiencies [17]. Transient hypothyroidism in infants can occur as a result of maternal iodine insufficiency, maternal TSH receptor-blocking antibodies, or exposure to antithyroid drugs; infants are rendered euthyroid once the offending agent (antibody or drug) is naturally cleared over several weeks following birth.

Medication-Induced Thyroid Dysfunction

Medications can affect thyroid function in several ways; these are summarized in Table 2.2.

Drugs that affect thyroid hormone synthesis and secretion include amiodarone and other iodine-containing drugs and radiographic agents, lithium, perchlorate, and others. Other drugs increase thyroxine requirements by either binding to exogenous thyroid hormone, e.g., calcium salts, sucralfate, and cholestyramine, or increasing its metabolism, e.g., rifampicin, carbamazepine, and phenytoin. Tyrosine kinase inhibitors such as sorafenib and sunitinib have been shown to cause hypothyroidism in up to 70% of patients, a side effect directly related to length of therapy [18]. The proposed mechanisms vary slightly between the different agents and include destructive thyroiditis with a reduction in thyroid hormone synthesis by inhibition of thyroid peroxidase activity. In patients already on thyroxine therapy, requirements increase, an effect thought to be mediated by type 3 deiodinase activity which increases the metabolism of T4 and T3 [19].

Medications that cause a reduction in TSH secretion, such as glucocorticoids, opiates, and dopamine agonists, are also implicated in causing hypothyroidism.

Immune checkpoint inhibitors have emerged as effective antitumor treatment for an increasing number of solid and hematologic tumors. The reported incidence of thyroid immune-related adverse effects varies based on medication type (anti-PD-1 vs. anti-CTLA-4) and seems to be more common when these drugs are used in combination as opposed to monotherapy. Overall, it is estimated between 5 and 10% and more commonly presents as thyrotoxicosis followed by hypothyroidism (62%) or overt hypothyroidism (22%) [20].

Table 2.2 Common medications that affect thyroid function

Drug	Mechanism
Inhibition of thyroid hormone synthesis and secretion	
Amiodarone	Inhibits type I and type II 5′ deiodinase, leading to decreased T3 generation from T4
Iodinated contrast agents	Inhibit type I and type II 5′ deiodinase, leading to decreased T3 generation from T4
	Decrease hepatic uptake of T4
	Inhibit T3 binding to its nuclear receptor
Thiocyanate, perchlorate	Inhibit iodide transport into the thyroid gland
Propylthiouracil, methimazole	Inhibit thyroid peroxidase; propylthiouracil additionally inhibits peripheral conversion of T4 to T3
Lithium	Inhibits iodide binding and thyroid hormone release
Decreased absorption of exogenous thyroid hormone	
Calcium compounds, sucralfate, aluminum hydroxide, ferrous compounds, cholestyramine, colesevelam, proton pump inhibitors, H2 blockers	Bind to levothyroxine and reduce its absorption
Increased T4 clearance	
Rifampin	Induces hepatic microsomal enzymes
Phenobarbital, carbamazepine	Induce hepatic microsomal enzymes
	Compete with thyroid hormone binding to TBG
	Accelerate the conjugation and hepatic clearance of T4/T3
Decreased TSH secretion	
Dopamine, L-dopa, bromocriptine	Increase T3 synthesis from T4 in the brain
Opiates	Block the breakdown of T3 in the brain
Others	
Estrogens, SERMs	Increase thyroid-binding globulin
Steroids	Influenced by dose, type, and route of administration of glucocorticoid. Inhibit deiodination of T4; suppress TSH secretion; increase in renal iodide clearance
Salicylates	Compete for thyroid hormone-binding sites on binding proteins
Thalidomide	Immune-mediated subacute destructive thyroiditis
Immune checkpoint inhibitors	Suggested to be immune-mediated thyroiditis

Central (Secondary and Tertiary) Hypothyroidism

Central hypothyroidism is caused by TSH deficiency from disorders of the pituitary gland or hypothalamus. It is usually accompanied by deficiencies of other pituitary hormones and can vary in severity. About 15% of the function of the thyroid gland is independent of TSH, and therefore central hypothyroidism may be milder clinically than primary hypothyroidism. Central hypothyroidism may be caused by tumors, surgery, and infiltrative, inflammatory, or infective processes and medications.

Generalized Thyroid Hormone Resistance

Thyroid hormone resistance is a rare, autosomal dominant disorder in which the majority of patients have a mutation in the thyroid receptor TR-beta gene. This results in reduced T3-binding affinity at the level of the thyroid hormone receptor and a reduced response to thyroid hormone. Two-thirds of patients have goiters, but their symptoms may be a mix of hypo- and hyperthyroid complaints. There is an increased prevalence of attention-deficit disorder which is present in about 10% of patients [21]. Laboratory testing shows an elevated free thyroxine with normal or slightly increased TSH levels; the disorder therefore has to be differentiated from a TSH-secreting pituitary tumor. Treatment with T4 or T3 may be beneficial in patients with symptoms of hypothyroidism.

Evaluation

Given the lack of sensitivity and specificity of clinical findings, laboratory testing is essential to confirm the diagnosis and identify the cause of hypothyroidism.

The most sensitive, "gold standard" test is measurement of TSH levels using a third-generation chemiluminescent immunoassay, which has the advantage of being more sensitive at the lower range than the second-generation test. The FT4 level will differentiate between overt and SCH. Equilibrium dialysis is the gold standard for the measurement of FT4; however, direct measurement via ultrafiltration is the most widely available method. It can also be measured indirectly through the FT4 index. Total thyroxine levels are affected by conditions that increase binding protein (e.g., pregnancy and illness) and must therefore be interpreted with caution. There is considerable debate about the upper limit of normal for the TSH reference range. There is also suggestion of differences in reference range by sex, age, and ethnicity [22]. Data from the NHANES studies has shown an age-specific distribution of TSH, with higher normal values being seen in the elderly [23].

There is possibility for laboratory interference with human anti-animal antibodies or high levels of drugs and supplements such as heparin or biotin. Consequently, interpretation of thyroid function testing should be interpreted carefully with consideration to the clinical presentation.

The diagnosis of Hashimoto's thyroiditis is confirmed by the presence of circulating TPO antibodies, but antibodies to thyroglobulin (TG) and the TSH receptor antibody (TRAb) may also be present. The presence of TPO antibodies is 92% sensitive and 93% specific for the diagnosis of Hashimoto's thyroiditis in the correct clinical setting [24]. Elevated titers of TPO antibodies can, however, be present in up to 11% of the general disease-free population [16]. In patients with SCH, the measurement of TPO antibodies is helpful in predicting the likelihood of progression to overt hypothyroidism.

Ultrasound of the thyroid gland is not routinely recommended but may confirm the diagnosis of Hashimoto's thyroiditis if the characteristic heterogeneous echotexture is seen.

Treatment

Thyroid hormone replacement is the mainstay of treatment of hypothyroidism. Levothyroxine (LT4) is the preferred agent as it allows for normal physiologic mechanisms to maintain T3 production in peripheral tissues. It has a half-life of 7 days, and therefore dose titration should be done after about 6 weeks, allowing for equilibration to be achieved. A TSH goal should be used to adjust the dose of therapy, except in patients without an intact hypothalamic-pituitary-thyroid axis, in which case FT4 is used. Patients with suspected glucocorticoid deficiency should be evaluated and treated prior to initiation of levothyroxine, as the latter may precipitate an adrenal crisis in untreated individuals.

The typical daily dose of LT4 in a patient without endogenous thyroid function is about 1.6 μg/kg body weight per day. Care should be taken when initiating treatment in elderly patients with angina, as thyroid hormone can increase myocardial oxygen demand. Therefore, a recommended starting dose of 25–50 μg/day is preferred with titration by 12.5–25 μg every few weeks in this population. Patients with SCH also require a lower starting dose of levothyroxine, if treatment is initiated.

Levothyroxine should be taken on an empty stomach, ideally separated from food by at least 1 hour. Several medications may affect the absorption of thyroid hormone (Table 2.2), and patients should be educated to allow at least 4 hours to pass after a meal prior to taking thyroid hormone. Gastric acid is required for complete absorption of thyroid hormone; in patients on acid-reducing medication, one strategy may be to administer the dose at night when there is

higher basal secretion of acid in combination with a slower intestinal transit time [25]. In patients who are unable to adhere to a daily dosing regimen, once-weekly dosing of levothyroxine with a dose slightly higher than seven times the daily dose has been shown to achieve biochemical euthyroidism without significant side effects [26].

Monitoring of therapy should be performed every 6 weeks after any change in treatment is made, be it to the dose or the brand of medication [27]. Among generic LT4 formulations, there is some variation in bioequivalence despite adherence to FDA standards. Therefore, in the athyreotic patient particularly, many practitioners advocate using brand name medication only. Once the ideal dose is achieved, monitoring can be done on an annual basis. Certain circumstances should prompt reassessment of thyroid function sooner, for example, pregnancy which can increase requirements by up to 50% [28]. Conversely, women on androgen therapy for breast cancer require less levothyroxine, as do hypothyroid patients in general as they get older. Medications can also interfere with thyroid hormone metabolism (Table 2.2), and these potential interactions should be kept in mind.

Therapeutic Target

The goal of treatment of hypothyroidism is to restore both biochemical and clinical euthyroidisms. Most patients achieve normal TSH levels within the first year of treatment. One study estimated this at 75% in patients with spontaneous hypothyroidism and 68% in those with hypothyroidism following surgery or RAI therapy. There should be avoidance of undertreatment and overtreatment. The same study observed overtreatment with LT4 in 4% to 6% of patients [29].

Given the fact that TSH normal level rises with the age, some groups have proposed targeting a lower TSH level within the reference range, particularly in younger individuals. There is however mixed evidence regarding benefit of such practices [30]. Controversy also continues regarding the benefits of thyroxine therapy in SCH, with some recommending treatment [31, 32] and others arguing against replacement therapy, particularly in the elderly [33].

Persistent Complaints Despite Normal TSH

In some patients, despite achieving biochemical euthyroidism, hypothyroid symptoms such as fatigue and weight gain persist. Many factors have been suggested as an explanation to this observation, including the presence of concomitant autoimmune diseases, other hormonal changes such as menopause, or genetic deiodinase polymorphism. Further, levothyroxine monotherapy does not restore physiologic ratios of T4 and T3 that are seen in euthyroid individuals.

Combination Therapy

The thyroid gland is responsible for 20% of the body's T3 secretion with the remainder derived from peripheral conversion of T4 to T3. The theory of, therefore, supplementing the athyreotic patient with T3 in order to restore "physiologic balance" is an appealing one. Several studies have looked at whether a replacement strategy with both LT4 and triiodothyronine (LT3) results in better outcomes. Overall, the majority of clinical studies did not demonstrate benefit of use of combination therapy to treat hypothyroid patients with regard to quality of life, fatigue, body weight, cognition, and mood [34, 35]. An early positive study showed improvement in mood and neuropsychological parameters in these patients but was criticized for its small number of patients, excessive use of thyroid hormone, and short follow-up [36]. Several subsequent, more rigorous studies and a large meta-analysis failed to replicate those results [37–42]. In addition, most of these trials have used once or twice daily dosing of T3, which is a short-acting preparation, and thus provided surges of free T3 rather than normalization of the steady-state levels.

The European Thyroid Association (ETA) and the Italian Association of Clinical Endocrinologists (AME) have suggested consideration of combination therapy on a trial basis to address patient well-being, with avoidance of such therapy in the pregnant and elderly population [34, 35]. The Italian Guide tabulated a possible approach for the combination therapy [35]. Additionally, the use of "non-solid" LT4 formulations may be considered in hypothyroid patients with gastroenteric diseases due to improved GI absorption of these products [35].

Commercially available desiccated animal thyroid preparations, usually porcine in origin, contain both T3 and T4. The ratio of T3 to T4 in these preparations tends to be higher than the ratio found in humans, thereby leading to supraphysiologic T3 levels. Additionally, due to the nature of the product, monitoring and standardization of desiccated thyroid preparations are lacking, leading to difficulty in dose adjustment. There is also insufficient information about the safety or benefit of the surge of free T3 that is seen shortly after the ingestion of such thyroid extracts [43].

Special Populations

Subclinical Hypothyroidism (SCH)

SCH is a biochemical diagnosis made in a patient with an elevated serum TSH level and normal serum free T4. Symptoms may be vague and nonspecific or similar to those with overt hypothyroidism. Its prevalence increases with age, and it is more common in women and in iodine-sufficient areas [44].

Some conditions need to be excluded prior to making this diagnosis. In a patient recovering from a non-thyroidal illness, there may be a transient increase in TSH. Similarly, often after the hyperthyroid phase of thyroiditis, there can be a transient period of hypothyroidism. There is also a diurnal variation and a nocturnal surge in TSH with the highest values being seen in the morning. Hence, the diagnosis of subclinical hypothyroidism should only be made in a patient in whom the biochemical abnormalities are reproducible after about 6 weeks and in whom there is an intact hypothalamic-pituitary-thyroid axis with no intercurrent illness.

The risk of progression from SCH to overt hypothyroidism is determined by the magnitude of TSH elevation and the presence of TPO antibodies [45]. In women with both high TSH values and high antibody concentrations, the cumulative incidence of hypothyroidism has been reported to be as high as 55% [46]. Conversely, normalization of TSH values occurs more frequently in people with concentrations of 4–6 mU/L [47]. The underlying etiology for SCH also influences the rate of progression to overt hypothyroidism. For example, patients who recently received radioiodine therapy or external beam radiation are more likely to progress to overt hypothyroidism than patients who received external beam radiation as children.

There is inconsistent data regarding the risk of cardiovascular disease, neuropsychiatric symptoms, and mortality rates in patients with SCH with studies demonstrating both an increased and decreased risk of each outcome measure.

Current guidelines recommend treating all patients with a TSH >10 mIU/L and those with positive TPO antibodies, because of a higher risk of progression to overt hypothyroidism [48]. Additionally pregnant women or women contemplating pregnancy should also be treated [49]. More unclear is the benefit of treating patients with TSH between 5 and 9 mIU/L. SCH might be associated with greater cardiovascular risk in young and middle-aged people than in those older than 65 years, and therefore treatment may be justifiable in this group [50]. Levothyroxine therapy has been shown to improve cholesterol levels as well as surrogate cardiovascular endpoints such as carotid intimal thickness, endothelial function, and left ventricular function in several studies, but the mortality benefit may only be seen after prolonged therapy [51, 52]. Symptomatic patients with TSH values between 5 and 9 mIU/L may benefit from treatment, although studies show the effects to be greatest in patients with TSH >10 mIU/L [53].

The goal of therapy should be to bring TSH to the lower range of normal (0.5–3.0 mIU/L) in patients <65 years of age and between 3 and 4.5 mIU/L in patients >65 years of age. In patients who do not clearly qualify for therapy, monitoring thyroid function every 6–12 months is a reasonable strategy.

Hypothyroidism and Pregnancy

Pregnancy results in a twofold increase in thyroid-binding globulin and stimulation of the TSH receptor by β-HCG, an effect that wanes with decreasing production of β-HCG as the pregnancy progresses. Therefore the recommendation by the American Thyroid Association that there should be trimester-specific reference ranges for TSH in pregnancy has a sound physiologic basis, but is not widely practiced by commercial laboratories [54].

This phenomenon has impacted the definitions of overt and subclinical hypothyroidism in pregnancy. Overt hypothyroidism is defined as having a TSH of >2.5 mIU/L with a corresponding trimester-specific low FT4 or a TSH of >10 mIU/L regardless of FT4 levels. SCH is defined as having TSH between 2.5 and 10 mIU/L with a normal FT4 level. About 10–20% of all pregnant women are TPO antibody positive and biochemically euthyroid. These women are more likely to have a TSH level that is >4.0 mIU/L by the third trimester, and up to half will develop PPT [55]. SCH can also persist postpartum, particularly in women with TPO antibodies.

Overt hypothyroidism in pregnancy, if left untreated, may result in adverse maternal and fetal outcomes including preterm delivery, low birth weight, miscarriage, increased risk of fetal loss, and gestational hypertension [56, 57]. The data in women with SCH with or without thyroid autoantibodies also shows an increase in adverse pregnancy outcomes, including preeclampsia, placental abruption, and neonatal mortality [58, 59]. However, there is less clear evidence that the neurocognitive development of the fetus is affected in women with untreated SCH [54, 60].

Thyroid autoimmunity itself may predispose to adverse fetal outcomes. In recent meta-analyses looking at euthyroid women with thyroid autoantibodies, there was a twofold increase in the rate of both spontaneous miscarriage and preterm delivery [61, 62].

There is currently insufficient evidence for universal TSH screening of all pregnant women in the first trimester of pregnancy. Clinical practice guidelines instead advocate a "case-finding" approach and recommend certain high-risk groups of women have their serum TSH checked at the confirmation of pregnancy (Table 2.3) [54, 63].

The current ATA recommendation is to treat all pregnant women with overt hypothyroidism as well as those with SCH and positive TPO antibodies and to consider treatment in pregnant women with negative TPO antibodies and a TSH ranging between the upper limit of normal and 10 mU/L [54]. If the decision is made not to treat women with SCH or thyroid autoimmunity, then monitoring thyroid function every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation is a reasonable strategy.

Table 2.3 Target populations for TSH screening during pregnancy

Women at high risk for overt hypothyroidism during pregnancy
History of thyroid dysfunction, postpartum thyroiditis, or prior thyroid surgery
Age >30 years
Symptoms of thyroid dysfunction or biochemical features suggestive of thyroid dysfunction including anemia, hypercholesterolemia, or hyponatremia
Presence of goiter
TPO antibody positivity
Type 1 diabetes or other autoimmune disorders
History of infertility, miscarriage, or preterm delivery Multiple prior pregnancies (≥2)
History of head or neck radiation
Family history of autoimmune thyroid disease or thyroid dysfunction
Use of amiodarone or lithium or recent administration of iodinated radiologic contrast
Residing in an area of known moderate-to-severe iodine insufficiency
Body mass index ≥40 kg/m^2

Women with preexisting hypothyroidism will likely require an increase in their dose of hormone replacement by up to 50% until delivery [64]. The dose of levothyroxine should be increased by about 30% as soon as pregnancy is confirmed and titrated to maintain a trimester-specific normal TSH. Practically speaking, this can be achieved by adding two extra doses of levothyroxine a week, i.e., nine doses, from seven. Ideally, preconception TSH should be <2.5 mIU/L to achieve the most favorable outcomes during pregnancy. Serum TSH should be monitored every 4 weeks in the first half of pregnancy and at least once between 26 and 32 weeks gestation. In the absence of laboratory-specific ranges, it is reasonable to use the following upper limits of normal for TSH: 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester, and 3.5 mIU/L in the third trimester [49, 54]. Postpartum, the patient should return to her pre-pregnancy dose of levothyroxine, and a serum TSH should be checked about 6 weeks later.

Myxedema Coma

Myxedema coma is the result of severe untreated hypothyroidism and manifests with hypothermia, generalized slowing of all organ functions, and decreased cognition. It is a medical emergency with a high mortality rate if left unrecognized and untreated. It can be a result of long-standing untreated hypothyroidism or may be precipitated by exposure to cold, infection, trauma, or central nervous system depressants particularly in the elderly population.

The typical patient presents with a history of known hypothyroidism and slowly worsening mental status changes. It is usually accompanied by a variety of clinical features which, in its most severe form, can include hypothermia, hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation. The myxedema is a result of abnormal mucin deposition in the tissues and manifests as non-pitting edema of the face, tongue, and peripheries. Pleural, pericardial, and peritoneal effusions are not uncommon. Seizures may be present, partially due to hyponatremia which is present in about 50% of patients [65].

The diagnosis should be considered in the hypothyroid patient who presents with typical clinical features and confirmed biochemically. Serum TSH, free T4, and cortisol levels should be drawn prior to administering any therapy. The majority of patients will have primary hypothyroidism, but an inappropriately normal TSH in the setting of a low free T4 would indicate a pituitary or a hypothalamic etiology.

Treatment should be initiated based on clinical suspicion, even before biochemical confirmation, due to the high mortality rate of this condition. Severe hypometabolism can impair drug absorption from the gut, and thus medications should be administered intravenously. Thyroid hormone replacement with both T4 and T3 is widely practiced as T3 has a faster onset of action and there is unpredictable T4-to-T3 conversion in the setting of severe hypothyroidism and concurrent non-thyroidal illness. A single loading dose of 400–500 μg of levothyroxine intravenously is initially given to replete the peripheral pool; this is converted to a daily dose of 1.6 μg/kg thereafter. The loading dose should be lowered in the elderly and in patients with cardiovascular disease. T3 may be administered simultaneously, with or without a loading dose, at a dose of 2.5–10 μg every 8 hours. Care must be taken to ensure that T3 levels are monitored appropriately as high levels have been shown to increase mortality [66]. Once the patient is able to tolerate oral medications, thyroid hormone replacement can be done orally at a dose of about three-quarters of the intravenous dose.

Glucocorticoids at stress doses should also be given until the diagnosis of adrenal insufficiency can be excluded. Additionally, supportive treatment, electrolyte monitoring, and treatment of any precipitating illness must be instituted. Hypothermia is best managed with passive warming as active warming may cause redistribution of blood flow to subcutaneous tissues and cardiovascular collapse. Hypotension generally resolves with thyroid hormone replacement over hours to days, but vasopressor support may be required temporarily.

Poor prognostic factors include increased age, reduced consciousness, persistent hypothermia, and sepsis. However, with expedient treatment, the mortality rate approaches that due to sepsis alone [67]. The key to successfully managing myxedema coma remains having a keen clinical suspicion for the condition and the prompt institution of thyroid hormone replacement.

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