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Thyroid function tests

See also the separate articles: Hyperthyroidism, Hyperthyroidism in Pregnancy, Thyroid Disease and Surgery, Hypothyroidism and Childhood and Congenital Hypothyroidism.

Thyroid disease is common (approximately 1% of the female population) [1]. It presents with wide-ranging and often nonspecific symptoms - so needs to be considered in many differentials and, once diagnosed, needs to be regularly monitored to optimise therapy.

Thyroid function tests (TFTs) are amongst the most commonly requested laboratory investigations in both primary and secondary care.

In primary care, the most common use of a TFT is as part of a screen for nonspecific fatigue or illness. The value of such tests without a goitre or other clinical features has been challenged and some advocate the use of watchful waiting with the delayed use of laboratory tests (at four weeks post-presentation) as a more appropriate strategy for investigating unexplained fatigue [2].

Physiology

An understanding of normal homeostatic mechanisms helps to interpret TFTs:

- The hypothalamus, pituitary gland and the thyroid all play a part in the feedback and regulatory mechanisms involved in the production of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland.
- Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates the production of the polypeptide thyroid-stimulating hormone (TSH) from the anterior pituitary.
- TSH then stimulates the production and release of T4 and T3 from the thyroid.

- Once released, T4 and T3 then exert a negative feedback mechanism on TSH production.
- T4 is the main hormone produced by the thyroid.
- T3 is mainly produced by peripheral conversion of T4.
- T3 and T4 are largely protein bound in the plasma, mainly to thyroxine-binding globulin (TBG). Only the unbound, or 'free', portion (FT3, FT4) is active.
- T3 and T4 both act via nuclear receptors to increase cell metabolism.
- Reverse T3 (rT3):
    - rT3 is a product of T4 degradation in peripheral tissues. It is also secreted by the thyroid gland but in very small amounts.
    - rT3 is elevated in patients with high TBG and in some individuals with familial dysalbuminaemic hyperthyroxinaemia.
    - Serum rT3 levels are normal in hypothyroid patients treated with T4, high in thyrotoxicosis and low in untreated hypothyroidism.

Indications

Diagnosis of possible thyroid disease

Consider where signs or symptoms are compatible with possible thyroid disease, as well as with:

- Goitre or thyroid nodule
- Atrial fibrillation (AF)
- Osteoporosis
- Subfertility
- Dyslipidaemia

Screening

Currently, screening for thyroid disease in the healthy adult population is not warranted but more limited screening should be performed in:

- Neonates, with the heel prick test for congenital hypothyroidism.
- All patients with diabetes (types 1 and 2) at the time of diagnosis.
- Women with type 1 diabetes pre-conception, at booking and three months postpartum.

Surveillance

Surveillance of certain groups is advocated:

- Women with a history of postpartum thyroiditis (annual TFTs, prenatally and postnatally in future pregnancies).
- Patients with type 1 diabetes mellitus (annual TFTs).
- Women with certain autoimmune disorders such as Addison's disease and coeliac disease.
- Down's syndrome and Turner syndrome (annual TFTs).
- Patients receiving amiodarone (pre-treatment, then every six months until off treatment for a year) or lithium (pre-treatment, every six to twelve months whilst on treatment).
- Following neck irradiation (annual TFTs).
- Following destructive treatment (radio-iodine or surgical) for thyrotoxicosis (four to eight weeks after treatment, three-monthly for the first year and then annually).

Monitoring

- For antithyroid drug treatment, check one- to three-monthly until stable and then annually if used long-term.
- For thyroxine replacement therapy, check TFTs annually once stable.

Using thyroid function tests[3]

When using TFTs to investigate a possible thyroid disorder, **regardless of whether the patient is thought to be hypothyroid or hyperthyroid**, the initial investigation should always be a sensitive serum TSH assay.

In unselected populations, measurement of serum TSH has a sensitivity of 89-95% and specificity of 90-96% for overt thyroid dysfunction. However, screening exclusively with TSH will result in misdiagnosis of some cases, whilst other conditions may be missed altogether[4]. Therefore, many laboratories now routinely offer combination screening with both T4 and TSH measurement.

- The TSH level will be raised in patients with hypothyroidism and reduced in patients with hyperthyroidism.
- The advent of the sensitive TSH assay allows for the diagnosis of subclinical disease in asymptomatic patients.
- The results of the TSH assay will determine which further investigations will need to be performed.

There are situations where TSH alone is unhelpful and may be misleading:

- Recent treatment of thyrotoxicosis.
- Pituitary disease.
- Non-thyroidal illness.
- TSH-secreting pituitary tumour.
- Thyroid hormone resistance.

The requesting doctor should provide adequate clinical information to guide the laboratory in the selection of the most appropriate TFTs. New cases of pituitary hypothyroidism are rare, but can present with very vague symptoms, so an additional request of FT3/FT4 should be considered where there is persistent fatigue with a normal TSH, particularly with signs or symptoms of gonadal dysfunction.

Hyperthyroidism

Hyperthyroidism occurs as a consequence of excessive thyroid hormone activity.

Diagnosis

- The initial laboratory investigation with a possible diagnosis of hyperthyroidism should be a sensitive serum TSH assay which will show reduced circulating levels of TSH.
- Note that low serum TSH (especially if below reference range but above 0.10 mU/L) is not specific for hyperthyroidism - it may also occur with 'non-thyroidal illness' or with the use of some commonly prescribed drugs.
- Patients who have a low TSH may then go on to have further investigations such as [5]:
    - FT4 and FT3 assays - a subnormal TSH should trigger the measurement of FT4. If this is not elevated, FT3 should be measured to identify cases of T3-thyrotoxicosis.
    - Thyroid auto-antibodies - eg, thyroid peroxidase antibodies (TPOAb), TSH-receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI) [6]
    - Radioactive isotope uptake - thyroid scanning, usually with ^{123}I, helps to determine the cause of hyperthyroidism - eg, diffuse pattern of uptake in Graves' disease compared with one or more 'hot' nodules in toxic nodular hyperthyroidism.

Interpreting thyroid function tests

Low TSH	**Raised FT3 or FT4**	**Common causes**: Primary hyperthyroidism - Graves' disease, multinodular goitre, toxic nodule. **Relatively common causes** with low radio-iodine uptake: Transient thyroiditis (postpartum, post-viral, De Quervain's thyroiditis). **Rare** with a low radio-iodine uptake: Thyroxine ingestion. Ectopic thyroid tissue. Iodine-induced. Amiodarone therapy. **Rare** with a positive pregnancy test: Gestational thyrotoxicosis with hyperemesis gravidarum. Hydatiform mole. **Rare**: Familial TSH receptor mutation.
Low TSH	**Normal FT3 or FT4**	**Common causes**: Subclinical hyperthyroidism. Thyroxine ingestion. **Rare causes**: Steroid therapy. Dopamine and dobutamine infusion. Non-thyroidal illness.
Low or normal TSH	**Low FT3 or FT4**	**Common causes**: Non-thyroidal illness. Recent treatment for hyperthyroidism. **Rare causes**: Pituitary disease. Congenital TSH or TRH deficiencies.

Guiding treatment

Following a diagnosis of hyperthyroidism, many patients are started on thionamides (carbimazole or propylthiouracil), usually followed by definitive treatment with radio-iodine or surgery.

- Response to treatment is judged by serial measurement of FT4 and TSH, allowing dose adjustment and avoidance of iatrogenic hypothyroidism. Note that use of TSH alone is inadequate, since TSH is frequently suppressed for many months following initiation of thionamides.
- Suggested intervals for TFTs are every six weeks after **radio-iodine** treatment in the first six months. If within reference range then monitor at 9, 12 and 18 months [5].
- Measure TSH and FT4 at two and six months after **surgery**, and then TSH once a year for adults, children and young people who have had a hemithyroidectomy.
- Monitor TSH, FT4 and FT3 every six weeks for those taking **antithyroid drugs** until their TSH is within the reference range, then every three months until antithyroid drugs are stopped.
- Reduce the dose where FT4 falls to low normal or below normal range or where TSH rises.
- 'Block and replace' regimens (where treatment is initially with thionamide alone, then adding thyroxine once FT4 has normalised) have been shown not to be superior to a dose titration regimen (as above) and may be associated with more side-effects.
- Persistently elevated FT4 despite seemingly adequate prescription of thionamides is most likely to indicate poor compliance.

Hypothyroidism

Primary hypothyroidism occurs as a result of undersecretion of thyroid hormone from the thyroid gland. Secondary hypothyroidism may occur as a result of damage or disease of the pituitary or hypothalamus.

Diagnosis

- To diagnose primary hypothyroidism, one needs to measure both TSH and FT4. Where TSH is >10 mU/L and FT4 below reference range, the diagnosis is overt primary hypothyroidism and the patient needs treatment with thyroid replacement therapy.

- Secondary hypothyroidism is suggested by low, within or mildly elevated TSH combined with a low FT4. Differentiating this from non-thyroidal illness can be difficult and clinical history, FT3 and sometimes anterior pituitary hormone tests are necessary.

Additional diagnostic tests may include:

- Thyroid auto-antibodies - antithyroid peroxidase and antithyroglobulin antibodies.
- Thyroid scan.
- Ultrasound examination of the thyroid gland.

Interpreting thyroid function tests

Raised TSH	**Low FT4 or FT3**	**Common causes**: Chronic autoimmune thyroiditis. Following radio-iodine. Following thyroidectomy. Transient thyroiditis - hypothyroid phase. **Rare causes** (anti-TPO negative): Following external beam radiotherapy to the neck. Drugs - amiodarone, lithium, interferons, interleukin-2. Iodine deficiency. Amyloid goitre. **Congenital causes**: Thyroid dysgenesis. Iodine transport defects. TSH-receptor defects. TSH resistance.
Raised TSH	**Normal FT4 or FT3**	**Common causes**: Subclinical autoimmune hypothyroidism. **Rare causes**: Drugs - amiodarone, sertraline, colestyramine. Recovery phase after non-thyroidal illness. Heterophile (interfering) antibody. **Congenital causes**: TSH-receptor defects. TSH resistance.
Normal or raised TSH	**Raised FT4 or FT3**	**Rare causes**: Amiodarone. Interfering antibodies. Familial. TSH-secreting pituitary tumour. Acute psychiatric illness.

Guiding treatment

- Thyroxine replacement therapy's goals are to make a patient feel well and to achieve a TSH within reference range. FT4 will be within or slightly above reference range.
- It takes at least two months to achieve a stable hormone concentration following dose adjustment of thyroxine so *do not* check TFTs sooner than this.
- Patients stabilised on long-term thyroxine should have annual TSH checks.

Subclinical disease

Subclinical thyroid disease is common. The prevalence of subclinical hypothyroidism after the age of 60 is about 10% in females [7].

Subclinical hyperthyroidism

This is diagnosed by low serum TSH, normal FT4 and FT3, in the absence of non-thyroidal illness or relevant drug therapy.

- The National Institute for Health and Care Excellence (NICE) recommends referring patients with persistent subclinical hyperthyroidism to a specialist if they have two TSH readings lower than 0.1 mIU/L at least three months apart **and** evidence of thyroid disease (for example, a goitre or positive thyroid antibodies) or symptoms of thyrotoxicosis [5]. Clinicians are advised to seek specialist advice on managing subclinical hyperthyroidism in all children and young people.
- NICE also suggests measuring TSH every six months for adults with untreated subclinical hyperthyroidism. If the TSH level is outside the reference range, consider measuring FT4 and FT3 in the same sample. TSH, FT4 and FT3 should be measured every three months for children and young people with untreated subclinical hyperthyroidism.
- TSH monitoring can be stopped in adults, children and young people with untreated subclinical hyperthyroidism if the TSH level stabilises (two similar measurements within the reference range three to six months apart).

Subclinical hyperthyroidism is associated with an increased risk of hip and other fractures, particularly among those with TSH levels of less than 0.10 mIU/L [8]. There is also an increased risk of developing AF and osteoporosis [9].

Subclinical hypothyroidism
This occurs where TSH is above reference range with a normal FT4.

- Diagnosis should be confirmed with repeat TFTs (TSH and FT4) after three months, having excluded non-thyroidal illness and drug interference. Measure TPO antibodies; if present, these increase the risk of developing hypothyroidism.
- Where positive, repeat TFTs on an annual basis.
- Elderly patients with high titres of antibodies have a risk of overt hypothyroidism of around 20% a year.
- Studies have shown an increased risk of coronary heart disease events, heart failure and cardiovascular mortality among affected adults [10].
- Where TSH is <10 mU/L, there is no consistent evidence of association with symptoms, hyperlipidaemias or increased risk of cardiovascular disease. Above this level, there is more evidence of progression to overt thyroid disease and worsening hyperlipidaemia.
- Thyroxine therapy is recommended if TSH >10 mU/L or, below this, if patients are pregnant, have a goitre or are trying to conceive [5] [11].
- Thyroxine treatment causes improvement in symptoms, mood and cognition.

Medication effects

Many commonly used medicines affect the regulation of thyroid function, either by altering production of the hormones along the regulatory pathway or the measured hormone levels due to changes in protein binding. Interpretation of TFTs may be more difficult as a consequence.

- Drugs with a direct effect on thyroid function (mostly suppression) include:
    - Amiodarone.
    - Lithium.
    - Corticosteroids.
    - Iodinated contrast media and other iodine preparations.
    - Interferons.
    - Dopamine, levodopa.
- Drugs which may cause analytical interference (increased FT4 by displacement) include:
    - Heparin.
    - Non-steroidal anti-inflammatory drugs.
    - High-dose aspirin (>2 g/day).
- Drugs which increase thyroxine replacement requirement (cytochrome P450 inducers):
    - Phenytoin.
    - Carbamazepine.
    - Ritonavir.
    - Rifampicin.
- Intestinal absorbers* include:
    - Sucralfate, colestyramine and colestipol, antacids containing aluminium.
    - Ferrous sulfate.
    - Proton pump inhibitors.

    **Take thyroxine at least four hours apart from these medications*.

Amiodarone

Amiodarone has multiple effects on the thyroid due to its high levels of iodine (one 100 mg tablet contains 250 x the recommended daily intake) and its direct toxicity on the thyroid. It can induce hyperthyroidism (primarily in iodine-deficient areas of the world) or hypothyroidism. Amiodarone often causes a decrease in the generation of T3 from T4 with a consequent increase in rT3. Hypothyroidism occurs in up to 15% of patients taking amiodarone (particularly women and those with positive antithyroid antibodies) [4].

There are two main types of thyrotoxicosis recognised: type 1 (large iodine load precipitating latent thyroid autonomy) and type 2 (destructive thyroiditis) in which amiodarone inhibits T4 → T3 conversion such that T4 is typically more markedly elevated than T3. Type 2 typically occurs in patients without underlying thyroid disease and is caused by a direct toxic effect of amiodarone on thyroid follicular cells. The thyrotoxic phase may last several weeks to several months and it is often followed by a hypothyroid phase with eventual recovery in most patients [12].

If this condition is suspected, refer for specialist assistance, since further investigations may be required and management is frequently complicated [13].

Special situations

TFTs in pregnancy [14]

- In pregnancy, oestrogen levels increase and TBG concentrations rise - this leads to an increase in total T4 and T3.
- In the first trimester, serum TSH also falls due to the effect of human chorionic gonadotrophin (hCG) and there may be a small fall in FT4.
- In the second and third trimesters, FT4 and FT3 decrease, sometimes below the non-pregnant women's reference level.
- The prevalence of undiagnosed subclinical hypothyroidism in pregnant women ranges from 3% to 15% [11].
- Trimester-related reference ranges for TSH and total and free thyroid hormones should always be used to assess pregnant patients' thyroid status [15].

- Changes in the immune system during and after pregnancy may alter the course of pre-existing autoimmune thyroid disease and predispose to relapse or to developing novel autoimmune thyroid disease.
- Screening for thyroid disease in pregnancy should be based on an initial determination of TSH performed early during the first trimester and then if abnormal should it be followed by either a free or total T4 measurement [16].
- Some feel that screening all pregnant women for thyroid disease should be undertaken but current British Thyroid Association recommendations are for screening, ideally pre-conceptually, in women with:
    - Type 1 diabetes.
    - Previous thyroid disease.
    - Current thyroid disease.
    - Family history of thyroid disease.
    - Goitre.
    - Symptoms of hypothyroidism.
- TFTs in pregnancy should comprise both TSH and FT4. TPOAb should also be considered, as it has predictive value for postpartum thyroiditis and fetal impairment [17].

Hypothyroid pregnancies [18]

- Increased fetal loss and IQ deficits in infants are associated with mothers who had undiagnosed or undertreated hypothyroidism during pregnancy. Thyroxine requirements are also likely to change during pregnancy. It is important that specialist medical-obstetric teams manage such pregnancies.

- The thyroid status of pregnant hypothyroid patients should be checked:

    - Prior to conception (where possible).
    - At diagnosis of pregnancy.
    - At antenatal booking.
    - At least once during the second and third trimesters and again postpartum.
    - If newly diagnosed, every four to six weeks until stable.

Hyperthyroid pregnancies [18]
Similarly, pregnancies in hyperthyroid women offer challenges and should be managed by specialists:

- Causes of hyperthyroidism in pregnancy include Graves' disease or autonomous adenoma, and transient gestational thyrotoxicosis as a consequence of excessive production of hCG by the placenta [19].
- In those receiving antithyroid drugs, TFTs should be checked prior to conception and drugs adjusted to a minimum dose of antithyroid drug only. Patients on carbimazole are often switched to propylthiouracil during their pregnancy.
- Breastfeeding is safe with all three antithyroid drugs.
- Recheck TFTs at the time of diagnosis of pregnancy and booking. Again, consider modifying therapy and dose reduction, if appropriate.
- FT4 should guide therapy and be maintained at the upper end of the trimester-related reference range.
- Those on antithyroid drugs need frequent TFTs during pregnancy, whilst women previously successfully treated and who are euthyroid at booking need checks again only in the second and third trimesters.
- All should be retested after delivery.

- Note that women, who have previously undergone thyroidectomy for Graves' disease and who are euthyroid or even hypothyroid during pregnancy, may nonetheless still have high titres of TSH-RAb and therefore their babies may be at risk of neonatal Graves' disease.

Neonatal screening for congenital hypothyroidism

Congenital hypothyroidism is common, affecting around 1 in 3,000 babies. It is a preventable cause of intellectual disability. If thyroid replacement is not initiated soon after birth, it becomes irreversible. See the separate Childhood and Congenital Hypothyroidism article.

- The UK has a national screening programme - all newborn babies have a bloodspot TSH measured from a heel prick sample taken on day two to eight after birth. See the separate Newborn Screening article.
- Where an elevated TSH level is found (>20 mU/L), confirmation of the diagnosis is based on measurement of maternal and neonatal TSH and FT4 as well as TSH-RAb in the mother. Maternal tests ensure that there has been no placental transfer of maternal auto-antibodies.
- Babies born at less than 32 weeks of gestation will need a repeat test which should be done at 28 days of postnatal age.
- Treatment should be started within the first 18 days of life.
- The outlook for this preventable cause of growth restriction and intellectual disability has been transformed by newborn screening [20].

Further reading

- Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, et al; The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014 Mar;99(3):923-31. doi: 10.1210/jc.2013-2409. Epub 2014 Jan 1.

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