

Part 1

Thyroid

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Anatomy and physiology of the thyroid

Anatomy

The thyroid gland comprises

- A midline isthmus lying horizontally just below the cricoid cartilage.
- 2 lateral lobes that extend upward over the lower half of the thyroid cartilage.

The gland lies deep to the strap muscles of the neck, enclosed in the pre-tracheal fascia, which anchors it to the trachea, so that the thyroid moves up on swallowing.

Histology

- Fibrous septa divide the gland into pseudolobules.
- Pseudolobules are composed of vesicles called follicles or acini, surrounded by a capillary network.
- The follicle walls are lined by cuboidal epithelium.
- The lumen is filled with a proteinaceous colloid, which contains the unique protein thyroglobulin. The peptide sequences of T_4 and T_3 are synthesized and stored as a component of thyroglobulin.

Development

- Develops from the endoderm of the floor of the pharynx with some contribution from the lateral pharyngeal pouches.
- Descent of the midline thyroid anlage gives rise to the thyroglossal duct, which extends from the foramen caecum near the base of the tongue to the isthmus of the thyroid.
- During development the posterior aspect of the thyroid becomes associated with the parathyroid gland and the parafollicular C cells, derived from the ultimo-branchial body, which become incorporated into its substance.
- The C cells are the source of calcitonin and give rise to medullary thyroid carcinoma when they undergo malignant transformation.
- The fetal thyroid begins to concentrate and organify iodine at about 10–12 weeks' gestation.
- Maternal TRH readily crosses the placenta, maternal TSH and T_4 do not.
- T_4 from the fetal thyroid is the major thyroid hormone available to the fetus. The fetal pituitary–thyroid axis is a functional unit distinct from that of the mother—active at 18–20 weeks.

Thyroid examination

Inspection

- Look at the neck from the front. If a goitre (enlarged thyroid gland of whatever cause) is present, the patient should be asked to swallow a mouthful of water. The thyroid moves up with swallowing.
- Watch for appearance of any nodule not visible before swallowing, e.g. in an elderly patient with kyphosis the thyroid may be partially retrosternal.

Palpation

- Is the thyroid gland tender to touch?
- With index and middle finger feel below thyroid cartilage where the isthmus of the thyroid gland lies over the trachea.
- Palpate the 2 lobes of the thyroid, which extend laterally behind the sternomastoid muscle.
- Ask the patient to swallow again while you continue to palpate the thyroid.
- Assess size, whether it is *soft*, *firm* or *hard*, it is *nodular* or *diffusely* enlarged and whether it *moves* readily on swallowing.
- Palpate along the medial edge of the sternomastoid muscle on either side to look for a pyramidal lobe.
- Palpate for lymph nodes in the neck.

Percussion

Percuss upper mediastinum for retrosternal goitre.

Auscultation

- Auscultate to identify bruits, consistent with Graves' disease.
- Occasionally inspiratory stridor can be heard with a large or retrosternal goitre causing tracheal compression (see Pemberton's sign p.48).

Assess thyroid status

- Observe for signs of thyroid disease—exophthalmos, proptosis, thyroid acropachy, pretibial myxoedema, hyperactivity, restlessness, or whether immobile and uninterested.
- Take pulse; note presence or absence of tachycardia, bradycardia, or atrial fibrillation.
- Feel palms—whether warm and sweaty or cold.
- Look for tremor in outstretched hands.
- Examine eyes: exophthalmos (forward protrusion of the eyes—proptosis); lid retraction: sclera visible above cornea; lid lag; conjunctival injection or oedema (cheimosis); periorbital oedema; loss of full-range movement.

Physiology

- Thyroid hormone contains iodine. Iodine enters the thyroid in the form of inorganic or ionic iodide, which is organized by the thyroid peroxidase enzyme at the cell–colloid interface. Subsequent reactions result in the formation of iodothyronines.
- The thyroid is the only source of T_4 .
- The thyroid secretes 20% of circulating T_3 ; the remainder is generated in extraglandular tissues by the conversion of T_4 to T_3 by deiodinases (largely in the liver and kidneys).

Synthesis of the thyroid hormones can be inhibited by a variety of agents termed *goitrogens*.

- Perchlorate and thiocyanate inhibit iodide transport.
- Thioureas and mercaptoimidazole inhibit the initial oxidation of iodide and coupling of iodothyronines.
- In large doses iodine itself blocks organic binding and coupling reactions.
- Lithium has several inhibitory effects on intrathyroidal iodine metabolism.

In the blood, T_4 and T_3 are almost entirely bound to plasma proteins. T_4 is bound in ↓ order of affinity to T_4 binding globulin (TBG), transthyretin (TTR), and albumin. T_3 is bound 10–20 times less avidly by TBG and not significantly by TTR. Only the free or unbound hormone is available to tissues. The metabolic state correlates more closely with the free than the total hormone concentration in the plasma. The relatively weak binding of T_3 accounts for its more rapid onset and offset of action. Table 1.1 summarizes those states associated with 1° alterations in the concentration of TBG. When there is primarily an alteration in the concentration of thyroid hormones, the concentration of TBG changes little (Table 1.2).

The concentration of free hormones does not necessarily vary directly with that of the total hormones; e.g. while the total T_4 level rises in pregnancy, the free T_4 level remains normal.

The levels of thyroid hormone in the blood are tightly controlled by feedback mechanisms involved in the hypothalamo–pituitary–thyroid axis (Fig. 1.1).

- TSH secreted by the pituitary stimulates the thyroid to secrete principally T_4 and also T_3 . TRH stimulates the synthesis and secretion of TSH. T_4 and T_3 inhibit TSH synthesis and secretion directly.
- T_4 and T_3 are bound to TBG, TTR, and albumin. The remaining free hormones inhibit synthesis and release of TRH and TSH to influence growth and metabolism.
- T_4 is converted peripherally to the metabolically active T_3 or the inactive reverse T_3 (rT_3).
- T_4 and T_3 are metabolized in the liver by conjugation with glucuronate and sulphate. Enzyme inducers such as phenobarbital, carbamazepine, and phenytoin increase the metabolic clearance of the hormones without ↓ the proportion of free hormone in the blood.

Table 1.1 Disordered thyroid hormone–protein interactions

	Serum total T ₄ and T ₃	Free T ₄ and T ₃
Primary abnormality in TBG		
▲ Concentration	↑	Normal
▼ Concentration	↓	Normal
Primary disorder of thyroid function		
Hyperthyroidism	↑	↑
Hypothyroidism	↓	↓

Table 1.2 Circumstances associated with altered concentration of TBG

↑ TBG	↓ TBG
Pregnancy	Androgens
Newborn state	Large doses of glucocorticoids; Cushings' syndrome
OCP and other sources of oestrogens	Chronic liver disease
Tamoxifen	Severe systemic illness
Hepatitis A; chronic active hepatitis	Active acromegaly
Biliary cirrhosis	Nephrotic syndrome
Acute intermittent porphyria	Genetically determined
Genetically determined	Drugs, e.g. phenytoin

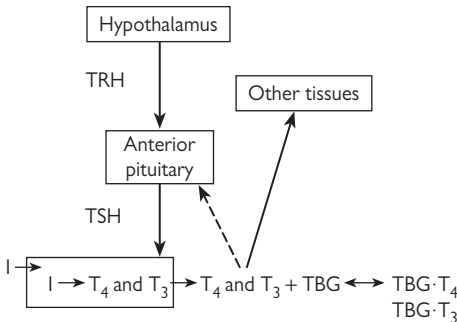


Fig. 1.1 Regulation of thyroid function. Solid arrows indicate stimulation, broken arrow indicates inhibitory influence. TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; T₄, thyroxine; T₃, tri-iodothyronine; I, iodine; TBG, thyroid binding globulin.

6 CHAPTER 1 Anatomy of the thyroid

Molecular action of thyroid hormone

T₃ is the active form of thyroid hormone. It binds to thyroid hormone receptors (TRs), of which there are several isoforms and which are members of the nuclear hormone receptor superfamily. TR/T₃ complexes elicit action by binding to response elements in the DNA of gene promoters. Recruitment of co-activators alters the chromatin configuration allowing gene transcription to proceed, whilst co-repressors cause the opposite effect.

Abnormalities of development

- Remnants of the thyroglossal duct may be found in any position along the course of the tract of its descent:
 - In the tongue, it is referred to as '*lingual thyroid*'.
 - *Thyroglossal cysts* may be visible as midline swellings in the neck.
 - *Thyroglossal fistula* develops an opening in the middle of the neck.
 - Thyroglossal nodules or
 - The '*pyramidal lobe*', a structure contiguous with the thyroid isthmus which extends upwards.
- The gland can descend too far down to reach the anterior mediastinum.
- Congenital hypothyroidism results from failure of the thyroid to develop (agenesis). More commonly, however, congenital hypothyroidism reflects enzyme defects impairing hormone synthesis.



Thyroid investigations

Tests of hormone concentration

Highly specific and sensitive chemiluminescent and radioimmunoassays are used to measure serum T_4 and T_3 concentrations. Free hormone concentrations usually correlate better with the metabolic state than do total hormone concentrations because they are unaffected by changes in binding protein concentration or affinity.

Tests of homeostatic control

See Table 2.1

- Serum TSH concentration is used as 1st line in the diagnosis of 1° hypothyroidism and hyperthyroidism. The test is misleading in patients with 2° thyroid dysfunction reflecting hypothalamic/pituitary disease.
- The TRH stimulation test, which can be used to assess the functional state of the TSH secretory mechanism, is now rarely used to diagnose 1° thyroid disease since it has been superseded by sensitive TSH assays. It is of limited use; its main use is in the differential diagnosis of elevated TSH in the setting of elevated thyroid hormone levels and in the differential diagnosis of resistance to thyroid hormone and a TSH-secreting pituitary adenoma (Table 2.3).

In interpreting results of TFTs, the effects of drugs that the patient might be on should be borne in mind. Table 2.2 lists the influence of drugs on TFTs. Table 2.3 sets out some examples of a typical thyroid function test.

Box 2.1 Thyroid hormone resistance (RTH)

- Syndrome characterized by reduced responsiveness to elevated circulating levels of free T_4 and free T_3 , non-suppressed serum TSH and intact TSH responsiveness to TRH. Clinical features apart from goitre are usually absent but may include short stature, hyperactivity, attention deficits with mental deficiency or learning disability, and goitre.
- The cause is a mutation in the thyroid hormone receptor.
- Differential diagnosis includes TSH-secreting pituitary tumour.
- Most cases require no treatment. If needed it is usually β -adrenergic blockers to ameliorate some of the tissue effects of raised thyroid hormone levels.

Table 2.1 Thyroid hormone concentrations in various thyroid abnormalities

Condition	TSH	Free T ₄	Free T ₃
1° hyperthyroidism	Undetectable	↑↑	↑
T ₃ toxicosis	Undetectable	Normal	↑↑
Subclinical hyperthyroidism	↓	Normal	Normal
2° hyperthyroidism (TSHoma)	↑ or normal	↑	↑
Thyroid hormone resistance	↑ or normal	↑	↑
1° hypothyroidism	↑	↓	↓ or normal
Subclinical hypothyroidism	↑	Normal	Normal
2° hypothyroidism	↓ or normal	↓	↓ or normal


Table 2.2 Influence of drugs on thyroid function tests

Metabolic process	↑	↓
TSH secretion	Amiodarone (transiently; becomes normal after 2–3 months) Sertraline St John's Wort	Glucocorticoids, dopamine agonists, phenytoin, dopamine
T ₄ synthesis/release	Iodide	Iodide, lithium
Binding proteins	Oestrogen, clofibrate, heroin	Glucocorticoids, androgens, phenytoin, carbamazepine
T ₄ metabolism	Anticonvulsants; rifampicin	
T ₄ /T ₃ binding in serum		Salicylates, furosemide, mefenamic acid

Table 2.3 Atypical thyroid function tests

Test	Possible cause
Suppressed TSH and normal free T ₄	T ₃ toxicosis (approximately 5% of thyrotoxicosis)
Suppressed TSH and normal free T ₄ and free T ₃	Subclinical thyrotoxicosis Recovery from thyrotoxicosis Excess thyroxine replacement Sick euthyroidism
Detectable TSH and elevated free T ₄ and free T ₃	TSH secreting pituitary tumour Thyroid hormone resistance Heterophile antibodies leading to spurious measurements of free T ₄ and free T ₃
Elevated free T ₄ and low normal free T ₃ , normal TSH	Amiodarone

Antibody screen

High titres of antithyroid peroxidase (anti-TPO) antibodies or antithyroglobulin antibodies are found in patients with autoimmune thyroid disease (Hashimoto's thyroiditis, Graves' disease, and sometimes euthyroid individuals).  See Table 2.4.

Screening for thyroid disease¹

The following categories of patients should be screened for thyroid disease:

- Patients with atrial fibrillation or hyperlipidaemia.
- Periodic (6-monthly) assessments in patients receiving amiodarone and lithium.
- Annual check of thyroid function in the annual review of diabetic patients.
- ♀ with type 1 diabetes in the 1st trimester of pregnancy and post delivery (because of the 3-fold increase in incidence of postpartum thyroid dysfunction in such patients).
- ♀ with past history of postpartum thyroiditis.
- Annual check of thyroid function in people with Down's syndrome, Turner's syndrome, and Addison's disease, in view of the high prevalence of hypothyroidism in such patients.
- ♀ with thyroid autoantibodies—8 × risk of developing hypothyroidism over 20 years compared to antibody -ve controls
- ♀ with thyroid autoantibodies and isolated elevated TSH—38x risk of developing hypothyroidism, with 4% annual risk of overt hypothyroidism.

¹ Tunbridge WM and MP Vanderpump MP (2000). Population screening for autoimmune thyroid disease. *Endocrinol Metab Clin N Am* **29**(2), 239–53.

Table 2.4 Antithyroid antibodies and thyroid disease

Condition	Anti-TPO	Anti-thyroglobulin	TSH receptor antibody
Graves' disease	70–80%	30–50%	70–100% (stimulating)
Autoimmune hypothyroidism	95%	60%	10–20% (blocking)

Note: TSH receptor antibodies may be stimulatory or inhibitory. Heterophile antibodies present in patient sera may cause abnormal interference causing abnormally low or high values of free T₄ and free T₃, and can be removed with absorption tubes.

Scintiscanning

Permits localization of sites of accumulation of radioiodine or sodium pertechnetate [^{99m}Tc], which gives information about the activity of the iodine trap (Table 2.5). This is useful:

- To define areas of \uparrow or \downarrow function within the thyroid (Table 2.6) which occasionally helps in cases of uncertainty as to the cause of the thyrotoxicosis.
- To detect retrosternal goitre.
- To detect ectopic thyroid tissue.

The scan may be altered by:

- Agents which influence thyroid uptake, including intake of high-iodine foods and supplements, such as kelp (seaweed).
- Drugs containing iodine, such as amiodarone.
- Recent use of radiographic contrast dyes can potentially interfere with the interpretation of the scan.

Table 2.5 Radioisotope scans

	¹²³ Iodine	⁹⁹ Technitium pertechnetate
Half-life	Short	Short
Advantage	Low emission of radiation Have higher energy photons. Hence useful for imaging a toxic goitre with a substernal component	Maximum thyroid uptake within 30 min of administration. Can be used in breast-feeding women (discontinue feeding for 24h)
Disadvantage		Technetium is only trapped by the thyroid without being organified
Use	Functional assessment of the thyroid	Rapid scanning

Table 2.6 Radionuclide scanning (scintigram) in thyroid disease

Condition	Scan appearance
Graves' hyperthyroidism	Enlarged gland ↑ homogeneous radionuclide uptake
Thyroiditis (e.g. de Quervain's)	Low or absent uptake
Toxic nodule	A solitary area of high uptake
Thyrotoxicosis factitia	Depressed thyroid uptake
Thyroid cancer	Successful ¹³¹ I uptake by tumour tissue requires an adequate level of TSH, achieved by stopping T ₃ replacement 10 days before scanning or giving recombinant TSH injection

Ultrasound (US) scanning

Provides an accurate indication of thyroid size and is useful for differentiating cystic nodules from solid ones, but cannot be used to distinguish between benign and malignant disease.

- Microcalcification within nodules favours the diagnosis of malignancy; micro-calcifications <2mm in diameter are observed in ~60% of malignant nodules, but in <2% of benign lesions.
- Calcification is a prominent feature of medullary carcinoma of the thyroid.
- It can detect whether a nodule is solitary or part of a multinodular process.
- Sequential scanning can be employed to assess changes in size of thyroid over time.

Note neither scintigraphy or US is routinely indicated in a patient with goitre.

Fine needle aspiration (FNAC) cytology

- FNAC is now considered the most accurate test for diagnosis of thyroid nodules. It is performed in an outpatient setting. 1–2 aspirations are carried out at different sites for each nodule. Cytologic findings are *satisfactory* or *diagnostic* in approximately 85% of specimens and *non-diagnostic* in the remainder.
- In experienced hands FNAC is an excellent diagnostic technique, as shown in Table 2.7.
- Repeat FNAC after 3–6 months further reduces the proportion of false –ves.
- It is impossible to differentiate between benign and malignant follicular neoplasm using FNAC. Therefore surgical excision of a follicular neoplasm is always indicated.
- 📖 See Table 2.8 for diagnostic categories from FNAC.

Table 2.7 Diagnostic features of FNAC

Feature	Range (%)	Mean value (%)
Accuracy	85–100	95
Specificity	72–100	92
Sensitivity	65–98	83
False –ve	1–11	5

Table 2.8 Diagnostic categories from FNAC

Category		Action
Thy 1	Non-diagnostic Inadequate	Repeat sampling, using US if necessary
Thy 2	Non-neoplastic	Two samples 3–6 months apart showing benign appearances are indicated to exclude neoplasia. If rapid growth/pressure effects/high risk diagnostic lobectomy may be indicated.
Thy 3	(i) Follicular lesions	Lobectomy, with completion thyroidectomy if malignant
	(ii) Other suspicious findings	Discussion at thyroid cancer MDT
Thy 4	Suspicious of malignancy e.g. papillary, medullary, or anaplastic carcinoma/ lymphoma	Surgical excision for differentiated tumour
Thy 5	Diagnosis of malignancy	Surgical excision for differentiated thyroid cancer. Radiotherapy/chemotherapy for anaplastic thyroid cancer, lymphoma/metastases

Computed tomography (CT)

- CT is useful in the evaluation of retrosternal and retrotracheal extension of an enlarged thyroid.
- Compression of the trachea and displacement of the major vessels can be identified with CT of the superior mediastinum.
- It can demonstrate the extent of intrathoracic extension of thyroid malignancy and infiltration of adjacent structures such as the carotid artery, internal jugular vein, trachea, oesophagus, and regional lymph nodes.

Additional laboratory investigations

Haematological tests

- Long-standing thyrotoxicosis may be associated with a *normochromic anaemia* and occasionally a *mild neutropaenia*, *lymphocytosis* and rarely a *thrombocytopenia*.
- In hypothyroidism a macrocytosis is typical, although concurrent vitamin B12 deficiency should be considered.
- There may also be a *microcytic anaemia* due to menorrhagia and impaired iron utilization.

Biochemical tests

- *Alkaline phosphatase* may be elevated in thyrotoxicosis.
- Mild *hypercalcaemia* occasionally occurs in thyrotoxicosis and reflects ↑ bone resorption. *Hypercalciuria* is more common.
- In a hypothyroid patient, *hyponatraemia* may be due to reduced renal tubular water loss or less commonly due to co-existing cortisol deficiency.
- In hypothyroidism *creatinine kinase* is often raised and the lipid profile altered with ↑ LDL cholesterol.

Endocrine tests

- In untreated hypothyroidism there may be inadequate responses to provocative testing of the hypothalamo–pituitary–adrenal (HPA) axis.
- In hypothyroidism, serum prolactin may be elevated because ↑ TRH leads to ↑ prolactin secretion.
- In thyrotoxicosis there is an increase in *sex hormone binding globulin* (SHBG), and a complex interaction with sex steroid hormone metabolism, resulting in changes in the levels of androgens and oestrogens. The net physiological result is an increase in *oestrogenic* activity, with *gynaecomastia* and a decrease in libido in ♂ presenting with thyrotoxicosis.

Sick euthyroid syndrome (non-thyroidal illness syndrome)

- Biochemistry:
 - Low T_4 and T_3 .
 - Inappropriately normal/suppressed TSH.
- Tissue thyroid hormone concentrations are very low.
- Context—starvation.
 - Severe illness e.g. ITU, severe infections, renal failure, cardiac failure, liver failure, end-stage malignancy.
- Thyroxine replacement is not indicated because there is no clear evidence that treatment provides benefit or is safe.

Atypical clinical situations

- *Thyrotoxicosis factitia*:
 - No thyroid enlargement.
 - Elevated free T_4 and suppressed TSH.
 - Depressed thyroid uptake on scintigraphy.
 - Low thyroglobulin differentiates from thyroiditis (which shows depressed uptake on scintigraphy but \uparrow thyroglobulin) and all other causes of elevated thyroid hormones.
- *Struma ovarii* (ovarian teratoma containing hyperfunctioning thyroid tissue):
 - No thyroid enlargement.
 - Depressed thyroid uptake on scintigraphy.
 - Body scan after radioiodine confirms diagnosis.
- *Trophoblast tumours* hCG has structural homology with TSH and leads to thyroid gland stimulation, and usually mild thyrotoxicosis.
- *Hyperemesis gravidarum* Thyroid function tests may be abnormal with a suppressed TSH (see Chapter 3, p.34 and Chapter 70, p.431).
- *Choriocarcinoma of the testes* may be associated with gynaecomastia and thyrotoxicosis—measure hCG.

Thyrotoxicosis

Aetiology

Epidemiology

- 10 × more common in ♀ than in ♂ in the UK.
- Prevalence is approximately 2% of the ♀ population.
- Annual incidence is 3 cases per 1000 ♀.

Definition of thyrotoxicosis and hyperthyroidism

- The term *thyrotoxicosis* denotes the clinical, physiological, and biochemical findings that result when the tissues are exposed to excess thyroid hormone. It can arise in a variety of ways (Table 3.1). It is essential to establish a specific diagnosis as this determines therapy choices and provides important information for the patient regarding prognosis.
- The term *hyperthyroidism* should be used to denote only those conditions in which hyperfunction of the thyroid leads to thyrotoxicosis.

Genetics of autoimmune thyroid disease (AITD)

- AITD consists of Graves' disease, Hashimoto's thyroiditis, atrophic autoimmune hypothyroidism, post-partum thyroiditis and thyroid associated ophthalmopathy, that appear to share a common genetic predisposition.
- There is a ♀ preponderance and sex steroids appear to play an important role.
- Twin studies show ↑ concordance for Graves' disease and autoimmune hypothyroidism, in monozygotic compared to dizygotic twins.
- It is estimated that genetic factors account for 79% of the susceptibility for Graves' disease.
- Sib studies indicate that sisters and children of ♀ with Graves' disease have a 5–8% risk of developing Graves' disease or autoimmune hypothyroidism.
- On the background of a genetic predisposition, environmental factors are thought to contribute to the development of disease.
- A number of interacting susceptibility genes are thought to play a role in the development of disease—a complex genetic trait.
- *CTLA-4* (cytotoxic T lymphocyte antigen 4) is associated with Graves' disease in Caucasian populations. In particular, the CT60 allele has a prevalence of 60% in the general population, but is also the allele most highly associated with Graves' disease. These data emphasise the complex nature of genetic susceptibility and the likely interplay of environmental factors.
- Association of major histocompatibility complex (MHC) loci with Graves' disease has been demonstrated in some populations, but not others. HLA-DR3 is associated with Graves' disease in whites. HLA-DQA1*0501 is associated in some populations, especially for men. However, the overall contribution of MHC genes to Graves' disease has been estimated to be only 10–20% of the inherited susceptibility.

Table 3.1 Classification of the aetiology of thyrotoxicosis

Associated with hyperthyroidism	
Excessive thyroid stimulation	Graves' disease, Hashitoxicosis
	Pituitary thyrotroph adenoma
	Pituitary thyroid hormone resistance syndrome (excess TSH)
	Trophoblastic tumours producing hCG with thyrotrophic activity
Thyroid nodules with autonomous function	Toxic solitary nodule, toxic multinodular goitre
	Very rarely, thyroid cancer
Not associated with hyperthyroidism	
Thyroid inflammation	Silent and postpartum thyroiditis, subacute (de Quervain's) thyroiditis
	Drug-induced thyroiditis (amiodarone)
Exogenous thyroid hormones	Overtreatment with thyroid hormone
	Thyrotoxicosis factitia (thyroxine use in non-thyroidal disease)
Ectopic thyroid tissue	Metastatic thyroid carcinoma
	Struma ovarii (teratoma containing functional thyroid tissue)

Manifestations of hyperthyroidism

Box 3.1 Manifestations of hyperthyroidism (all forms)



Symptoms

- Hyperactivity, irritability, altered mood, insomnia.
- Heat intolerance, ↑ sweating.
- Palpitation.
- Fatigue, weakness.
- Dyspnoea.
- Weight loss with ↑ appetite (weight gain in 10% of patients).
- Pruritus.
- ↑ stool frequency.
- Thirst and polyuria.
- Oligomenorrhoea or amenorrhoea, loss of libido.




Signs


- Sinus tachycardia, atrial fibrillation.
- Fine tremor, hyperkinesia, hyperreflexia.
- Warm, moist skin.
- Palmar erythema, onycholysis.
- Hair loss.
- Muscle weakness and wasting.
- Congestive (high output) heart failure, chorea, periodic paralysis (primarily in Asian ♂), psychosis (rare).

Investigation of thyrotoxicosis

- Thyroid function tests raised free T₄ and suppressed TSH (raised free T₃ in T₃ toxicosis).
- Thyroid antibodies— see Table 2.4, p.11.
- Radionuclide thyroid scan if diagnosis uncertain ( see p.12) but is seldom required.

Manifestations of Graves' disease (in addition to those in Box 3.1)

- Diffuse goitre.
- Ophthalmopathy ( see Graves' ophthalmopathy, p.42).
 - A feeling of grittiness and discomfort in the eye.
 - Retrobulbar pressure or pain, eyelid lag or retraction.
 - Periorbital oedema, chemosis*, scleral injection.*
 - Exophthalmos (proptosis)*.
 - Extraocular muscle dysfunction.*
 - Exposure keratitis.*
 - Optic neuropathy.*
- Localized dermopathy (pretibial myxoedema,  see Graves' dermopathy, p.46).
- Lymphoid hyperplasia.
- Thyroid acropachy ( see Thyroid acropathy, p.46).

*Combination of these suggests congestive ophthalmopathy. Urgent action necessary if: corneal ulceration, congestive ophthalmopathy, or optic neuropathy ( see Graves' ophthalmopathy, p.42).

Conditions associated with Graves' disease

- Type 1 diabetes mellitus.
- Addison's disease.
- Vitiligo.
- Pernicious anaemia.
- Alopecia areata.
- Myasthenia gravis.
- Coeliac disease (4.5%).
- Other autoimmune disorders associated with the HLA-DR3 haplotype.

Treatment

Medical treatment

In general, the standard policy in Europe is to offer a course of antithyroid drugs (ATD) first. In the USA, radioiodine is more likely to be offered as first-line treatment.

Aims and principles of medical treatment

- To induce remission in Graves' disease.
- Monitor for relapse off treatment initially 6–8-weekly for 6 months, then 6-monthly for 2 years, and then annually thereafter or sooner if symptoms return.
- Use of a computerized thyroid follow-up register greatly facilitates monitoring and reduces the necessity for out-patient appointments.
- For relapse, consider definitive treatment such as radioiodine or surgery. A 2nd course of ATD almost never results in remission.

Choice of drugs—thionamides

- *Carbimazole*, which can be given as a single dose, is usually the drug of 1st choice in the UK. Carbimazole is converted to methimazole by cleavage of a carboxyl side chain on 1st liver passage. Methimazole and propylthiouracil are used widely in the USA and elsewhere in the world.
- During pregnancy and lactation *propylthiouracil* is the drug of choice because of its lower concentration in breast milk and the possible association of carbimazole with aplasia cutis.

Action of thionomides

- Thyroid hormone synthesis is inhibited by blockade of the action of thyroid peroxidase.
- Thionomides are especially actively accumulated in thyrotoxic tissue.
- Propylthiouracil also inhibits the deiodinase type 1 activity, and thus may have advantages when given at high doses in severe thyrotoxicosis.

Dose and effectiveness

- 5mg of carbimazole is roughly equivalent to 50mg of propylthiouracil. Propylthiouracil has a theoretical advantage of inhibiting the conversion of T_4 to T_3 , and T_3 levels decline more rapidly after starting the drug.
- 30–40% of patients treated with an ATD remain euthyroid 10 years after discontinuation of therapy. If hyperthyroidism recurs after treatment with an ATD, there is little chance that a 2nd course of treatment will result in permanent remission. Young patients, smokers, those with large goitres, ophthalmopathy, or high serum concentrations of thyrotropin receptor antibody at the time of diagnosis are unlikely to have a permanent remission.
- β -Adrenergic antagonists Propranolol 20–80mg 3 \times daily. Considerable relief from such symptoms as anxiety, tremor, and palpitations may be gained in the initial 4–8 weeks of treatment.

Atrial fibrillation

Should if present convert to sinus rhythm—otherwise cardiovert after 4 months euthyroid.

Side effects

- ATDs are generally well tolerated. Uncommonly, patients may complain of GI symptoms or an alteration in their sense of taste and smell.
- Agranulocytosis represents a potentially fatal but rare side effect of ATD occurring in 0.1–0.5% of patients. It is less frequent with carbimazole than with propylthiouracil and because cross reactivity of this reaction has been reported, one drug should never be substituted for the other after this reaction has been diagnosed. Agranulocytosis usually occurs within the first 3 months after initiation of therapy (97% within the first 6 months, especially on higher doses) but it is important to be aware of the documented cases, which have occurred (less frequently) a long time after starting treatment.
- As agranulocytosis occurs very suddenly and is potentially fatal, routine monitoring of FBC is thought to be of little use. Patients typically present with fever and evidence of infection, usually in the oropharynx, and *each patient should therefore receive written instructions to discontinue the medication and contact their doctor for a blood count should the situation arise.*
- Neutrophil dyscrasias occur more frequently in ♂, and are more often fatal in the elderly.
- Much more common are the allergic type reactions of rash, urticaria, and arthralgia, which occur in 1–5% of patients taking these drugs. These side effects are often mild and do not usually necessitate drug withdrawal, although one ATD may be substituted for another in the expectation that the second agent may be taken without side effects.
- Thionamides may cause cholestatic jaundice and elevated serum aminotransaminases have been reported, as has fulminant hepatic failure.
- All patients should be given written and verbal warnings about the potential side effects of thionamides.
- Rarely anti-neutrophil cytoplasmic antibody (ANCA) +ve vasculitis develops with propylthiouracil therapy. It may cause arthralgia, skin lesions, glomerulonephritis, fever, and alveolar haemorrhage. Skin lesions include ulcers. Biopsy reveals vasculitis. Propylthiouracil should be stopped and steroids may be needed.

Treatment regimen

Two alternative regimens are practised for Graves' disease: dose titration and block and replace.

Dose titration regime

- The 1st aim is to achieve a euthyroid state with relatively high drug doses and then to maintain euthyroidism with a low stable dose. The dose of carbimazole or propylthiouracil is titrated according to the thyroid function tests performed every 4–8 weeks, aiming for a serum free T₄ in the normal range and a detectable TSH. High serum TSH indicates the need for a dose reduction. TSH may remain suppressed for weeks or months.
- The typical starting dose of carbimazole is 20–30mg/day. Higher doses (40–60mg) may be indicated in severe cases, with very high levels of JT4.

- The treatment is continued for 18 months, as this appears to represent the length of therapy which is generally optimal in producing the remission rate of up to 40% at 5 years after discontinuing therapy.
- Relapses are most likely to occur within the 1st year and may be more likely in the presence of a large goitre and high T_4 level at the time of diagnosis, or the presence of TSH-receptor antibodies at the end of treatment (see p.22.)
- Patients with multinodular goitres and thyrotoxicosis always relapse on cessation of antithyroid medication, and definitive treatment with radioiodine or surgery is usually advised. Long-term thionamide therapy at low dose is also an option.

Block and replace regimen

- After achieving an euthyroid state on carbimazole alone, carbimazole at a dose of 40mg daily together with T_4 at a dose of 100mcg can be prescribed. This is usually continued for 6 months.
- The main advantages are fewer hospital visits for checks of thyroid function and shorter duration of treatment.
- Most patients achieve an euthyroid state within 4 – 6 weeks of carbimazole therapy.
- During treatment, FT_4 values are measured 4 weeks after starting thyroxine and the dose of thyroxine altered, if necessary, in 25mcg increments to maintain FT_4 in the normal range. Most patients do not require any dose adjustment.
- The originally reported higher remission rate was not confirmed in a large prospective multicentre European trial when combination treatment was compared to carbimazole alone but side effects were more common.¹
- Relapses are most likely to occur within the 1st year.

¹ Reinwein D, Benker G, Lazarus JH, et al. (1993). A prospective randomized trial of antithyroid drug dose in Graves' disease therapy. European Multicenter Study Group on Antithyroid Drug Treatment. *J Clin Endocrinol Metab* **76**, 1516–21.

Radioiodine treatment—radioiodine therapy

See Table 3.2.

Indications

- Definitive treatment of multinodular goitre or adenoma.
- Relapsed Graves' disease.

Table 3.2 Recommended activity of radioiodine

Aetiology	Comments	Guide dose (MBq)
Graves' disease	First presentation; no significant eye disease Moderate goitre (40–50g)	400–600
Toxic multinodular goitre in older person	Mild heart failure; atrial fibrillation or other concomitant disease, e.g. cancer	500–800
Toxic adenoma	Usually mild hyperthyroidism	500
Severe Graves' disease with thyroid eye disease	Postpone radioiodine till eye disease stable. Prednisolone 40mg to be administered at same time as radioiodine and for further 4–6 weeks (see below)	500–800
Ablation therapy	Severe accompanying medical condition such as heart failure; atrial fibrillation or other concurrent medical disorders (e.g. psychosis)	500–800

Data taken from the use of radioiodine in benign thyroid disease. Royal College of Physicians, 2007.

Contra-indications

- Young children, because of the potential risk of thyroid carcinogenesis.
- Pregnant and lactating ♀.
- Situations where it is clear that the safety of other people cannot be guaranteed.
- *Graves' ophthalmopathy* There is some evidence that Graves' ophthalmopathy may worsen after the administration of radioactive iodine, especially in smokers. In cases of moderate-to-severe ophthalmopathy radioiodine may be avoided. Alternatively steroid cover in a dose of 40mg prednisolone should be administered on the day of administering radioiodine, 30mg daily for the next 2 weeks, 20mg daily for the following 2 weeks, reducing to zero over subsequent 3 weeks. It is essential that euthyroidism is closely maintained following radioiodine to avoid worsening of ophthalmopathy.

Caveats

- The control of disease may not occur for a period of weeks or a few months.
- >1 treatment may be needed in some patients, depending on the dose given; 15% require a 2nd dose and a few patients require a 3rd dose. The 2nd dose should be considered only at least 6 months after the 1st dose.
- Compounds that contain iodine, such as amiodarone, block iodine uptake for a period of several months following cessation of therapy; iodine uptake measurements may be helpful in this instance in determining the activity required and the timing of radioiodine therapy.
- ♀ of childbearing age should avoid pregnancy for a minimum of 6 months following radioactive iodine ablation.
- The prevalence of hypothyroidism is about 50% at 10 years, and continues to increase thereafter.

Side effects are rare

- Anterior neck pain caused by radiation-induced thyroiditis.
- Transient rise (72 hours) in thyroid hormone levels which may exacerbate heart failure if present.

Hypothyroidism after radioiodine

- After radioiodine administration, ATDs may be recommenced. The ATDs should be withdrawn gradually guided by a 6–8-weekly thyroid function test. Early post-radioiodine hypothyroidism may be transient. TSH should be monitored initially, then annually after radioiodine to determine late hypothyroidism.
- In patients treated for autonomous toxic nodules the incidence of hypothyroidism is lower since the toxic nodule takes up the radioactive iodine while the surrounding tissue will recover normal function once the hyperthyroidism is controlled, though this is disputed by some experts.

Cancer risk after radioiodine therapy

In a recent large series, no overall excess risk of cancer was found. It is unclear whether the risk of death from thyroid cancer is slightly ↑.


Clinical guidelines

The recommendation is to administer enough radioiodine to achieve euthyroidism with the acceptance of a moderate rate of hypothyroidism, e.g. 15–20% at 2 years.

Instructions to patients before treatment

Discontinue ATDs 2–7 days before radioiodine administration since their effects last for 24h or more, though propylthiouracil has a prolonged radio-protective effect. ATDs may be recommenced 3–7 days after radioiodine administration without significantly affecting the delivered radiation dose.

Administration of radioiodine (Table 3.2)

- Radioactive iodine-131 is administered orally as a capsule or a drink.
- There is no universal agreement regarding the optimal dose. Dosing according to size alone is not successful in 90% of cases.
- A dose of 400–800MBq should be sufficient to cure hyperthyroidism in 90%.
- Most patients are treated with 400–600MBq as the first dose, and 600–800MBq if thyrotoxicosis persists 6–12 months after the 1st dose.
- For precaution  see Table 3.3.

Outcomes of radioiodine treatment¹

- In general 50–70% of patients have restored normal thyroid function within 6–8 weeks of receiving radioiodine. Shrinkage of goitre occurs but is slower.

¹ Royal College of Physicians of London (2007). *The use of radioiodine in benign thyroid disease.*

Instructions to patients after treatment

Precautions for patients following treatment with radioiodine are summarized in Table 3.3.


Table 3.3 Number of days to apply caution after radioiodine

Precaution	Administered activity of ^{131}I MBq			
	≤ 200	≤ 400	≤ 600	≤ 800
Avoid journeys on public transport >1h	0	0	0	6
Avoid places of entertainment or close contact with other people (duration 3h)	1	5	8	11
Stay off work when travel alone by private transport and work does not involve close contact with other people	0	0	0	0
Stay off work which involves prolonged contact with other people at a distance of 1m, e.g. bank cashier	8	13	16	18
Stay off work which involves close contact with other people including pregnant ♀ or children, work of a radiosensitive nature, or commercial food production	11	17	20	22
Avoid non-essential close contact (<1m) with children, teenagers, pregnant women within the family	16*	22*	25*	27*
Avoid non-essential close contact and sleeping with another person	4	9	13	15

*These times need to be extended if the child concerned is young, fretful, and needs a lot of close contact

Note: These apply only in the UK, they are less stringent in the USA

Surgery

Total thyroidectomy is now considered the operation of choice because of the risk of relapse with partial thyroidectomy. All such patients go home on T4.  See Box 3.2.

Box 3.2 Complications of thyroidectomy

Immediate

- Recurrent laryngeal nerve damage.
- Hypoparathyroidism.
- Thyroid crisis.
- Local haemorrhage, causing laryngeal oedema.
- Wound infection.

Late

- Hypothyroidism.
- Keloid formation.

Indications

- Documented suspicious or malignant thyroid nodule by FNAC.
- Pregnant mothers who are not adequately controlled by ATDs or in whom serious allergic reactions develop while being treated medically. Thyroidectomy is usually performed in the 2nd trimester.
- Patients:
 - Who reject or fear exposure to radiation.
 - With poor compliance to medical treatment.
 - In whom a rapid control of symptoms is desired.
 - With severe manifestations of Graves' ophthalmopathy, as total or near total thyroidectomy does not worsen eye manifestations.
 - With relapsed Graves' disease.
 - With local compressive symptoms which may not improve rapidly with radioiodine, whereas operation removes these symptoms in most patients.
 - With large thyroid glands and relatively low radioiodine uptake.

Preparation of patients for surgery

- ATDs should be used preoperatively to achieve euthyroidism.
- Propranolol may be added to achieve β -blockade especially in those patients where surgery must be performed sooner than achieving euthyroid state.
- Potassium iodide, 60mg 3 \times daily can be used during the preoperative period to prevent an unwanted liberation of thyroid hormones during surgery. Preoperatively it should be given for 10 days. Operating later than this can be associated with exacerbation of thyrotoxicosis as the thyroid escapes from the inhibitory effect of the iodide. In practice it is rarely needed as good control of thyrotoxicosis can be achieved with ATDs in the majority of patients.
- In the patient who appears to be non-compliant with ATDs and remains thyrotoxic prior to surgery, it may be necessary to admit them as an inpatient for supervised administration of high dose ATDs, together with β -blockade, and measurement of FT₄ and FT₃ twice weekly. There is a risk of thyroid crisis, or storm if a patient undergoes operation when thyrotoxic. Most patients can be rendered euthyroid within 2–4 weeks and potassium iodide can be administered as above to coincide with the timing of surgery.
- Additional measures are as for thyroid storm.

Thyroid crisis (storm)

Thyroid crisis represents a rare but life-threatening exacerbation of the manifestations of thyrotoxicosis. It should be promptly recognized since the condition is associated with a significant mortality (30–50% depending on series), see Box 3.3. Thyroid crisis develops in hyperthyroid patients who:

- Have an acute infection.
- Undergo thyroidal or non thyroidal surgery or (rarely) radioiodine treatment.

Thyroid crisis should be considered in a very sick patient if there is:

- Recent history suggestive of thyrotoxicosis.
- Acute stressful precipitating factor such as surgery.
- History of previous thyroid treatment.

Box 3.3 Clinical signs suggestive of a thyroid storm

- Alteration in mental status.
- High fever.
- Tachycardia or tachyarrhythmias.
- Severe clinical hyperthyroid signs.
- Vomiting, jaundice, and diarrhoea.
- Multisystem decompensation: cardiac failure, respiratory distress, congestive hepatomegaly, dehydration, and prerenal failure.

Laboratory investigations

- Routine haematology may indicate a leukocytosis, which is well-recognized in thyrotoxicosis even in the absence of infection.
- The biochemical screen may reveal a raised alkaline phosphatase and mild hypercalcaemia.
- Thyroid function tests and thyroid antibodies should be requested although treatment should not be delayed while awaiting the results.
- The levels of thyroid hormones will be raised but may not be grossly elevated and are usually within the range of uncomplicated thyrotoxicosis.

Treatment

General supportive therapy

- The patient is best managed in an intensive care unit where close attention can be paid to the cardiorespiratory status, fluid balance, and cooling.
- Standard anti-arrhythmic drugs can be used, including digoxin (usually in higher than normal dose) after correction for hypokalaemia. If anticoagulation is indicated because of atrial fibrillation then it must be remembered that thyrotoxic patients are very sensitive to warfarin.
- Chlorpromazine (50–100mg IM) can be used to treat agitation and because of its effect in inhibiting central thermoregulation it may be useful in treating the hyperpyrexia.
- Broad-spectrum antibiotics should be given if infection is suspected.

Specific treatment

- Aim: to inhibit thyroid hormone synthesis completely.
 - Propylthiouracil 200–300mg 6-hourly via NG tube. Propylthiouracil is preferred because of its ability to block T_4 to T_3 conversion in peripheral tissues. There are no clinical data comparing propylthiouracil and carbimazole in this situation. ATDs should be commenced first.
- Potassium iodide 60mg via NG tube, 6-hourly, 6h *after* starting propylthiouracil will inhibit thyroid hormone release.
- B-adrenergic blocking agents are essential in the management to control tachycardia, tremor, and other adrenergic manifestations:
 - Propranolol 160–480mg/day in divided doses or as an infusion at a rate of 2–5mg/h.
- Calcium channel blockers can be tried in patients with known bronchospastic disease where β -blockade is contraindicated.
- High doses of glucocorticoids are capable of blocking T_4 to T_3 conversion: Prednisolone 60mg daily or hydrocortisone 40mg IM, 4 \times daily.
- Plasmapheresis and peritoneal dialysis may be effective in cases resistant to the usual pharmacological measures.
- Colestyramine (3g tds) reduces the entero-hepatic circulation of thyroid hormones and may help improve thyrotoxicosis.

Subclinical hyperthyroidism

- Values of thyroid hormones should be repeated to exclude non thyroidal illness.
- Subclinical hyperthyroidism is defined as undetectable thyrotropin (TSH) concentration in patients with normal levels of T₄ and T₃. Subtle symptoms and signs of thyrotoxicosis may be present.
- May be classified as endogenous in patients with thyroid hormone production associated with nodular thyroid disease or underlying Graves' disease; and as exogenous in those with undetectable serum thyrotropin concentrations as a result of treatment with levothyroxine.

The evidence that subclinical hyperthyroidism is a risk factor for the development of atrial fibrillation or osteoporosis is definitive¹.


- The ↑ risk of fracture reported in older ♀ taking thyroid hormone disappears when those with a history of hyperthyroidism are excluded.
- In many patients with endogeneous subclinical hyperthyroidism who do not have nodular thyroid disease or complications of excess thyroid hormone, treatment is unnecessary, but thyroid-function tests should be performed every 6 months. In older patients with atrial fibrillation or osteoporosis that could have been caused or exacerbated by the mild excess of thyroid hormone, ablative therapy with ¹³¹I is the best initial option.
- In patients with exogeneous subclinical hyperthyroidism, the dose of levothyroxine should be reduced, excluding those with prior thyroid cancer in whom thyrotropin suppression may be required. The dose of levothyroxine used for treating hypothyroidism may be reduced if the patient develops:
 - New atrial fibrillation, angina or cardiac failure.
 - Accelerated bone loss.
 - Borderline high serum triiodothyronine concentration.

¹ Parle JV, Maisonneuve P, Sheppard MC, et al. (2001). Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet* 358(9285), 861–5.

Thyrotoxic hypokalaemic periodic paralysis

- More common in Asians (5–10% of all with thyrotoxicosis due to Graves' disease or multinodular goitre) (0.1–0.2% of non-Asian Europeans/North Americans).
- Aetiology is probably due to disordered function of ion channels in cell membranes.
- Most common form of acquired periodic paralysis.
- Usual age of onset 20–40 years, mostly σ .
- Recurrent episodes of muscle weakness.
- Duration minutes to days.
- Flaccid paralysis, usually spreading from legs proximally.
- Clinical manifestations of thyrotoxicosis may be few and thus TSH should be checked in anyone presenting with periodic paralysis.
- Improves as thyrotoxicosis treated.
- Low serum potassium during attacks.
- CPK \uparrow during recovery phase.
- Precipitated by carbohydrates, insulin, cold, vigorous exercise.
- Treatment with potassium replacement, usually by oral route, and treatment of thyrotoxicosis.
- Symptoms usually improve within 2–4 hours, full resolution in 24–48 hours.
- Non-selective β -blockers, such as propranolol (3mg/kg) help prevent attacks until a euthyroid state achieved.

Thyrotoxicosis in pregnancy

( also see p.428.)

- Thyrotoxicosis occurs in about 0.2% of pregnancies.
- Graves' disease accounts for 90% of cases.
- Less common causes include toxic adenoma and multinodular goitre.
- Other causes are gestational hyperthyroidism (hyperemesis gravidarum) and trophoblastic neoplasia.
- Diagnosis of thyrotoxicosis during pregnancy may be difficult or delayed.
- Physiological changes of pregnancy are similar to those of hyperthyroidism.
- Total T₄ and T₃ are elevated in pregnancy because of an elevated level of TBG but, with free hormone assays available, this is no longer a problem.
- Physiological features of normal pregnancy include an increase in basal metabolic rate, cardiac stroke volume, palpitation, and heat intolerance.
- Serum free T₃ concentrations remain within the normal range in most pregnant ♀; serum TSH concentration decreases during the 1st trimester.

Symptoms

- Hyperemesis gravidarum is the classic presentation ($\frac{1}{3}$ are toxic). Tiredness, palpitations, insomnia, heat intolerance, proximal muscle weakness, shortness of breath, and irritability may be other presenting symptoms.
- Thyrotoxicosis may occasionally be diagnosed when the patient presents with pregnancy-induced hypertension or congestive heart failure.

Signs

- Failure to gain weight despite a good appetite.
- Persistent tachycardia with a pulse rate >90 beats/min at rest.
- Other signs of thyrotoxicosis as described previously.

Natural history of Graves' disease in pregnancy

There is aggravation of symptoms in the 1st half of the pregnancy; amelioration of symptoms in the 2nd half of the pregnancy, and often recurrence of symptoms in the postpartum period.


Transient hyperthyroidism of gestational hyperthyroidism (hyperemesis gravidarum)

- The likely mechanism is a raised β -hCG level.
- β hCG, LH, FSH, and TSH are glycoprotein hormones that contain a common α -subunit and a hormone-specific β -subunit. There is an inverse relationship between the serum levels of TSH and hCG, best seen in early pregnancy. There is also structural homology of the TSH and hCG receptors.
- Serum free T_4 concentration may be \uparrow and the TSH levels suppressed in ♀ with hyperemesis gravidarum.
- Thyroid function tests recover after the resolution of hyperemesis.
- Pregnant ♀ with gestational hyperthyroidism (hyperemesis gravidarum), (which only accounts for 2/3 of hyperemesis) are not usually given ATD treatment but managed supportively with fluids, antiemetics, and nutritional support.
- There is no \uparrow risk of thyrotoxicosis in subsequent pregnancies.
- Can be differentiated from Graves' disease by the absence of a goitre, antithyroid antibodies, or family history of Graves' disease, a history of other autoimmune phenomena and a previous history of ophthalmic Graves'.


Management of Graves' disease in the mother

- Aim of treatment is alleviation of thyroid symptoms and normalization of tests in the shortest time. Patients should be seen every 4–8 weeks and TFTs performed. Serum free T_4 is the best test to follow the response to ATDs. Block and replace regimen should not be used as this will result in fetal hypothyroidism.
- Both propylthiouracil (150mg bd.) and carbimazole (10–20mg once daily) are effective in controlling the disease in pregnancy. As propylthiouracil is more bound to plasma proteins, theoretically less of the drug would be transferred to the fetus. Most use propylthiouracil in pregnancy because this not associated with aplasia cutis which may be the case for carbimazole. A β -blocker (propranolol 20–40mg 6–8-hourly) is effective in controlling the hypermetabolic symptoms but should be used only for a few weeks until symptoms abate.
- The dosage of ATDs is frequently adjusted during the course of the pregnancy; therefore thyroid tests should be done at 2–4 week intervals, with the goal of keeping free thyroid hormone levels in the upper 1/3 of the reference range.
- Thyroid tests may normalize spontaneously with the progression of a normal pregnancy as a result of immunological changes.
- The use of iodides and radioiodine is contraindicated in pregnancy.
- Surgery is rarely performed in pregnancy. It is reserved for patients not responding to ATDs. It is preferable to perform surgery in the 2nd trimester.
- Breast-feeding mothers should be treated with the lowest possible dose of propylthiouracil.

Prepregnancy counselling

- Hyperthyroid ♀ who want to conceive should attain euthyroidism before conception, since uncontrolled hyperthyroidism is associated with an ↑ risk of congenital abnormalities (stillbirth and cranial synostosis are the most serious complications).  See Box 3.4.
- There is no evidence that radioactive iodine treatment given to the mother 6 months or more before pregnancy has an adverse effect on the fetus or on an offspring in later life.
- Antithyroid medication requirements decrease during gestation; in about 50–60% of the dose may be discontinued in the last few weeks of gestation.
- The risk of recurrent hyperthyroidism should be discussed with the patient
- The rare occurrence of fetal and neonatal hyperthyroidism should be included during counselling sessions and the diagnosis of Graves' hyperthyroidism conveyed to the obstetrician and neonatologist.

Management of the fetus

- The hypothalamo–pituitary–thyroid axis is well developed at 12 weeks gestation but remains inactive until 18–20 weeks. Circulating TSH receptor antibodies (TSH-RAB) in the mother can cross the placenta. The risk of hyperthyroidism to the neonate can be assessed by measuring TSH-RAB in the maternal circulation at the beginning of the 3rd trimester. Antithyroglobulin antibody and thyroid peroxidase antibodies have no effect on the fetus.
- Long-term follow-up studies of children whose mothers received either carbimazole or propylthiouracil have not shown an ↑ incidence of any physical or psychological defects. The block and replace regimen using relatively high doses of carbimazole is contraindicated because the ATDs cross the placenta, but replacement T_4 does not, thus potentially rendering the fetus hypothyroid.
- Monitoring the fetal heart rate and growth rates are the standard means whereby fetal thyrotoxicosis may be detected. A rate >160 beats/min is suspicious of fetal thyrotoxicosis in the 3rd trimester. Fetal thyrotoxicosis may complicate the latter part of the pregnancy of ♀ with Graves' disease even if they have previously been treated with radioiodine or surgery since TSH receptor antibodies may persist. If there is evidence of fetal thyrotoxicosis, the dose of the ATD should be ↑. If this causes maternal hypothyroidism a small dose of T_4 can be added since, unlike carbimazole, T_4 crosses the placenta less. A paediatrician should be involved to monitor neonatal thyroid function and detect thyrotoxicosis.
- Hypothyroidism in the mother should be avoided because of the potential adverse effect on subsequent cognitive function of the neonate,  see Box 3.4.
- If the mother has been treated with carbimazole, the post-delivery levels of T_4 may be low and neonatal levels of T_4 may only rise to the thyrotoxic range after a few days. In addition, TSH is usually absent in neonates who subsequently develop thyrotoxicosis. Clinical indicators of neonatal thyrotoxicosis include low birth weight, poor weight gain, tachycardia, and irritability. Carbimazole can be given at a dose of 0.5 mg/kg per day and withdrawn after a few weeks after the level of TSH-RAB declines.

Box 3.4 Potential maternal and fetal complications in uncontrolled hyperthyroidism in pregnancy

Maternal

- Pregnancy induced hypertension
- Preterm delivery
- Congestive heart failure
- Thyroid storm
- Miscarriage
- Abruptio placentae
accidental haemorrhage

Fetal

- Hyperthyroidism
- Neonatal hyperthyroidism
- Intrauterine growth retardation
- Small-for-gestation age
- Prematurity
- Stillbirth
- Cranial synostosis

Postpartum thyroiditis

- Defined as a syndrome of postpartum thyrotoxicosis or hypothyroidism in ♀ who were euthyroid during pregnancy.
- Postpartum thyroid dysfunction, which occurs in ♀ with autoimmune thyroid disease, is characterized in a 1/3 by a thyrotoxic phase occurring in the first 3 months postpartum, followed by a hypothyroid phase that occurs 3–6 months after delivery, followed by spontaneous recovery. In the remaining 2/3, a single-phase pattern or the reverse occurs.
- 5–7% percent of ♀ develop biochemical evidence of thyroid dysfunction after delivery. An ↑ incidence is seen in patients with type I diabetes mellitus (25%), other autoimmune diseases, in the presence of anti-TPO antibodies and in the presence of a family history of thyroid disease.
- Hyperthyroidism due to Graves' disease accounts for 10–15% of all cases of postpartum thyrotoxicosis. In the majority of cases hyperthyroidism occurs later in the postpartum period (>3–6 months) and persists.
- Providing the patient is not breast-feeding, a radioiodine uptake scan can differentiate the 2 principal causes of autoimmune thyrotoxicosis by demonstrating ↑ uptake in Graves' disease and low uptake in postpartum thyroiditis.
- Graves' hyperthyroidism should be treated with ATDs. Propylthiouracil is preferable if the patient is breast-feeding. Thyrotoxic symptoms due to postpartum thyrotoxicosis are managed symptomatically using propranolol.
- 1/3 of affected ♀ with postpartum thyroiditis develop symptoms of hypothyroidism and may require T₄ for 6–12 months. There is a suggestion of an ↑ risk of postpartum depression in those with hypothyroidism.
- Histology of the thyroid in the case of postpartum thyroiditis shows lymphocytic infiltration with destructive thyroiditis and predominantly occurs at 16 weeks in ♀ with +ve antimicrosomal antibodies.
- There is an ↑ chance of subsequent permanent hypothyroidism in 25–30%. Patients with a history of postpartum thyroiditis should be followed up with annual TSH measurements.

Hyperthyroidism in children

Epidemiology

Thyrotoxicosis is rare before the age of 5 years. Although there is a progressive increase in incidence throughout childhood it is still rare and accounts for <5% of all cases of Graves' disease.

Clinical features

- Behavioural abnormalities, hyperactivity, declining school performance may bring the child to medical attention. Features of hyperthyroidism are as described previously.
- Acceleration of linear growth is common in patients increasing in height percentiles on the growth charts. The disease may be part of McCune–Albright syndrome and café-au-lait pigmentation, precocious puberty, and bony abnormalities should be considered during clinical examination.

Investigations

The cause of thyrotoxicosis in children is nearly always Graves' disease (with +ve antibodies to thyroglobulin, thyroid peroxidase, or both) although thyroiditis and toxic nodules have been described and a radioiodine scan may be useful if the diagnosis is not clear. Hereditary syndromes of thyroid hormone resistance often misdiagnosed as Graves' disease are now being increasingly recognized in children.

Treatment

ATDs represent the treatment of choice for thyrotoxic children. Therapy is generally started with propylthiouracil 2.5–5mg/kg (initial dose 75–150mg/day) or carbimazole 250mcg/kg (initial dose 10mg/day). Since relapse after withdrawal of ATDs is common, these drugs are often continued long term, until education is complete and definitive treatment with surgery or radioiodine can be offered.

Secondary hyperthyroidism

An elevated serum free T₄ and non-suppressed serum TSH are characteristic of TSH secreting adenomas or resistance to thyroid hormone. These conditions must be differentiated (Table 3.4).

TSH-secreting pituitary tumours

- <1% of all pituitary tumours.
- There are characteristically *elevated* serum free T₄ and T₃ concentrations and *non-suppressed* (inappropriately normal or frankly elevated) serum TSH levels.
- Among the 280 TSHomas reported in the literature (until 1998), 72% secreted TSH alone; the remainder co-secreted growth hormone (16%), prolactin (11%), or rarely gonadotrophins. Approximately 90% were macroadenomas (>1cm in diameter) and 71% exhibited suprasellar extension, invasion, or both into adjacent tissues (see p.160).
- Patients with pure TSHomas present with typical symptoms and signs of thyrotoxicosis and the presence of a diffuse goitre. Patients may exhibit features of over secretion of the other pituitary hormones, e.g. prolactin or growth hormone. Headaches, visual field defects, menstrual irregularities, amenorrhoea, delayed puberty, and hypogonadotrophic hypogonadism have also been reported. Careful establishment of the diagnosis is the key to treatment. Inappropriate treatment of such patients with subtotal thyroidectomy or radioiodine administration not only fails to cure the underlying disorder but may be associated with subsequent pituitary tumour enlargement and an ↑ risk of invasiveness into adjacent tissues.
- Treatment options are:
 - Trans-phenoidal surgery.
 - Pituitary radiotherapy if surgical results are unsatisfactory, or surgery is contraindicated or not desired.
 - Medical therapy with somatostatin analogues such as octreotide or lanreotide may be useful preoperatively and suppresses TSH secretion in 80% of the cases.

Resistance to thyroid hormones

- Patients with generalized resistance to thyroid hormone (GRTH) may present with mild hyperthyroidism, deaf mutism, delayed bone maturation, raised circulating thyroid hormone concentrations, non-suppressed TSH, and failure of TSH to decrease normally upon administration of supraphysiological doses of thyroid hormones. Most patients present with goitre or incidentally found abnormal TFTs. Treatment is determined by thyroid status.
- In selective pituitary resistance to thyroid hormones (PRTH) the thyroid hormone resistance is more pronounced in the pituitary; thus the patient exhibits definite clinical manifestations of thyrotoxicosis.
- About 90% of thyroid hormone resistance syndromes result from mutations in the gene encoding TR β . Mutant receptors have a reduced affinity for T₃ and are functionally deficient. It is usually inherited in

an autosomal dominant pattern with the affected individuals being heterozygous for the mutation.

- A subset of RTH receptors has been identified that are capable of inhibiting wild type receptor action. When co-expressed, the mutant proteins are able to inhibit the function of their wild type counterparts in a dominant –ve manner.
- Common features of patients with the thyroid hormones resistance syndromes include goitre (most commonly), and less so, tachycardia, hyperkinetic behaviour, emotional disturbances, ear, nose, and throat infections, language disabilities, auditory disorders, low body weight, cardiac abnormalities, and subnormal intelligence quotients.

Treatment options in RTH are not usually necessary. In PTR treatment may be needed but this is uncommon. Chronic suppression of TSH secretion with D T₄, triiodo-thyroacetic acid, octreotide, or bromocriptine. If this is ineffective, thyroid ablation with radioiodine or surgery with subsequent close monitoring of thyroid hormone status and pituitary gland size.

Table 3.4 Tests useful in the differential diagnosis of TSHomas, PRTH, and GRTH

Test	TSHomas	PRTH	GRTH
Clinical thyrotoxicosis	Present	Present	Absent
Family history	Absent	Present	Present
TSH response to TRH	No change	Increase	Increase
TSH response to T ₃ (100mcg/day + β -blockers)	No change	Decrease	Decrease
SHBG	Elevated–92% ^a	Normal ^b	Normal
α -subunit	Elevated–65%	2% elevated	
Pituitary MRI	Tumour–30% micoradenoma ^c	Normal	Normal
Fall in TSH on octreotide LAR 20mg/month for 2 months	95%	No change	No Change

^a Not usually raised in mixed GH/TSH tumour.

^b Peripheral markers of toxicosis sometimes affected (8% SHBG elevated).

^c The best biochemical test is an elevated α -subunit

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Graves' ophthalmopathy, dermopathy, and acropachy

Graves' ophthalmopathy

([✓] see European Working Group on Graves' Ophthalmopathy www.EUGOGO.org)

- An organ-specific autoimmune disorder characterized by swelling of the extra-ocular muscles, lymphocytic infiltration, late fibrosis, muscle tethering, and proliferation of orbital fat and connective tissue.
- Clinically evident in ~30% of patients. Most have mild disease, but 5% have severe disease that threatens sight.
- Incidence higher in ♀ (except for severe disease where equal sex-incidence)
- Bimodal age distribution in ♀, with peak onsets between 40–44 years and 60–64 years. In ♂, a single peak incidence occurs at 65–69 years.
- There are 2 stages in the development of the disease, which can be recognized as an active inflammatory (dynamic) stage and a relatively quiescent static stage. 5% of patients with Graves' ophthalmopathy have hypothyroidism and 5% are euthyroid. 75% of patients develop Graves' disease within a year either side of Graves' ophthalmopathy developing. The lesions are due to localized accumulation of glycosaminoglycans.
- The appearance of eye disease follows a different time course to thyroid dysfunction and in a minority there is a lag period between the presentation of hyperthyroidism and the appearance of eye signs.
- Smoking and hypothyroidism moderately worsen Graves' ophthalmopathy.
- Current smokers (>20/day) are more likely to develop ophthalmopathy.
- The role of an endocrinologist during a routine review of Graves' patients is to record accurately the clinical features of Graves' eye disease and to identify ocular emergencies, such as corneal ulceration, congestive ophthalmopathy, and optic neuropathy, which should be referred urgently to an ophthalmologist.

Clinical features

- Retraction of eyelids is extremely common in thyroid eye disease. The margin of the upper eyelid normally rests about 2 mm below the limbus and retraction can be suspected if the lid margin is either level or above the superior limbus allowing the sclera to be visible. The lower lid normally rests at the inferior limbus and retraction is suspected when the sclera shows above the lid.
- Proptosis or exophthalmos can result in failure of lid closure, ↑ the likelihood of exposure keratitis and the common symptom of gritty eyes. This can be confirmed with a fluorescein or Rose Bengal stain. As papilloedema can occur, fundoscopy should be performed. Proptosis may result in periorbital oedema and chemosis because the displaced orbit results in less efficient orbital drainage.

- Persistent visual blurring may indicate an optic neuropathy and requires urgent treatment.
- Severe conjunctival pain may indicate corneal ulceration requiring urgent referral.
- Features are unilateral in approximately 15% of cases.

Investigation of proptosis

The 'NOSPECS' classification is not universally accepted, for detailed classification see ¹ www.EUGOGO.org and The European Group on Graves' Orbitopathy¹.

- *Documentation using a Hertel exophthalmometer* The feet of the apparatus are placed against the lateral orbital margin as defined by the zygomatic bones. The marker on the body of the exophthalmometer is then superimposed on the reflection of the contralateral one by adjusting the scale. The position of each cornea can be read off against the reflections on a millimetre scale as seen on the mirror of the apparatus. A normal result is generally taken as being <20mm (<18mm in Asians, <22 in Afro-Caribbeans). A reading of 21mm or more is abnormal and a difference of 2mm between the eyes is suspicious.
- *Soft tissue involvement* Soft tissue signs and symptoms include conjunctival hyperaemia, chemosis, and foreign body sensation. The soft tissue changes can be 2° to exposure but are often seen in the absence of these aetiological factors.
- *CT or MRI scan of the orbit* demonstrates enlargement of the extra-ocular muscles and this can be useful in cases of diagnostic difficulty. This is also more accurate for demonstration of proptosis.

Ophthalmoplegia

- Patients may complain of diplopia due to ocular muscle dysfunction caused by either oedema during the early active phase or fibrosis during the later phase. Assessment using a Hess chart may be helpful. Intra-optic pressure may increase on upgaze and result in compression of the globe by a fibrotic inferior rectus muscle. Ocular mobility may be restricted by oedema during the active inflammatory phase or by fibrosis during the fibrotic stage.
- The 2 most common findings are defective elevation caused by fibrotic contraction of the inferior rectus muscle and a convergence defect caused by fibrotic contraction of the medial rectus. Disorders of the medial rectus, superior rectus, and lateral rectus muscle produce typical signs of defective adduction, depression and abduction respectively.

¹ The European Group on Graves' Orbitopathy (2006). Clinical assessment of patients with Graves' orbitopathy: recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol* 155(3), 387–9.

Examining for possible optic neuropathy

- History of *poor vision*, a recent or *rapid change in vision*, or *poor colour vision* are reasons for prompt referral.
- A *visual acuity* of <6/18 warrants referral to an ophthalmologist. For *colour vision*, each eye should be evaluated by using a simple 15-plate Ishihara colour vision test. Colour vision is a subtle indicator of optic nerve function. Failure to identify >2 of the plates with either eye is an indication for referral. This is unhelpful in the 8% of σ who may be colour blind.
- *Marcus Gunn pupil* The 'swinging flashlight' test detects the presence of an *afferent pupillary defect*.

Medical treatment

📖 See Box 4.1.

Simple treatment for lid retraction

- Most patients do not require any treatment, since clinical signs usually improve with treatment of hyperthyroidism or spontaneously with time (40%).
- Sunglasses help with photophobia and excess tears.
- In patients with significant lid retraction and exposure keratopathy, topical lubricants improve symptoms (surgery to reduce the vertical lid fissures can be considered).
- Botulinum toxin injection may reduce upper lid retraction.
- Head elevation during sleep and diuretics may help congestion.

Acute treatment for active ophthalmopathy threatening sight

- Glucocorticoids at high dose (60–80mg/day) improve ophthalmopathy in 60–75% of cases.
- Effectiveness is more likely in those with diplopia at neutral gaze and an inflammatory component to ophthalmoplegia.
- Treatment should be given for 2 weeks and then tapered gradually.
- Urgent referral to ophthalmologist is indicated for any suspicion of optic neuropathy or corneal ulceration.

Orbital radiotherapy

- Indications for lens-sparing orbital radiotherapy are similar to those for high-dose glucocorticoids.
- Radiotherapy probably works by reducing the activity and number of activated lymphocytes in the retrobulbar tissues.
- 20 Gray delivered over 10 fractions is the standard regimen.
- Treatment with both radiotherapy and glucocorticoids is more effective than either alone.
- Effectiveness in 60% of cases <40 years.

Other medical therapies

- Other immunosuppressive regimens have no proven place in the general management of Graves' ophthalmopathy.
- Use of depot octreotide has been shown to be of no benefit in management.

Surgical treatment

See Box 4.1.

Surgery for decompression

- Orbital decompression may be indicated for urgent treatment of optic neuropathy.
- Posteromedial wall of orbit usually removed.
- Complications include dysmotility of the eye, blindness, orbital cellulitis, CSF leak, cerebral haematoma, obstruction to nasolacrimal flow and anosmia.

Surgery for strabismus

- Should be performed after any necessary orbital decompression.
- Aims to allow correct binocular vision.
- Is performed when eyes are in a quiescent phase for at least 6 months after active disease.
- Involves alteration, loosening or tightening of eye muscles, often over several operations, to improve binocular vision.

Eye lid surgery

Is the final stage of any surgical approach and aims to adjust upper and lower eyelid position to improve comfort and appearance.

Box 4.1 Treatment of Graves' ophthalmopathy

General measures:

- Stop smoking
- Dark glasses, with eye protection
- Control thyroid function

Specific measures:

Problem	Treatment
Grittiness	Artificial tears and simple eye ointment
Eyelid retraction	Tape eyelids at night to avoid corneal damage. Surgery if risk of exposure keratopathy
Proptosis	Head elevation during sleep Diuretics Systemic steroids Radiotherapy Orbital decompression
Optic neuropathy	Systemic steroids Radiotherapy Orbital decompression
Ophthalmoplegia	Prisms in the acute phase Orbital decompression Orbital muscle surgery

Graves' dermatopathy

- This is a rare complication of Graves' thyrotoxicosis (0.5%). It is usually pre-tibial in location (99%) and hence called *pre-tibial myxoedema*.
- Associated with ophthalmopathy (97%) and acropachy (18%)
- It typically appears as raised, discoloured, and indurated lesions on the front or back of the legs, or on the dorsum of the feet, and has occasionally been described in other areas, including the hands and the face.
- The lesions are due to localized accumulation of *glycosaminoglycans*. It is now recognized that there is a lymphocytic infiltrate. Lesions are characteristically asymptomatic but they can also be pruritic and tender. They can be very disfiguring.
- **Treatment** Usually not treated. Potent topical fluorinated steroids such as flucinolone acetonide may be effective (4–8 weeks), not only in the treatment of localized pain and tenderness but also in some resolution of the visible skin signs. Surgery may worsen the condition.
- 25% remit completely; 50% are chronic on no therapy. topical steroids on remission rates is unproven.

Thyroid acropachy

- This is the rarest manifestation of Graves' disease.
- It presents as clubbing of the digits and sub-periosteal new bone formation. The soft tissue swelling is similar to that seen in localized myxoedema and consists of glycosaminoglycan accumulation.
- Patients almost inevitably have Graves' ophthalmopathy or pretibial myxoedema. If not, an alternative cause of clubbing should be looked for.
- It is typically painless and there is no effective treatment.

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Multinodular goitre and solitary adenomas

Background

Nodular thyroid disease denotes the presence of single or multiple palpable or non-palpable nodules within the thyroid gland.

- Prevalence rates range from 5–50% depending on population studied and sensitivity of detection methods. Prevalence increases linearly with age, exposure to ionizing radiation and iodine deficiency.
- Clinically apparent thyroid nodules are evident in ~10% of the UK population.
- Incidence of thyroid nodules is about 4 × more in ♀.
- Thyroid nodules always raise the concern of cancer, but <5% are cancerous.

Clinical evaluation

- An asymptomatic thyroid mass may be discovered either by a clinician on routine neck palpation or by the patient during self-examination.
- History should concentrate on:
 - An enlarging thyroid mass.
 - A previous history of radiation, especially childhood head and neck irradiation.
 - A family history of thyroid cancer.
 - The development of hoarseness or dysphagia.
- Nodules are more likely to be malignant in patients <20 or >60 years.
- Thyroid nodules are more common in ♀ but more likely to be malignant in ♂.
- Physical findings suggestive of malignancy include a firm or hard non-tender nodule; a recent history of enlargement, fixation to adjacent tissue, and the presence of regional lymphadenopathy.
- *Pemberton's sign* is facial erythema and jugular venous distension on raising the arms. It is a sign of superior venacaval obstruction caused by a sub-sternal mass.
- A hot nodule on a radioisotope scan makes malignancy less likely.
- 📖 See Box 5.1 for aetiology of thyroid nodules.

Box 5.1 Aetiology of thyroid nodules**Common causes**

- Colloid nodule.
- Cyst.
- Lymphocytic thyroiditis.
- Benign neoplasms;
 - Hurthle cell.
 - Follicular.
- Malignancy:
 - Papillary.
 - Follicular.

Uncommon causes

- Granulomatous thyroiditis.
- Infections.
- Malignancy:
 - Medullary.
 - Anaplastic.
 - Metastatic.
 - Lymphoma.

Clinical features raising the suspicion of thyroid malignancy

- Age (childhood or elderly).
- Short history of enlarging nodule.
- Local symptoms including dysphagia, stridor, or hoarseness.
- Previous exposure to radiation.
- +ve family history of thyroid cancer or MEN syndrome.
- Gardner's syndrome (familial large intestinal polyposis).
- Familial polyposis coli.
- Cowden syndrome (autosomal dominantly inherited hamartoma syndrome).
- Lymphadenopathy.
- History of Hashimoto's disease (↑ incidence of lymphoma).

Investigations

- FNAC (see p.14).
- Serum TSH concentration.
- Respiratory flow loop especially for a large goitre possibly causing tracheal obstruction.
- CT scan or MRI if there are concerns about retrosternal goitre or tracheal compression.

Treatment

Toxic multinodular goitre or nodule

The patient should initially be rendered euthyroid with medical treatment.

ATDs

ATDs are effective in controlling the hyperthyroidism but are not curative. As the hot nodules are autonomous the condition will recur after stopping the drugs. Carbimazole is useful treatment to gain control of the disease in preparation for surgery or as long-term treatment in those patients unwilling to accept radioiodine or surgery.

Radioiodine

- This form of treatment is often considered as 1st choice for definitive treatment. ^{131}I is preferentially accumulated in hot nodules but not in normal thyroid tissue which, because of the thyrotoxic state, is non-functioning.
- Radioiodine treatment commonly induces a euthyroid state as the hot nodules are destroyed and the previously non-functioning follicles gradually resume normal function. A dose of 500–800MBq for small-to-medium and 600 or 800MBq for medium-to-large goitres is recommended

Surgery

- The aim of surgery is to remove as much of the nodular tissue as possible and if the goitre is large to relieve local symptoms. Postoperative follow-up should involve checks of thyroid function.
- Goitre recurrence, although rare, does occasionally occur.

Non-toxic multinodular goitre

Surgery

- Is the preferred treatment for patients with:
 - Local compression symptoms.
 - Cosmetic disfigurement.
- Solitary nodule with FNAC suspicious of malignancy.

Radioiodine

- Radioiodine may be particularly indicated in elderly patients in whom surgery is not appropriate. It may require admission. Up to 50% shrinkage of goitre mass has been reported in recent studies.
- Hypothyroidism following radioiodine is relatively low but is still recognized.

Medical treatment

Use of T_4 to suppress TSH is associated with risk of cardiac arrhythmias and bone loss. T_4 is useful only if TSH is detectable but is not generally indicated.

Box 5.2 Aetiology of goitre

- Autoimmune thyroid disease.
- Sporadic.
- Endemic (iodine deficiency, dietary origins).
- Pregnancy.
- Drug-induced (ATDs, lithium, amiodarone).
- Thyroiditis syndromes.

Pathology

Thyroid nodules may be described as *adenomas* if the follicular cell differentiation is enclosed within a capsule; *adenomatous* when the lesions are circumscribed but not encapsulated.

Thyroid nodules in pregnant mothers

- Increase in size during gestation.
- Increase in number.
- Need FNA as higher risk of malignancy.
- Can be operated upon in 2nd trimester or post-partum.

Thyroiditis

Background

Inflammation of the thyroid gland often leads to a transient thyrotoxicosis followed by hypothyroidism. Overt hypothyroidism caused by autoimmunity has two main forms: *Hashimoto's (goitrous) thyroiditis* and *atrophic thyroiditis*.

Table 6.1 Causes and characteristics of thyroiditis

Cause	Characteristic features
Autoimmune thyroiditis (Hashimoto's)	Grossly lymphocytic and fibrotic thyrotoxicosis or hypothyroidism
Postpartum thyroiditis	Lymphocytic thyroiditis, transient thyrotoxicosis or hypothyroidism
Drug induced	Particularly with amiodarone
Sub-acute (de Quervain)	Thought to be viral in origin, multinuclear giant cells
Riedel thyroiditis	Extensive fibrosis of the thyroid
Radiation thyroiditis	Radiation injury, transient thyrotoxicosis
Pyogenic (rare)	<i>Staph. aureus</i> , streptococci, <i>E. coli</i> , tuberculosis, fungal

Table 6.2 Clinical presentation of thyroiditis

Form of thyroiditis	Clinical presentation	Thyroid function
Suppurative (acute)	Painful, tender thyroid, fever	Usually normal
Subacute (de Quervain)	Painful anterior neck, arthralgia, antecedent upper respiratory tract infection; generalized malaise.	Early thyrotoxicosis, occasionally late hypothyroidism
Autoimmune	Hashimoto's : goitre Atrophic: no goitre	Usually hypothyroid Sometimes euthyroid Rarely early thyrotoxicosis
Riedel	Hard woody consistency of thyroid	Usually normal

Chronic autoimmune (atrophic or Hashimoto's) thyroiditis

See Tables 6.1 and 6.2

- *Hashimoto's thyroiditis* Characterized by a painless, variably sized goitre with rubbery consistency and an irregular surface. The normal follicular structure of the gland is extensively replaced by lymphocytic and plasma cell infiltrates with formation of lymphoid germinal centres. The patient may have normal thyroid function, or subclinical, or overt hypothyroidism. Occasional patients present with thyrotoxicosis in association with a thyroid gland that is unusually firm and with high titres of circulating antithyroid antibodies.
- *Atrophic thyroiditis* Probably indicates end-stage thyroid disease. These patients do not have goitre and are antibody +ve. Biochemically, the picture is that of frank hypothyroidism.

Investigations

Investigations which are useful in establishing a diagnosis of Hashimoto's thyroiditis include:

- Testing of thyroid function.
- Thyroid antibodies (antithyroglobulin antibodies +ve in 20–25%, and antithyroperoxidase antibodies in >90%).
- Occasionally a thyroid biopsy to exclude malignancy in patients who present with a goitre and dominant nodule.

Prognosis

The long-term prognosis of patients with chronic thyroiditis is good because hypothyroidism can easily be corrected with T_4 and the goitre is not usually of sufficient size to cause local symptoms. In the atypical situation where Hashimoto's thyroiditis presents with rapidly enlarging goitre and pain a short course of prednisolone at a dose of 40mg daily may prove helpful.


Any unusual increase in size of the thyroid in patients known to suffer from Hashimoto's thyroiditis should be investigated with a FNA and possibly later a biopsy since there is an association between this condition and thyroid lymphoma (rare but risk ↑ by a factor of 70).

Other types of thyroiditis

Silent thyroiditis

Associated with transient thyrotoxicosis or hypothyroidism. A significant percentage of patients have a personal or family history of autoimmune thyroid disease. It may progress to permanent hypothyroidism.

Postpartum thyroiditis

 also see p.433. Thyroid dysfunction occurring within the first 6 months postpartum. Prevalence ranges from 5–7%. Postpartum thyroiditis develops in 30–52% of ♀ who have +ve thyroid peroxidase (TPO) antibodies. Most patients have a complete remission but some may progress to permanent hypothyroidism. It is thrice as common in patients with type I diabetes mellitus.

Chronic fibrosing (Riedel's) thyroiditis

A rare disorder characterized by intense fibrosis of the thyroid gland and surrounding structures leading to induration of the tissues of the neck. May be associated with mediastinal and retroperitoneal fibrosis, salivary gland fibrosis, sclerosing cholangitis, lachrymal gland fibrosis, and parathyroid gland fibrosis leading to hypoparathyroidism. Patients are usually euthyroid. Main differential diagnosis is thyroid neoplasia.

Management

Corticosteroids are usually ineffective. Surgery may be required to relieve obstruction and to exclude malignancy. Tamoxifen may be of benefit.

Pyogenic thyroiditis

- Rare. Usually anteceded by a pyogenic infection elsewhere. Characterized by tenderness and swelling of the thyroid gland, redness and warmth of the overlying skin, and constitutional signs of infection.
- Piriform sinus should be excluded. Excision of tract is preferable to incision and drainage.
- Treatment consists of antibiotic therapy and incision and drainage if a fluctuant area within the thyroid should occur.

Sub-acute thyroiditis (granulomatous, giant cell or de Quervain's thyroiditis)

- Viral in origin. Symptoms include pronounced asthenia, malaise, pain over the thyroid or pain referred to lower jaw, ear, or occiput. Less commonly the onset is acute with fever, pain over the thyroid, and symptoms of thyrotoxicosis. Characteristically signs include exquisite tenderness and nodularity of the thyroid gland. There is characteristically an elevated ESR and a depressed radionuclide (^{99m}Tc can be used) uptake. Biochemically, the patient may be initially thyrotoxic though later the patient may become hypothyroid (15%).

- In mild cases, non-steroidal anti-inflammatory agents offer symptom relief. In severe cases glucocorticoids (prednisolone 20–40mg/day) are effective. Propranolol can be used to control associated thyrotoxicosis. Treatment can be withdrawn when T_4 returns to normal. T_4 replacement is required if the patient becomes hypothyroid. Treatment with carbimazole or propylthiouracil is not indicated.

Drug-induced thyroiditis

Causes include:

- Amiodarone.
- Lithium.
- Interferon- α (15% develop thyroid peroxidase antibodies and or thyroid dysfunction).
- Interleukin 2.

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Hypothyroidism

Background

Hypothyroidism results from a variety of abnormalities that cause insufficient secretion of thyroid hormones (Table 7.1). The commonest cause is autoimmune thyroid disease. *Myxoedema* is severe hypothyroidism in which there is accumulation of hydrophilic mucopolysaccharides in the ground substance of the dermis and other tissues leading to thickening of the facial features and doughy induration of the skin.

Epidemiology

- High TSH in 7.5% of ♀ and 2.5% of ♂ >65 years, 1.7% overt hypothyroidism, 13.7% subclinical hypothyroidism (Whickham Survey, UK).
- Incidence higher in whites than Hispanics or African-American populations.
- Incidence higher in areas of high iodine intake.
- An elevated TSH is associated with higher serum lipid concentrations, which may be an additional reason to initiate therapy.

Table 7.1 Classification of the causes of hypothyroidism

	TSH	Free T ₄
<i>Non-goitrous</i>	↑	↓
Postablative (radioiodine, surgery)		
Congenital development defect		
Atrophic thyroiditis		
Postradiation (e.g. for lymphoma)		
<i>Goitrous</i>	↑	↓
Chronic thyroiditis (Hashimoto's thyroiditis)		
Iodine deficiency		
Drug elicited (amiodarone, aminosalicic acid, iodides, phenylbutazone, lithium aminoglutethimide, interferon α, thalidomide, bexarotene, stavudine—antiretroviral)		
Heritable biosynthetic defects		
Maternally transmitted (antithyroid agents, iodides)		
<i>Pituitary</i>	↓	↓
Panhypopituitarism		
Isolated TSH deficiency		
<i>Hypothalamic</i>	↓	↓
Neoplasm		
Infiltrative (sarcoidosis)		
Congenital defects		
Infection (encephalitis)		
<i>Self-limiting</i>		
Following withdrawal of suppressive thyroid therapy		
Subacute thyroiditis and chronic thyroiditis with transient hypothyroidism		
Postpartum thyroiditis		

Clinical picture

Adult

- Insidious non-specific onset.
- Fatigue, lethargy, constipation, cold intolerance, muscle stiffness, cramps, carpal tunnel syndrome, menorrhagia, later oligo- or amenorrhoea.
- Slowing of intellectual and motor activities.
- ↓ appetite and weight gain.
- Dry skin; hair loss.
- Deep hoarse voice, ↓ visual acuity.
- Obstructive sleep apnoea.

Myxoedema

- Dull expressionless face, sparse hair, periorbital puffiness, macroglossia.
- Pale, cool skin that feels rough and doughy.
- Enlarged heart (dilation and pericardial effusion).
- Megacolon/ intestinal obstruction.
- Cerebellar ataxia.
- Prolonged relaxation phase of deep tendon reflexes.
- Peripheral neuropathy.
- Encephalopathy.
- Hyperlipidaemia.
- Hypercarotenaemia (also caused by hyperlipidaemia, diabetes mellitus, and porphyria).
- Psychiatric symptoms e.g. depression, psychosis.

Myxoedema coma

- Predisposed to by cold exposure, trauma, infection, administration of central nervous system depressants.
- Marked respiratory depression with ↑ arterial P_{CO_2}
- Hyponatraemia from impaired water excretion and disordered regulation of vasopressin secretion.



Subclinical hypothyroidism

- This term is used to denote raised TSH levels in the presence of normal concentrations of free thyroid hormones.
- Treatment is indicated if the biochemistry is sustained in patients with a past history of radioiodine treatment for thyrotoxicosis or +ve thyroid antibodies as in these situations progression to overt hypothyroidism is almost inevitable (at least 5% per year of those with +ve antithyroid peroxidase antibodies).
- 2 samples should be taken 2–3 months apart to distinguish from non-thyroidal illness.
- There is controversy over the advantages of T₄ treatment in patients with –ve thyroid antibodies and no previous radioiodine treatment.
- If treatment is not given, follow up with annual thyroid function tests is important.
- There is no generally accepted consensus of when patients should receive treatment. Some authorities suggest treatment when the serum TSH is >10U/L, because of ↑ rate of progression to overt hypothyroidism.
- Increased incidence of cardiac risk probably greater if < 65 years old.

Management

See Fig. 7.1.

Treatment of hypothyroidism

- Normal metabolic state should be restored gradually as rapid increase in metabolic rate may precipitate cardiac arrhythmias
- The average replacement dose is 1.6mcg/kg/day, probably best at night.
- In the younger patients, start thyroxine at 50–100mcg. In the elderly, with a history of ischaemic heart disease, an initial dose of levothyroxine 25–50mcg can be ↑ by 25mcg increments at 4-week intervals until normal metabolic state is attained.
- Optimum dose determined by clinical criteria, the objective of treatment being to restore serum TSH to the normal range.
- TSH should be checked only 2 months after any dose change. Once stabilized TSH should be checked on an annual basis.
- In patients with 2° hypothyroidism, free T₄ is the most useful parameter to follow.
- Dose requirements can increase by 25–50% in pregnancy due to the increase in thyroid binding globulin (TBG). Recent data have shown that mild maternal hypothyroidism in the 1st trimester is associated with slightly impaired cognitive function in offspring. Thus, some now recommend routinely ↑ levothyroxine dose by 25mcg in any ♀ on replacement therapy when she learns she is pregnant.

Combined T₄ and T₃ replacement

Some studies have suggested that the additional replacement with T₃ and T₄ in combination improves well-being and cognitive function in patients in comparison to treatment with T₄ alone. A recent meta-analysis of double-blind cross-over studies showed no benefit of this therapy and is therefore not recommended.

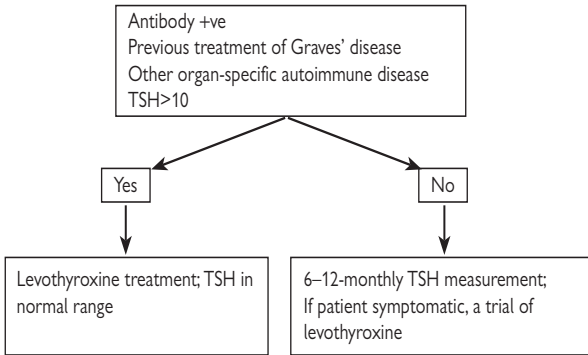


Fig. 7.1 Algorithm for management of subclinical hypothyroidism. Adapted from Lindsay and Toft (1997). Hypothyroidism. *Lancet* **349**, 413–17. Copyright 1997, with permission from Elsevier.

Management of myxoedema coma

- Identify and treat concurrent precipitating illness.
- Antibiotic therapy after blood cultures.
- Management of hypothermia by passive external rewarming.
- Manage in intensive treatment unit if comatose.
- Give warm humidified oxygen by facemask. Mechanical ventilation needed if hypoventilating.
- Aim for slow rise in core temperature (0.5°C/h).
- Cardiac monitor for supraventricular arrhythmias.
- Correct hyponatraemia (mild fluid restriction), hypotension (cautious volume expansion with crystalloid or whole blood), and hypoglycaemia (glucose administration).
- Monitor rectal temperature, oxygen saturation, BP, CVP, and urine output hourly.
- Take blood samples for thyroid hormones, TSH and cortisol before starting treatment. If hypocortisolaemic, administer glucocorticoids.
- Thyroid hormone replacement: no consensus has been reached. The following is an accepted regimen:
 - T₄ 300–500mcg IV or by NG tube as a starting dose followed by 50–100mcg daily until oral medication can be taken
 - If no improvement within 24–48h, T₃ 10mcg IV 8-hourly or 25mcg IV 8-hourly can be given in addition to above.
- Give hydrocortisone 50–100mg 6–8-hourly in case of cortisol deficiency.

Management of persistently elevated TSH despite thyroxine replacement

( See Fig. 7.2).

- Elevated TSH despite thyroxine replacement is common, most usually due to lack of compliance.
- If TSH still elevated when levothyroxine dose at 1.6mcg/kg/day or higher careful questioning of compliance is needed.
- Consider malabsorption.
- Consider other drugs that may interfere with levothyroxine absorption (Box 7.1).

Box 7.1 Interference with absorption of thyroxine

- Coeliac disease.
- Drugs—colestyramine, aluminum hydroxide, sucralfate, omeprazole, rifampicin, phenytoin, iron, and calcium carbonate.
- Atrophic gastritis in *H. pylori* infection (↓ T₄ by 30%)

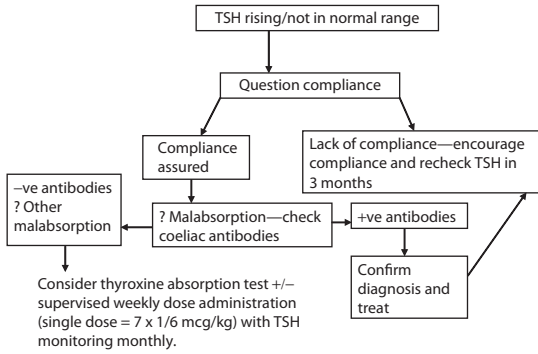


Fig. 7.2 Suggestions for investigations of elevated TSH despite thyroxine replacement therapy to $>1.6\text{mcg/kg/day}$

Congenital hypothyroidism

Incidence—about 1 in 5000 neonates. All neonates should be screened.

Thyroid agenesis

Occurs 1 in 1800 births.

Thyroid hormone dysgenesis

- Caused by inborn errors of thyroid metabolism. The disorders may be autosomal recessive, indicating single protein defects.
- Can be caused by inactivation of the TSH receptor, abnormalities of the thyroid transcription factors TTF1, TTF2, and PAX8, or due to defects in iodide transport, organification (peroxidase), coupling, deiodinase, or thyroglobulin synthesis.
- In a large proportion of patients with congenital hypothyroidism, the molecular background is unknown.

Pendred's syndrome

Characterized by overt or subclinical hypothyroidism, goitre, and moderate to severe sensorineural hearing impairment. The prevalence varies between 1 in 15 000 and 1 in 100 000. There is a partial iodide organification defect detected by ↑ perchlorate discharge. Thyroid hormone synthesis is only mildly impaired and so may not be detected by neonatal thyroid screening.

Box 7.2 Clinical features and congenital hypothyroidism

The following features are late sequelae of congenital hypothyroidism and, with routine screening now available, should never be seen nowadays.

- Physiological jaundice.
- Goitre.
- Hoarse cry, feeding problems, constipation, somnolence.
- Delay in reaching normal milestones of development; short stature.
- Coarse features with protruding tongue, broad flat nose, widely-set eyes.
- Sparse hair and dry skin, protuberant abdomen with umbilical hernia.
- Impaired mental development, retarded bone age.
- Epiphyseal dysgenesis, delayed dentition.

Laboratory tests

- Neonatal screening by measurement of serum TSH.
- Imaging procedure: ultrasonography or ^{123}I scintigraphy.
- Measurement of serum thyroglobulin and low molecular weight iodopeptides in urine to discriminate between the various types of defects.
- Measurement of neonatal and maternal autoantibodies as an indication of possible transient hypothyroidism.

Treatment

Irrespective of the cause of congenital hypothyroidism, early treatment is essential to prevent cerebral damage. Sufficient T₄ should be given to maintain the TSH in the normal range.

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Amiodarone and thyroid function

Background

- Amiodarone has a high concentration of iodine (39% by weight). It is a benzofuranic derivative and its structural formula closely resembles that of thyroxine. On a dose of amiodarone between 200–600mg daily, 7–21mg iodine is made available each day. The optimal daily iodine intake is 150–200mcg. Amiodarone is distributed in several tissues from where it is slowly released. In one study terminal elimination half-life of amiodarone averaged 52.6 days with a standard deviation of 23.7 days.
- Abnormalities of thyroid function occur in up to 50% of patients (Table 8.1).
- In the UK and USA, 2% of patients on amiodarone develop thyrotoxicosis and about 13% develop hypothyroidism.
- Patients residing in areas with high iodine intake develop amiodarone induced hypothyroidism (AIH) more often than amiodarone induced thyrotoxicosis (AIT), but AIT occurs more frequently in regions with low iodine intake.
- AIT can present several months after discontinuing the drug because of its long half-life.
- Hypothyroidism is commoner in ♀ and in patients with thyroid autoantibodies.
- Thyroid function tests should be monitored initially and then every 6 months in patients taking amiodarone.

Pathogenesis

- The high iodine content of amiodarone may inhibit thyroid hormone synthesis and release causing AIH or leading to iodine-induced thyrotoxicosis (Jod-Basedow phenomenon).
- Thyrotoxicosis resulting from iodine excess and therefore ↑ hormone synthesis is referred to as *AIT type I*. Thyrotoxicosis due to a direct toxic effect of amiodarone is referred to as *AIT type II* (Table 8.2).
- Drug-induced destructive thyroiditis results in leakage of thyroid hormones from damaged follicles into the circulation and like subacute thyroiditis can be followed by a transient hypothyroid state before euthyroidism is restored.

Table 8.1 Thyroid function tests in clinically euthyroid patients after administration of amiodarone

Tests	1–3 months	>3 months
Free T ₃	Decreased	Remains slightly decreased, but within normal range
TSH	Transient increase	Normal
Free T ₄	Modest increase	Slightly increased compared to pretreatment values, may be in normal range or slightly increased.
Reverse T ₃	Increased	Increased

Table 8.2 Characteristics of AIT (Some patients have a mixed form and classification is not always possible)

	AIT type I (10%)	AIT type II (90%)
Aetiology	Iodine toxicity	Thyroiditis
Signs of clinical thyroid disease	Yes	No
Goitre	Frequent	Infrequent
Thyroid antibodies	Positive	Negative
Radioiodine uptake	Normal	Decreased
Thyroglobulin	Normal or slightly elevated	Very elevated
Serum IL6 (research test)	Normal	Very elevated
Late hypothyroidism	No	Possible
Vascularity (Doppler)	Increased/normal	Reduced

Diagnosis and treatment

📖 See Table 8.3.

- After chronic administration of amiodarone, a steady state is achieved, typically reflected in mild elevation of free T_4 and reduction in free T_3 . Thus in clinically euthyroid patients on amiodarone a slightly elevated T_4 is not indicative of hyperthyroidism, nor is a low T_3 indicative of hypothyroidism.
- Hyperthyroidism is indicated by significantly \uparrow free T_4 , together with elevated free T_3 and suppressed serum TSH.
- Hypothyroidism is indicated by elevation of TSH with low serum free T_4 .
- Discontinuation of amiodarone does not always control the thyrotoxic state because of its long half-life (particularly in the obese) due to its very high volume of distribution and fat solubility.
- Numerous complex published algorithms exist for management, but since classification into type I and type II is often difficult (📖 see Table 8.2), in practice most patients are treated with a ATDs \pm glucocorticoids (📖 see Table 8.4)
- The 1st line of treatment is ATDs (carbimazole or propylthiouracil).
- A combination of corticosteroids and ATDs may be effective in AIT type II. A high dose of prednisolone, 40–60mg daily, may be required for 8–12 weeks; studies where steroids have been discontinued after 2–3 weeks have been associated with a high relapse rate.
- Radioiodine is not usually effective because of reduced uptake by the thyroid gland reflecting the iodine load associated with the drug.
- Surgery remains a very successful form of treatment, with euthyroidism being restored within a matter of days. Achieving preoperative euthyroidism may be difficult, however.
- Cardiac function may be compromised by propranolol used in combination with amiodarone, since this may produce bradycardia and sinus arrest.
- Potassium perchlorate inhibits iodide uptake by the thyroid gland, reduces intrathyroidal iodine, and renders thionomides more effective. It can be given as a 1g daily dose together with carbimazole, a regimen shown to restore euthyroidism in a large percentage of patients with both type I and type II AIT. In small case studies a combination of potassium perchlorate and carbimazole has been effective while treatment with amiodarone was continued.

Box 8.1 Treatment of amiodarone induced hypothyroidism**Underlying thyroid abnormality (usually Hashimoto's thyroiditis):**

- Amiodarone therapy can be continued.
- Add thyroxine replacement therapy.

Apparently normal thyroid:

- Discontinue amiodarone if possible and follow up for restoration of euthyroidism.
 - If amiodarone cannot be withdrawn, start thyroxine replacement therapy.

Table 8.3 Side effects and complications of amiodarone therapy

Side effect	Incidence (%)
Corneal microdeposits	100
Anorexia and nausea	80
Photosensitivity; blue/grey skin discolouration	55–75
Ataxia, tremors, peripheral neuropathy	48
Deranged liver function tests	25
Abnormal thyroid function tests	14–18
Interstitial pneumonitis	10–13
Cardiac arrhythmias	2–3

Table 8.4 Treatment of amiodarone induced thyrotoxicosis

	Type 1 AIT	Type 2 AIT
Step 1 Aim: Restore euthyroidism	Carbimazole up to 40mg/day or propylthiouracil 400mg/day in combination if necessary with potassium perchlorate 1g/day for 16–40 days. If possible discontinue amiodarone*	Discontinue amiodarone if possible* Prednisolone 40mg/day. In mixed forms add carbimazole or propylthiouracil as in type 1 AIT
Step 2: Definitive treatment	Radioiodine treatment or thyroidectomy	Follow up for possible spontaneous progression to hypothyroidism

*If amiodarone cannot be withdrawn and medical therapy is unsuccessful, consider total thyroidectomy.

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Thyroid cancer

Epidemiology

- Clinically detectable thyroid cancer is rare. It accounts for <1% of all cancer and <0.5% of cancer deaths.
- Thyroid microcarcinoma (diameter <1cm) may be found in multinodular goitres.
- Thyroid cancers are commonest in adults aged 40–50, and rare in children and adolescents.
- ♀ are affected more frequently than ♂.

Table 9.1 Classification of thyroid cancer

Cell of origin	Tumour type	Frequency (%)
Papillary	Differentiated:	
	Papillary	>80
	Follicular	10
	Undifferentiated (anaplastic)	1–5
C-cells	Medullary	5–10
Lymphocytes	Lymphoma	1–5

Table 9.2 Comparison of papillary, follicular and anaplastic carcinomas of the thyroid

Characteristic	Papillary Ca	Follicular Ca	Anaplastic Ca
Age at presentation	30–50 (mean 44)	40–50	60–80
Spread	Lymphatic	Haematogenous	Haematogenous
Prognosis	Good	Good	Poor
Treatment	Initially: near total thyroidectomy Postoperative TSH suppression. High-risk patient: ¹³¹ I remnant ablation Postoperative total body radioiodine scan	Initially: near total thyroidectomy Postoperative TSH suppression ¹³¹ I remnant ablation Postoperative total body radioiodine scan	Total thyroidectomy with lymph node clearance Chemotherapy with doxorubicin and cisplatin External beam irradiation

Aetiology

Irradiation

- There does not appear to be a threshold dose of external irradiation for thyroid carcinogenesis; doses of 200–500cGy seem to produce thyroid cancer at a rate of about 0.5%/year.
- There is no evidence that therapeutic or diagnostic ^{131}I administration can induce thyroid cancer, although there is a small increase in death rates from thyroid cancer after ^{131}I . At present it is unclear whether this is due to an effect of ^{131}I or part of the natural history of the underlying thyroid disease.
- External irradiation at an age <20 years is associated with an ↑ risk of thyroid nodule development and thyroid cancer (most commonly papillary). The radioactive fallout from the Chernobyl nuclear explosion in 1986, resulted in a 4.7-fold increase in thyroid cancer in the regions of Belarus from 1985 to 1993, including a 34-fold increase in children. Most of these were papillary carcinomas.
- The risk is greater for ♀ and when irradiation occurs at a younger age.
- There is a latency of at least 5 years with maximum risk at 20 years following exposure, though this was not seen following the Chernobyl disaster.

Other environmental factors

Most investigators agree that iodine supplementation has resulted in a decrease in the incidence of follicular carcinoma.

Genetic syndromes and oncogenes

- *RET/PTC1* proto-oncogene abnormalities in the long arm of chromosome 10 are associated with some papillary tumours (5–30%), especially after irradiation (60–80%). It is similar to the abnormality associated with medullary thyroid carcinoma in MEN2A.
- 2 new proto-oncogenes have been identified: *RET/PTC2* and *RET/PTC3 TRK* (less common).
- The tumour suppressor gene *p53* has been found to be mutated in some de-differentiated cancers.
- Overexpression of the *ras* and *PTTG* oncogenes is found in papillary thyroid cancers and were found to be markers for adverse prognosis.
- *c-myc* mRNA expression has been correlated with histologic markers of papillary cancer aggression.

Papillary microcarcinoma of the thyroid (PMC)

- PMC is defined by WHO as a tumour focus of 1.0cm or less in diameter. It is detected coincidentally on histopathological examination of the thyroid following resection of multinodular goitre or any thyroid resected
- Autopsy studies show:
 - Prevalence ranges from 1–35.6%.
 - No significant difference in the prevalence rates of papillary micro-carcinoma has been demonstrated between the sexes.
 - PMC rarely progresses to clinically apparent thyroid cancer with advancing age.

- PMC can be multifocal.
- Cervical lymph node metastasis from PMC ranges from 4.3–18.2%.
- Lymph node metastasis was most often associated with multifocal tumours.
- Although exposure to irradiation increases the likelihood of developing papillary thyroid cancer, the tumours will usually be >1.0cm in diameter and thus not PMC.
- Follow-up studies suggest that PMC is a slow growing lesion which rarely spreads to distant sites and which carries a good prognosis.
- The recommendations for treatment of PMC vary widely:
 - The low morbidity and long survival mean that collection of randomized prospective data has never been performed and comparisons of therapies are based on retrospective studies.
 - The treatment of PMC should not cause more morbidity than the disease process itself.
 - Surgical treatment recommendations range from simple excision to ipsilateral lobectomy.
 - With adjuvant therapy the consensus is routine use of T₄, but not the use of radioiodine as there is no difference in the recurrence rate. There is some evidence to keep TSH below the reference range but robust data are not available.

Papillary thyroid carcinoma

- Constitutes almost >80% of all thyroid cancers.
- Commoner in ♀ (3:1).
- Rare in childhood, peaks occur in 2nd and 3rd decades and again in later life (bimodal frequency).
- Incidence: 3–5 per 100 000 population.

Pathology

- Slow growing, usually non-encapsulated, may spread through the thyroid capsule to structures in the surrounding neck, especially regional lymph nodes. Multifocal in 30% of cases.
- Recognized variants are follicular, papillary, dorsal, columnar cell, tall cell, and diffuse sclerosing.
- *Histology* the tumour contains complex branching papillae that have a fibrovascular core covered by a single layer of tumour cells.
- Nuclear features include:
 - Large size with pale staining, 'ground-glass' appearance (*orphan Annie-eye nucleus*).
 - Deep nuclear grooves.
- The characteristic and pathognomonic cytoplasmic feature is the 'psammoma body' which is a calcified, laminated, basophilic, stromal structure.
- It is confined to the neck in over 95% of cases, although 15–20% have local extra thyroidal invasion. Metastases (1–2% of patients) occur via lymphatics to local lymph nodes and more distantly to lungs.
- Several prognostic scoring systems are in use, none of which permits definitive decisions to be made for individual patients.
- Low risk—JNM stage I (under 45, no metastases)

Management

Primary treatment: surgery

- Should be performed by an experienced thyroid surgeon at a centre with adequate case load to maintain surgical skills.
- In general, as near total thyroidectomy as possible should be performed.
- Clinically evident cervical lymph node metastasis is best treated with radical modified neck dissection with preservation of sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein.

Adjuvant therapy—radioiodine therapy

- Postoperative radioiodine therapy is advised in the high-risk patient with differentiated thyroid cancer. After surgery in a low risk group, some thyroidologists argue that ^{131}I is not required. A dose of 3.1GBq is used for thyroid ablation. A whole body scan done 4–6 months after administration of 150MBq ^{131}I helps determine the presence of any residual disease. In the presence of metastasis a dose of approximately 5.5–7.4GBq radioiodine is used. Liothyronine should be administered for 4–6 weeks in place of thyroxine. It is then omitted for 10 days prior to the scan, allowing TSH to rise. A low-iodine diet for 2 weeks increases the effective specific activity of the administered iodine.

- The patient should be isolated until residual dose meter readings indicate <30 MBq.
- Chronic suppression of serum TSH levels to <0.10mU/L is standard practice in patients with differentiated thyroid carcinoma. Inhibition of TSH secretion reduces recurrence rate as TSH stimulates growth of the majority of thyroid cancer cells.

Patients are followed up with thyroglobulin levels. After effective treatment thyroglobulin levels are undetectable. A trend of ↑ thyroglobulin values should be investigated with a radioiodine uptake scan. Liothyronine (T₃) is substituted for T₄ 4–6 weeks before the scan, and omitted for 10 days immediately beforehand.

Thyroglobulin

- A very sensitive marker of recurrence of thyroid cancer.
- Secreted by the thyroid tissue.
- After total thyroidectomy and radioactive iodine ablation, the levels of thyroglobulin should be <2ng/L.
- Measurement of thyroglobulin levels could be made difficult in the presence of antithyroglobulin antibodies, which should be checked.
- There is controversy over whether the patient should come off T₄ or T₃ or be started on recombinant TSH before checking the thyroglobulin levels. Coming off thyroid hormones or giving TSH increases the sensitivity of thyroglobulin to detect recurrence, but this may not affect survival rates.

Recurrent disease/distant metastases

- In the case of recurrence, treatment employs all methods used in 1^o and adjuvant therapy.
- Surgery for local metastases.
- External radiotherapy is indicated in tumours that do not take up ¹³¹I.
- Bony and pulmonary metastases (usually osteolytic) may be treated with ¹³¹I.
- Unfortunately only 50% of metastases concentrate ¹³¹I and bony metastases are often very difficult to irradiate.
- Some advocate use of external beam radiation.
- Response to chemotherapy is usually poor.

Recombinant TSH

- Avoids morbidity of hypothyroidism during T₄ withdrawal.
- Useful for patients with TSH deficiency (hypopituitarism).
- Comparable thyroglobulin rise but reduced ¹³¹I scan sensitivity compared to T₄ withdrawal.
- Give 0.9mg of recombinant TSH on day 1 and 2 and measure thyroglobulin on day 5.

Follicular carcinoma (FTC)

- Constitutes 15% of all thyroid cancers.
- Mean patient age in most studies is 50 years.
- Commoner in ♀ (2:1).
- Relatively more common in endemic goitre areas.

Pathology

- Follicular carcinoma is a neoplasm of the thyroid epithelium that exhibits follicular differentiation and shows capsular or vascular invasion.
- Differentiation of benign follicular adenoma from encapsulated low-grade or minimally invasive tumours can be impossible to diagnose, particularly for the cytopathologist, and surgery is usually necessary for a follicular adenoma.
- FTC may be minimally invasive or widely invasive.
- Metastases (15–20% cases) are more likely to be spread by haematogenesis to the lung and bones and less likely to local lymph nodes.
- Hurthle cell carcinoma is an aggressive type of follicular tumour with a poor prognosis because it fails to concentrate ¹³¹I.

Treatment

📖 as for Papillary thyroid carcinoma, pp.74–75.



Follow-up of papillary and FTC

- Follow-up usually involves an annual clinical review, with clinical examination for presence of suspicious lymph nodes and measurements of serum TSH (to ensure adequate TSH suppression to $<0.1\text{mU/L}$) and thyroglobulin.
- Serum thyroglobulin should be undetectable in patients with total thyroid ablation. However, detectable levels may be seen for up to 6 months after thyroid ablation. A trend of \uparrow thyroglobulin level requires investigations with ^{131}I uptake scan (off thyroid hormones or with TSH stimulation) and other imaging modalities, such as u/s of the neck, CT scan of the lungs, or bone scans. Thyroglobulin antibodies must be checked, as there may be interactions with the thyroglobulin assays.
- Radioiodine scans are done annually for the first 3 years and if –ve, not repeated unless there are clinical indications, like an \uparrow thyroglobulin level.
- Isolated lymph node metastases can occasionally be associated with normal thyroglobulin. Stopping thyroid hormone replacement, or using recombinant TSH, before the measurement of thyroglobulin can increase sensitivity of detecting persistent recurrent disease.
- Detectable thyroglobulin and absent uptake on radioiodine uptake scan may be due to dedifferentiation of the tumour and failure to take up iodine. A PET scan may be useful in this situation. If a PET scan is not available, an iodine uptake scan following $150\text{MBq }^{131}\text{I}$ can be useful.

Box 9.1 Thyroid cancer in children

- Uncommon, with an incidence of 0.2–5 per million per year.
- $>85\%$ are papillary, but with more aggressive behaviour than in adults (local invasion and distant metastases are commoner).
- Recently an \uparrow incidence in children in Belarus and Ukraine has been reported following the Chernobyl nuclear accident in 1986. RET oncogene rearrangements are common in these tumours.
- Management is similar to adults, with a similar controversy as to the extent of initial surgery.
- Various studies report an overall recurrence rate of 0–39%; disease-free survival of 80–93%, and disease-specific mortality of 0–10%.
- Evidence is currently lacking on the independent risks or benefits of radioactive iodine or extensive surgery.
- Many investigators recommend lifelong follow-up with a combination of thyroglobulin and radionuclide scanning.

Thyroid cancer and pregnancy

- The natural course of thyroid cancer developing during pregnancy may be different from that in non-pregnant ♀.
- Any ♀ presenting with a thyroid nodule in pregnancy appears to have an ↑ risk for thyroid cancer.
- Evaluation should be undertaken with FNAC. Radioiodine scan is contraindicated.
- Lesions <2cm diameter or any lesion appearing after 24 weeks' gestation should be treated with TSH suppression and further evaluations carried out postpartum.
- If FNAC is suspicious or diagnostic, operation should be performed at the earliest safe opportunity—generally the 2nd trimester or immediately postpartum.
- ¹³¹I ablation should be scheduled for the postpartum period and the mother advised to stop breast-feeding.
- Avoid pregnancy for 6 months after any ¹³¹I ablation.

Medullary thyroid carcinoma (MTC)

also see Chapter 100, MEN type 2, p.622.

- Accounts for 5–10% of all thyroid cancers.
- Should be managed by a dedicated regional service.

Presentation

- Lump in neck.
- Systemic effects of calcitonin-flushing/diarrhea.

Diagnosis

- FNAC
- Unsuspected at surgery.
- Comprehensive family history and screening in search for features of MEN-2 is needed.
- Pathology specimens show immunostaining for calcitonin and staining for amyloid.

Management

- Baseline plasma calcitonin.
- Baseline biochemical investigations for pheochromocytoma and hyperparathyroidism.
- Genetic screening.
- Staging with thoraco-abdominal CT/MRI.
- MIBG and pentavalent ^{99m}Tc DMSA scintigraphy may also be used.

Treatment

- Total thyroidectomy and central node dissection is the 1^o treatment modality.
- Germline RET mutation carriers should ideally undergo thyroidectomy before 5 years of age.

Adjuvant therapy

- Radioiodine and TSH suppression does not play a role.
- External radiotherapy and systemic chemotherapy has not been shown to be benefit.
- Therapeutic MIBG may help in some cases.

Follow-up

All patients should have lifelong follow-up at the dedicated regional service.

Anaplastic (undifferentiated) thyroid cancer

- Rare.
- Peak incidence: 7th decade. ♀:♂ = 1:1.5.
- Characterized by rapid growth of a firm/hard fixed tumour.
- Often infiltrates local tissue such as larynx and great vessels and so does not move on swallowing. Stridor and obstructive respiratory symptoms are common.
- Aggressive, with poor long-term prognosis—7% 5-year survival rate and a mean survival of 6 months from diagnosis.
- Optimal results occur following total thyroidectomy. This is usually not possible and external irradiation is used, sometimes in association with chemotherapy.

Lymphoma

- Uncommon.
- Almost always associated with autoimmune thyroid disease (Hashimoto's thyroiditis). Occurs more commonly in ♀ and in patients aged >40 years.
- Characterized by rapid enlargement of the thyroid gland.
- May be limited to thyroid gland or part of a more extensive systemic lymphoma (usually non-Hodgkin's lymphoma). Trucut biopsy may be required.
- Treatment with radiotherapy alone or chemotherapy if more extensive often produces good results.

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