NICE National Institute for Health and Care Excellence

NICE guideline

Thyroid disease: assessment and management

NICE guideline

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

Overview

This guideline covers investigating all suspected thyroid disease and managing primary thyroid disease (related to the thyroid rather than the pituitary gland). It does not cover managing thyroid cancer or thyroid disease in pregnancy. It aims to improve quality of life by making recommendations on diagnosis, treatment, long-term care and support.

NICE is also developing a guideline on thyroid cancer.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- People with thyroid disease, their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Information for people with thyroid disease, their families and carers

Presenting information

1.1.1 Ensure that information is presented to facilitate shared decision making, as recommended in the NICE guideline on patient experience in adult NHS services.

General information

1.1.2 Explain to people with thyroid disease who need treatment, and their family or carers if appropriate, that:

- Thyroid disease usually responds well to treatment.
- The goal of treatment is to alleviate symptoms and align thyroid function tests within or close to the reference range.
- People may feel well even when their thyroid function tests are outside the reference range.
- Even when there are no symptoms, treatment may be advised to reduce the risk of long-term complications.
- Even when thyroid function tests are within the reference range, changes to treatment may improve symptoms for some people.
- Symptoms may lag behind treatment changes for several weeks to months.

- Day-to-day changes in unexplained symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine.

1.1.3 Provide people with thyroid disease, and their family or carers if appropriate, with written and verbal information on:

- their underlying condition, including the role and function of the thyroid gland and what the thyroid function tests mean
- risks of over- and under-treatment
- their medicines
- need for and frequency of monitoring
- when to seek advice from a healthcare professional
- how thyroid disease and medicines may affect pregnancy and fertility.

See the recommendations on testing for coeliac disease in people with a diagnosis of autoimmune thyroid disease in the NICE guideline on coeliac disease.

Hypothyroidism (underactive thyroid)

1.1.4 Provide people with hypothyroidism, and their family or carers if appropriate, with written and verbal information on:

- possible drug interactions of thyroid hormone replacements, including interactions with over-the-counter medicines
- how and when to take levothyroxine.

Thyrotoxicosis (overactive thyroid)

1.1.5 Provide people with thyrotoxicosis, and their family or carers if appropriate, with written and verbal information on:

- the different causes of thyrotoxicosis
- the consequences of untreated thyrotoxicosis
- the suitability of individual treatment options (for example, antithyroid drugs may be

- more suitable for mild uncomplicated Graves' disease, surgery may be best for an enlarged thyroid causing compression, radioactive iodine is not usually suitable before puberty)
- the possible benefits/advantages of the treatment options (for example, antithyroid drugs and radioactive iodine are non-invasive treatments, surgery offers rapid relief of symptoms and there is no need to delay pregnancy or fathering a child)
- the possible risks/disadvantages of the treatment options (for example, antithyroid drugs may have side effects, radioactive iodine means limited contact with other people for a few weeks and a need to delay pregnancy or fathering a child, surgery is an invasive treatment that leaves scarring on the neck)
- the risk of and impact of different treatment options on new and existing thyroid eye disease (for example, radioactive iodine may precipitate or worsen thyroid eye disease)
- the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.

Thyroid enlargement (also known as goitre)

1.1.6 Provide people with thyroid enlargement, and their family or carers if appropriate, with written and verbal information on:

- the causes of thyroid enlargement, including the fact that goitre and nodules are common and are usually not cancerous
- red flag symptoms to look out for (for example, shortness of breath, rapid growth of nodules, hoarse voice, swallowing difficulties)
- treatment options.

To find out why the committee made the recommendations on information and how they might affect practice, see rationale and impact.

1.2 Investigating suspected thyroid dysfunction or thyroid enlargement

Indications for tests for thyroid dysfunction

1.2.1 Consider tests for thyroid dysfunction for adults, children and young people if

there is a clinical suspicion of thyroid disease, but bear in mind that 1 symptom alone may not be indicative of thyroid disease.

1.2.2 Offer tests for thyroid dysfunction to adults, children and young people with:

- type 1 diabetes or other autoimmune diseases, **or**
- new-onset atrial fibrillation.

1.2.3 Consider tests for thyroid dysfunction for adults, children and young people with depression or unexplained anxiety.

1.2.4 Consider tests for thyroid dysfunction for children and young people with abnormal growth, or unexplained change in behaviour or school performance.

1.2.5 Be aware that in menopausal women symptoms of thyroid dysfunction may be mistaken for menopause.

1.2.6 Do not test for thyroid dysfunction during an acute illness unless you suspect the acute illness is due to thyroid dysfunction, because the acute illness may affect the test results.

1.2.7 Do not offer testing for thyroid dysfunction solely because an adult, child or young person has type 2 diabetes.

To find out why the committee made the recommendations on indications for tests for thyroid dysfunction and how they might affect practice, see rationale and impact.

Tests when thyroid dysfunction is suspected

1.2.8 Consider measuring thyroid-stimulating hormone (TSH) alone for adults when secondary thyroid dysfunction (pituitary disease) is not suspected. Then:

- if the TSH is above the reference range, measure free thyroxine (FT4) in the same sample
- if the TSH is below the reference range, measure FT4 and free tri-iodothyronine (FT3) in the same sample.

1.2.9 Consider measuring both TSH and FT4 for:

- adults when secondary thyroid dysfunction (pituitary disease) is suspected
- children and young people.

If the TSH is below the reference range, measure FT3 in the same sample.

1.2.10 Consider repeating the tests for thyroid dysfunction in recommendations 1.2.8 or 1.2.9 if symptoms worsen or new symptoms develop (but no sooner than 6 weeks from the most recent test).

> To find out why the committee made the recommendations on tests when thyroid dysfunction is suspected and how they might affect practice, see rationale and impact.

1.3 Managing primary hypothyroidism

Tests for people with confirmed primary hypothyroidism

Adults

1.3.1 Consider measuring thyroid peroxidase antibodies (TPOAbs) for adults with TSH levels above the reference range, but do not repeat TPOAbs testing.

Children and young people

1.3.2 Measure TPOAbs for children and young people with TSH levels above the reference range, with possible repeat TPOAbs testing at the time of transition to adult services.

> To find out why the committee made the recommendations on tests for people with confirmed primary hypothyroidism and how they might affect practice, see rationale and impact.

Managing primary hypothyroidism

1.3.3 Offer levothyroxine as first-line treatment for adults, children and young people with primary hypothyroidism.

1.3.4 Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain.

1.3.5 Do not offer natural thyroid extract for primary hypothyroidism[1] because there is not enough evidence that it offers benefits over levothyroxine, and its long-term adverse effects are uncertain.

1.3.6 Consider starting levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for adults under 65 with primary hypothyroidism and no history of cardiovascular disease.

1.3.7 Consider starting levothyroxine at a dosage of 25 to 50 micrograms per day with titration for adults aged 65 and over and adults with a history of cardiovascular disease.

To find out why the committee made the recommendations on managing primary hypothyroidism and how they might affect practice, see rationale and impact.

1.4 Follow-up and monitoring of primary hypothyroidism

Tests for follow-up and monitoring of primary hypothyroidism

1.4.1 Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing, but avoid using doses that cause TSH suppression or thyrotoxicosis.

1.4.2 Be aware that the TSH level can take up to 6 months to return to the reference range for people who had a very high TSH level before starting treatment with levothyroxine or a prolonged period of untreated hypothyroidism. Take this into account when adjusting the dose of levothyroxine.

Adults

1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider

measuring TSH every 3 months until the level has stabilised (2 similar measurements within the reference range 3 months apart), and then once a year.

1.4.4 Consider measuring FT4 as well as TSH for adults who continue to have symptoms of hypothyroidism after starting levothyroxine.

Children and young people aged 2 years and over

1.4.5 For children aged 2 years and over and young people taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH:

- every 6 to 12 weeks until the TSH level has stabilised (2 similar measurements within the reference range 3 months apart), then
- every 4 to 6 months until after puberty, then
- once a year.

Children under 2 years

1.4.6 For children aged between 28 days and 2 years who are taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH:

- every 4 to 8 weeks until the TSH level has stabilised (2 similar measurements within the reference range 2 months apart), then
- every 2 to 3 months during the first year of life, and
- every 3 to 4 months during the second year of life.

To find out why the committee made the recommendations on tests for monitoring and follow-up of primary hypothyroidism and how they might affect practice, see rationale and impact.

1.5 Managing and monitoring subclinical hypothyroidism

Tests for people with confirmed subclinical hypothyroidism

Adults

1.5.1 Consider measuring TPOAbs for adults with TSH levels above the reference range, but do not repeat TPOAbs testing.

Treating subclinical hypothyroidism

1.5.2 When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous radioactive iodine treatment or thyroid surgery, or raised levels of thyroid autoantibodies.

Adults

1.5.3 Consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mIU/litre or higher on 2 separate occasions 3 months apart. Follow the recommendations in section 1.4 on follow-up and monitoring of hypothyroidism.

1.5.4 Consider a 6-month trial of levothyroxine for adults under 65 with subclinical hypothyroidism who have:

- a TSH above the reference range but lower than 10 mIU/litre on 2 separate occasions 3 months apart, **and**
- symptoms of hypothyroidism.

If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment.

Children and young people aged 2 years and over

1.5.5 Consider levothyroxine for children aged 2 years and over and young people with subclinical hypothyroidism who have:

- a TSH level of 20 mIU/litre or higher, **or**
- a TSH level between 10 and 20 mIU/litre on 2 separate occasions 3 months apart, **or**
- a TSH level between 5 and 10 mIU/litre on 2 separate occasions 3 months apart, and
  - thyroid dysgenesis (an underdeveloped thyroid gland), or
  - signs or symptoms of thyroid dysfunction.

  During levothyroxine treatment, follow the recommendations in section 1.4 on follow-up and monitoring.

Children under 2 years

1.5.6 Consider levothyroxine for children aged between 28 days and 2 years with subclinical hypothyroidism who have a TSH level of 10 mIU/litre or higher. During levothyroxine treatment, follow the recommendations in section 1.4 on follow-up and monitoring.

Monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment

Adults

1.5.7 For adults with untreated subclinical hypothyroidism or adults who have stopped levothyroxine treatment for subclinical hypothyroidism, consider measuring TSH and FT4:

- once a year if they have features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, **or**
- once every 2 to 3 years if they have no features suggesting underlying thyroid disease.

Children and young people

1.5.8 Consider measuring TSH and FT4 for children aged 2 years and over and young

people with untreated subclinical hypothyroidism and a TSH lower than 10 mIU/litre:

- every 3 to 6 months if they have features suggesting underlying thyroid disease, such as thyroid dysgenesis (an underdeveloped thyroid gland) or raised levels of thyroid autoantibodies, **or**
- every 6 to 12 months if they have no features suggesting underlying thyroid disease.

1.5.9 Consider measuring TSH and FT4 every 1 to 3 months for children aged between 28 days and 2 years with untreated subclinical hypothyroidism.

1.5.10 Consider stopping TSH and FT4 measurement in children and young people if the TSH level has stabilised (2 similar measurements within the reference range 3 to 6 months apart) and there are no features suggesting underlying thyroid disease.

> To find out why the committee made the recommendations on managing and monitoring subclinical hypothyroidism and how they might affect practice, see rationale and impact.

1.6 Managing thyrotoxicosis

Tests for people with confirmed thyrotoxicosis

Adults

1.6.1 Differentiate between thyrotoxicosis with hyperthyroidism (for example, Graves' disease or toxic nodular disease) and thyrotoxicosis without hyperthyroidism (for example, transient thyroiditis) in adults by:

- measuring TSH receptor antibodies (TRAbs) to confirm Graves' disease
- considering technetium scanning of the thyroid gland if TRAbs are negative.

1.6.2 Only consider ultrasound for adults with thyrotoxicosis if they have a palpable thyroid nodule.

Children and young people

1.6.3 Differentiate between thyrotoxicosis with hyperthyroidism (Graves' disease) and thyrotoxicosis without hyperthyroidism (for example, transient thyroiditis) in children and young people by:

- measuring TPOAbs and TRAbs
- considering technetium scanning of the thyroid gland if TRAbs are negative.

1.6.4 Only offer ultrasound to children and young people with thyrotoxicosis if they have a palpable thyroid nodule or the cause of thyrotoxicosis remains unclear following thyroid autoantibody testing and technetium scanning.

> To find out why the committee made the recommendations on tests for people with confirmed thyrotoxicosis and how they might affect practice, see rationale and impact.

Initial treatment in primary/non-specialist care

1.6.5 Be aware that transient thyrotoxicosis without hyperthyroidism usually only needs supportive treatment (for example, beta-blockers).

1.6.6 Consider antithyroid drugs[2] along with supportive treatment for adults with hyperthyroidism who are waiting for specialist assessment and further treatment.

> To find out why the committee made the recommendations on initial management in primary/non-specialist care for people with thyrotoxicosis and how they might affect practice, see rationale and impact.

Initial treatment in secondary/specialist care

1.6.7 Discuss with adults, children and young people with thyrotoxicosis with hyperthyroidism (and their families and carers as appropriate):

- the possible benefits and risks of all treatment options (antithyroid drugs, radioactive iodine, surgery)
- the likelihood of a good response to each option.

1.6.8 Ensure that people can actively participate in decisions about their treatment by following the recommendations in the NICE guideline on patient experience in adult NHS services. This includes presenting information about possible outcomes in a way the person (and their families and carers as appropriate) can understand.

1.6.9 Offer antithyroid drugs[2] to control hyperthyroidism in adults, children[3] and young people who are waiting for treatment with radioactive iodine or surgery.

Adults with Graves' disease

1.6.10 Offer radioactive iodine[4] as first-line definitive treatment for adults with Graves' disease, unless antithyroid drugs are likely to achieve remission (see recommendation 1.6.11), or it is unsuitable (for example, there are concerns about compression, malignancy is suspected, they are pregnant or trying to become pregnant or father a child within the next 4 to 6 months, or they have active thyroid eye disease).

1.6.11 Offer a choice of antithyroid drugs[2] (a 12- to 18-month course) or radioactive iodine[4] as first-line definitive treatment for adults with Graves' disease if antithyroid drugs are likely to achieve remission (for example, mild and uncomplicated Graves' disease).

1.6.12 Offer antithyroid drugs[2] (a 12- to 18-month course) as first-line definitive treatment for adults with Graves' disease if radioactive iodine and surgery are unsuitable.

1.6.13 Offer total thyroidectomy as first-line definitive treatment for adults with Graves' disease if:

- there are concerns about compression, or
- thyroid malignancy is suspected, or
- radioactive iodine and antithyroid drugs are unsuitable.

1.6.14 Consider radioactive iodine[4] or surgery for adults with Graves' disease who have had antithyroid drugs but have persistent or relapsed hyperthyroidism.

To find out why the committee made the recommendations on treatment for adults with Graves' disease and how they might affect practice, see rationale and impact.

Adults with toxic nodular goitre

1.6.15 Offer radioactive iodine[4] as first-line definitive treatment for adults with hyperthyroidism secondary to multiple nodules unless it is unsuitable (for example, there are concerns about compression, thyroid malignancy is suspected, they are pregnant or trying to become pregnant or father a child within the next 4 to 6 months, or they have active thyroid eye disease).

1.6.16 Offer total thyroidectomy or life-long antithyroid drugs[2] as first-line definitive treatment for adults with hyperthyroidism secondary to multiple nodules if radioactive iodine is unsuitable.

1.6.17 Offer radioactive iodine[4] (if suitable) or surgery (hemithyroidectomy) as first-line definitive treatment for adults with hyperthyroidism secondary to a single nodule, or life-long antithyroid drugs[2] if these options are unsuitable.

To find out why the committee made the recommendations on treatment for adults with toxic nodular goitre and how they might affect practice, see rationale and impact.

Children and young people with Graves' disease or toxic nodular goitre

1.6.18 Offer antithyroid drugs[2],[3] for at least 2 years and possibly longer as first-line definitive treatment for children and young people with Graves' disease.

1.6.19 Consider continuing or restarting antithyroid drugs or discussing radioactive iodine or surgery (total thyroidectomy) for children and young people with Graves' disease who have had a course of antithyroid drugs but have relapsed hyperthyroidism.

1.6.20 For children and young people with hyperthyroidism secondary to a single or multiple nodules:

- offer antithyroid drugs using a titration regimen of carbimazole[2],[3], **and**
- discuss the role of surgery and radioactive iodine with the child, young person and family, following input from the multidisciplinary team.

To find out why the committee made the recommendations on treatment for children and young people with Graves' disease or toxic nodular goitre and how they might affect practice, see rationale and impact.

Antithyroid drugs for adults, children and young people with hyperthyroidism

1.6.21 Before starting antithyroid drugs for adults, children and young people with hyperthyroidism, check full blood count and liver function tests.

1.6.22 When offering antithyroid drugs as first-line definitive treatment to adults with Graves' disease, offer carbimazole[2] for 12 to 18 months, using either a block and replace or a titration regimen, and then review the need for further treatment.

1.6.23 When offering antithyroid drugs to children and young people with Graves' disease, offer carbimazole[2],[3], using a titration regimen, and review the need for treatment every 2 years.

1.6.24 When offering life-long antithyroid drugs to adults with hyperthyroidism secondary to a single or multiple toxic nodules, consider treatment with a titration regimen of carbimazole[2].

1.6.25 Consider propylthiouracil for adults:

- who experience adverse reactions to carbimazole
- who are pregnant or trying to become pregnant within the following 6 months
- with a history of pancreatitis.

1.6.26 Stop and do not restart any antithyroid drugs if a person develops agranulocytosis. Consider referral to a specialist for further management options.

To find out why the committee made the recommendations on antithyroid drugs for adults, children and young people with hyperthyroidism and how they might affect practice, see rationale and impact.

1.7 Follow-up and monitoring of hyperthyroidism

Monitoring after radioactive iodine treatment

1.7.1 Consider measuring TSH, FT4 and FT3 levels in adults, children and young people every 6 weeks for the first 6 months after radioactive iodine treatment until TSH is within the reference range.

1.7.2 For adults, children and young people who have hypothyroidism after radioactive iodine treatment and are not on antithyroid drugs, offer levothyroxine replacement therapy and follow recommendations 1.3.6 and 1.3.7 on dosage of levothyroxine for adults and 1.4.1 to 1.4.6 on monitoring of hypothyroidism.

1.7.3 For adults, children and young people with TSH in the reference range 6 months after radioactive iodine treatment, consider measuring TSH (with cascading) at 9 months and 12 months after treatment.

1.7.4 For adults, children and young people with TSH in the reference range 12 months after radioactive iodine treatment, consider measuring TSH (with cascading) every 6 months unless they develop hypothyroidism (then follow recommendation 1.7.2).

1.7.5 If hyperthyroidism persists after radioactive iodine treatment in adults, children and young people, consider antithyroid drugs[2] until the 6-month appointment.

1.7.6 If hyperthyroidism persists 6 months after radioactive iodine treatment in adults, children and young people, consider further treatment.

Monitoring after surgery

1.7.7 Offer levothyroxine to adults, children and young people after a total thyroidectomy and follow recommendations 1.3.6 and 1.3.7 on dosage of levothyroxine for adults and 1.4.1 to 1.4.6 on monitoring of hypothyroidism.

1.7.8 Consider measuring TSH and FT4 at 2 and 6 months after surgery, and then TSH (with cascading) once a year for adults, children and young people who have had a hemithyroidectomy.

Monitoring of antithyroid drugs

1.7.9 For adults, children and young people who are taking antithyroid drugs for hyperthyroidism, consider measuring:

- TSH, FT4 and FT3 every 6 weeks until their TSH is within the reference range, then
- TSH (with cascading) every 3 months until antithyroid drugs are stopped.

1.7.10 Do not monitor full blood count and liver function for adults, children and young people taking antithyroid drugs for hyperthyroidism unless there is a clinical suspicion of agranulocytosis or liver dysfunction.

1.7.11 For adults who have stopped antithyroid drugs, consider measuring:

- TSH (with cascading) within 8 weeks of stopping the drug, then
- TSH (with cascading) every 3 months for a year, then
- TSH (with cascading) once a year.

1.7.12 For children and young people who have stopped antithyroid drugs, consider measuring:

- TSH, FT4 and FT3 within 8 weeks of stopping the drug, then
- TSH, FT4 and FT3 every 3 months for the first year, then
- TSH (with cascading) every 6 months for the second year, then
- TSH (with cascading) once a year.

To find out why the committee made the recommendations on follow-up and monitoring of hyperthyroidism and how they might affect practice, see rationale and impact.

1.8 Managing and monitoring subclinical hyperthyroidism

Treating subclinical hyperthyroidism

1.8.1 Consider seeking specialist advice on managing subclinical hyperthyroidism in adults if they have:

- 2 TSH readings lower than 0.1 mIU/litre at least 3 months apart **and**
- evidence of thyroid disease (for example, a goitre or positive thyroid antibodies) or symptoms of thyrotoxicosis.

1.8.2 Consider seeking specialist advice on managing subclinical hyperthyroidism in all children and young people.

Untreated subclinical hyperthyroidism

1.8.3 Consider measuring TSH every 6 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.

1.8.4 Consider measuring TSH, FT4 and FT3 every 3 months for children and young people with untreated subclinical hyperthyroidism.

1.8.5 Consider stopping TSH measurement for adults, children and young people with untreated subclinical hyperthyroidism if the TSH level stabilises (2 similar measurements within the reference range 3 to 6 months apart).

To find out why the committee made the recommendations on managing and monitoring subclinical hyperthyroidism and how they might affect practice, see rationale and impact.

1.9 Diagnosing, managing and monitoring thyroid enlargement with normal thyroid function

Investigating thyroid enlargement

The following recommendations apply to adults, children and young people with normal thyroid function.

1.9.1 Offer ultrasound to image palpable thyroid enlargement or focal nodularity in adults, children and young people with normal thyroid function if malignancy is suspected.

1.9.2 Consider ultrasound of incidental findings on imaging if clinical factors suggest malignancy as a possibility.

1.9.3 When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance that takes into account:

- echogenicity
- microcalcifications
- border
- shape in transverse plane
- internal vascularity
- lymphadenopathy.

1.9.4 Reports of ultrasound findings should:

- specify which grading system has been used for the assessment.
- include information on the features in recommendation 1.9.3 **and**
- provide an overall assessment of malignancy, **and**
- confirm that both lobes have been assessed, **and**

- document assessment of cervical lymph nodes.

1.9.5 Use ultrasound guidance when performing fine needle aspiration cytology.

1.9.6 See the NICE guideline on suspected cancer for recommendations on referral for suspected head and neck cancers (including thyroid cancer).

> To find out why the committee made the recommendations on investigating thyroid enlargement and how they might affect practice, see rationale and impact.

Managing non-malignant thyroid enlargement

1.9.7 Do not offer treatment to adults with non-malignant thyroid enlargement, normal thyroid function and mild or no symptoms unless:

- they have breathing difficulty **or**
- there is clinical concern, for example, because of marked airway narrowing.

1.9.8 Repeat thyroid ultrasound and TSH measurement for adults with non-malignant thyroid enlargement who are not receiving treatment, if:

- malignancy is subsequently suspected, **or**
- compression is suspected.

1.9.9 Consider repeating thyroid ultrasound and TSH measurement for adults with non-malignant thyroid enlargement who are not receiving treatment, if:

- the person's symptoms worsen **or**
- they develop symptoms, such as hoarseness, or shortness of breath.

1.9.10 For children and young people with non-malignant thyroid enlargement and normal thyroid function, discuss management with a specialist multidisciplinary team.

1.9.11 For adults with normal thyroid function and a cyst or predominantly cystic nodule with no vascular components, offer aspiration if it is causing compressive symptoms, with possible ethanol ablation if there is re-accumulation of cyst

fluid later.

1.9.12 For adults with normal thyroid function and a non-cystic nodule or multinodular or diffuse goitre, consider the following if they have compressive symptoms relating to thyroid enlargement:

- surgery, particularly if there is marked airway narrowing **or**
- radioactive iodine ablation, if there is demonstrable radionuclide uptake, **or**
- percutaneous thermal ablation (see the NICE interventional procedures guidance on ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules).

To find out why the committee made the recommendations on managing thyroid enlargement and how they might affect practice, see rationale and impact.

Terms used in this guideline

Adults

People aged 16 years and over.

Cascading

Measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.

Children and young people

People under 16 years.

Hyperthyroidism

Excess production and/or secretion of thyroid hormones (overactive thyroid gland).

Hypothyroidism

Inadequate production and secretion of thyroid hormones (underactive thyroid gland).

Menopausal women

This includes women in perimenopause and post menopause.

Subclinical hyperthyroidism

TSH levels below the reference range, with FT3 and FT4 within the reference range.

Subclinical hypothyroidism

TSH levels above the reference range, with FT4 within the reference range.

Thyrotoxicosis

Thyrotoxicosis is a disorder of excess circulating thyroid hormones caused by increased production and secretion (hyperthyroidism) or by the release of stored thyroid hormones (thyroiditis).

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[1] Natural thyroid extract does not have a UK marketing authorisation so its safety is uncertain.

[2] Use of carbimazole is subject to MHRA advice on contraception (Drug Safety Update, February 2019) and risk of acute pancreatitis (Drug Safety Update, February 2019).

[3] At the time of publication (November 2019), carbimazole did not have a UK marketing authorisation for children under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[4] Healthcare professionals should follow the 2017 regulations on medical exposure to ionising radiation.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Levothyroxine–liothyronine combination therapy for hypothyroidism

What is the clinical and cost effectiveness of levothyroxine (T4) and liothyronine (T3) combination therapy compared with T4 alone for people with hypothyroidism whose symptoms have not responded sufficiently to T4 alone? Does DiO2 polymorphism affect the response to combination therapy with T4 and T3?

To find out why the committee made the research recommendation on levothyroxine-liothyronine combination therapy for hypothyroidism see rationale and impact.

2 Long-term health outcomes for people with subclinical hyperthyroidism

What is the clinical and cost effectiveness of treatment (antithyroid drugs or radioactive iodine) for improving long-term health outcomes for people with subclinical hyperthyroidism?

To find out why the committee made the research recommendation on improving long-term health outcomes for people with subclinical hyperthyroidism see rationale and impact.

3 Antithyroid drugs in subgroups with Graves' disease

Are there subgroups of people with Graves' disease who have a particularly good response to antithyroid drugs?

To find out why the committee made the research recommendation on antithyroid drugs in subgroups of people with Graves' disease see rationale and impact.

4 Long-term effectiveness and safety of radioactive iodine therapy for hyperthyroidism

What is the long-term clinical and cost effectiveness, including safety, of radioactive iodine for hyperthyroidism?

To find out why the committee made the research recommendation on long-term effectiveness and safety of radioactive iodine therapy see rationale and impact.

5 Dosimetry-guided radioactive iodine therapy for hyperthyroidism

What is the clinical and cost effectiveness of dosimetry-guided radioactive iodine strategies for hyperthyroidism?

To find out why the committee made the research recommendation on the use of dosimetry-guided radioactive iodine therapy for hyperthyroidism see rationale and impact.

Other recommendations for research

6 Antithyroid drug regimens for T3 thyrotoxicosis due to Graves' disease

What is the clinical and cost effectiveness of different durations of antithyroid drug regimens for people with T3 thyrotoxicosis due to Graves' disease?

7 Levothyroxine for subclinical hypothyroidism in people under 65

What is the clinical and cost effectiveness of levothyroxine for people under 65 with symptomatic subclinical hypothyroidism?

8 Antithyroid drug regimens for Graves' disease

What is the clinical and cost effectiveness of a block and replace regimen compared with a titration regimen of antithyroid drugs for Graves' disease?

9 Percutaneous ablation for benign thyroid nodules

What is the clinical and cost effectiveness of percutaneous thermal ablation for benign thyroid nodules?

10 Iodine for subclinical hypothyroidism

What is the clinical and cost effectiveness of iodine for people with subclinical hypothyroidism?

11 Selenium for subclinical hypothyroidism

What is the clinical and cost effectiveness of selenium for people with subclinical hypothyroidism?

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice. They link to details of the evidence and a full description of the committee's discussion.

Information for people with thyroid disease, their families and carers

Recommendations 1.1.1 to 1.1.6.

Why the committee made the recommendations

The committee based the recommendations on the views and themes from qualitative studies combined with their own experience of treating or living with thyroid disease.

The committee agreed it was important for all people with thyroid disease to understand the disease, the goals of treatment and the complex interaction between thyroid function tests and symptoms. The specific recommendations for people with hypothyroidism centred around the use of thyroid hormone replacement. Levothyroxine is frequently taken incorrectly, which can lead to suboptimal treatment. The specific recommendations for thyrotoxicosis centred around what people should know about their treatment options and the consequences of untreated thyrotoxicosis. The specific recommendations on thyroid enlargement focused on reassuring people that enlargement is common and generally non-cancerous, while also alerting them to red flag symptoms that should prompt further action.

How the recommendations might affect practice

The recommendations provide guidance on the type of information and support that should be provided to people with thyroid disease so that they can make informed decisions about management. The committee noted that currently there is variation in the information provided. In some areas there may be additional resource use, for example, if longer or more consultations are needed. But this may lead to later benefits and reductions in resource use, if, for example, it leads to better understanding and use of medication.

Full details of the evidence and the committee's discussion are in evidence review A: information for people with thyroid disease.

Return to recommendations

Indications for tests for thyroid dysfunction

Recommendations 1.2.1 to 1.2.7

Why the committee made the recommendations

The committee noted that thyroid dysfunction affects many systems in the body, and the symptoms are often non-specific. They agreed, based on evidence and their experience, that most single common symptoms alone are not predictive of thyroid dysfunction. The decision to test should be based on an overall clinical suspicion, taking into account the nature and severity of symptoms, clinical signs and coexisting conditions.

The evidence showed that type 1 diabetes, an autoimmune disease, is associated with thyroid dysfunction. In the committee's experience, this is also likely to apply to other autoimmune diseases and justifies testing for thyroid dysfunction in these conditions.

There was little evidence on thyroid disease in people with atrial fibrillation. However, the committee agreed that the potential importance of thyroid disease and its impact on the treatment of atrial fibrillation is sufficient to justify testing.

Limited evidence showed that depression can be associated with thyroid dysfunction. The committee agreed that, in their experience, this can also apply to anxiety.

The committee noted that in children and young people, thyroid dysfunction may be accompanied by abnormal growth or a change in behaviour or school performance that is unexplained by other factors. They agreed, based on their experience, that testing for thyroid dysfunction should be considered for children and young people presenting with those features. Thyroid function tests may be abnormal in people who are acutely unwell with non-thyroid disease and the committee agreed that decisions on treatment of thyroid dysfunction should not be based solely on these results. Tests for thyroid dysfunction should be performed when the acute illness has resolved, unless the acute illness may be due to thyroid dysfunction.

Evidence showed that type 2 diabetes is not associated with thyroid dysfunction, so the committee concluded that thyroid function tests should not be performed solely because a person has this condition.

How the recommendations might affect practice.

The recommendations to test for thyroid dysfunction in people with autoimmune disease, atrial fibrillation, anxiety or depression are broadly in line with current practice. Checking thyroid function in people with type 2 diabetes and during acute illness is also current practice in some areas. The recommendations to avoid this should be cost saving for the NHS.

Full details of the evidence and the committee's discussion are in evidence review B: indications for testing.

Return to recommendations

Tests when thyroid dysfunction is suspected

Recommendations 1.2.8 to 1.2.10

Why the committee made the recommendations

No evidence was identified on which tests should be used when thyroid dysfunction is suspected so the committee used their experience to develop the recommendations. The committee agreed that in general TSH alone is an appropriate first test for people in whom thyroid dysfunction is suspected. Subsequent tests (cascading) are only needed if TSH is abnormal (with FT4 if the TSH suggests hypothyroidism and both FT4 and FT3 if the TSH suggests hyperthyroidism). This approach reduces unnecessary testing compared with simultaneous TSH, FT4 and FT3 testing for all people. However, tests should be done in a way to minimise potential delays and the need for additional appointments, for example, by laboratories keeping original samples and performing subsequent tests on the same samples. The committee agreed based on their experience that this approach did not apply to adults in whom secondary thyroid dysfunction is suspected or in children and young people, where both TSH and FT4 are needed by default because of the differing likely causes of dysfunction. The committee further agreed that tests may need repeating when new symptoms develop or worsen, but that this should not be within 6 weeks of the last test because this is unlikely to provide new information.

How the recommendations might affect practice.

The recommendations broadly reflect current practice, although not all laboratories currently follow the cascading approach to testing.

Where FT4 is currently a routine test for thyroid dysfunction, cascading will reduce NHS costs by

avoiding extra tests for people with a TSH within the reference range. In areas where FT3 is not currently being measured, cascading will mean a cost increase. But this will be offset by the benefits of correctly diagnosing and managing thyrotoxicosis.

Full details of the evidence and the committee's discussion are in evidence review C: thyroid function tests.

Return to recommendations

Tests for people with confirmed primary hypothyroidism

Recommendations 1.3.1 and 1.3.2

Why the committee made the recommendations

No evidence was identified on the use of antibodies to investigate hypothyroidism so the committee used their experience to develop the recommendations. They agreed that testing for thyroid peroxidase antibodies (TPOAbs) may be useful in the early investigation of the underlying cause of hypothyroidism. However, for adults there was no role for remeasuring TPOAbs because changes in levels are unlikely to guide treatment decisions. The committee agreed that for young people it may be useful to repeat TPOAbs at the point of transition to adult services.

How the recommendations might affect practice

The recommendations broadly reflect current practice so the committee agreed there should be no substantial change. By avoiding re-testing in adults, there could be some cost savings.

Full details of the evidence and the committee's discussion are in evidence review D: tests for confirmed primary hypothyroidism.

Return to recommendations

Managing primary hypothyroidism

Recommendations 1.3.3 to 1.3.7

Why the committee made the recommendations

Thyroid hormone replacement

The committee agreed that hypothyroidism needs thyroid hormone replacement. Potential treatments are levothyroxine, usually prescribed to everyone, liothyronine, which is sometimes prescribed when levothyroxine fails, and natural thyroid extracts (which is currently unlicensed for use in the UK). Overall the evidence from 7 randomised controlled trials suggested that combination treatment with levothyroxine and liothyronine did not offer any important health benefits compared with levothyroxine monotherapy and was significantly more expensive. However, the committee noted that some of the trials did show some small benefits in specific quality of life domains and anecdotal evidence from some committee members suggested beneficial effects of combination treatment with levothyroxine and liothyronine in small subgroups of patients. The committee were aware that some people reported still feeling unwell with levothyroxine monotherapy and agreed that in this group adding liothyronine could potentially have greater benefit than in the general population with hypothyroidism, although there are no trials in this population. Some evidence suggested that combination therapy with levothyroxine and liothyronine could be harmful because it may suppress the production of TSH and its long-term adverse effects are uncertain. The committee was aware that the use of combination therapy is a critical issue in hypothyroidism. They could not recommend liothyronine either alone or in combination treatment based on the evidence available and its current list price but agreed a research recommendation to help inform future guidance in this important area[5].

The committee agreed that the evidence for natural thyroid extracts showed no benefit over levothyroxine. The committee also noted that the proportion of T3 to T4 is higher in natural thyroid extracts than produced in the human body and the adverse effects are uncertain. Natural thyroid extracts are an unlicensed medication in the UK and overall the committee agreed they should not be offered.

Levothyroxine starting dose

Some evidence showed that a high starting dose of levothyroxine produced more rapid improvements in quality of life than a lower starting dose followed by titration. The committee agreed that this was also their experience and therefore recommended a high starting dose (1.6 micrograms per kilogram body weight per day) in adults unless contraindicated (adults over 65 or with a history of cardiovascular disease). Although evidence about dosing was very limited, the committee agreed that adults over 65 years are more likely to have cardiovascular comorbidities. Most studies of hypothyroidism and subclinical hypothyroidism use 65 as a cut-off when defining older adults. The committee agreed to recommend a lower starting dose with titration for people

over 65.

The committee were unable to make recommendations on iodine or selenium supplements because of a lack of evidence.

How the recommendations might affect practice

The recommendations on thyroid hormone replacement and natural thyroid extract reinforce current practice and are not expected to have a significant cost impact. Currently everyone is offered levothyroxine as thyroid hormone replacement and small subgroups of people who do not feel well on levothyroxine are sometimes offered liothyronine.

Full details of the evidence and the committee's discussion are in evidence review E: managing hypothyroidism.

Return to recommendations

Follow-up and monitoring of primary hypothyroidism

Recommendations 1.4.1 to 1.4.6

Why the committee made the recommendations

Evidence showed no clinically important benefits of maintaining TSH levels in the lower rather than higher end of the TSH reference range. Given the need for additional medication to achieve a TSH level in the lower end of the reference range, with the potential for adverse effects and increased cost, the committee concluded that as a starting point TSH levels could be maintained at any point within the reference range. Nevertheless, the committee acknowledged that some people may still have troublesome symptoms even with TSH levels in the reference range. Therefore, they recommended adjusting the dose of levothyroxine if symptoms persist to achieve optimal wellbeing for individual patients. The committee also agreed that it was important not to use doses high enough to cause TSH suppression or thyrotoxicosis.

The committee agreed that TSH levels can take up to 6 months to return to the reference range if they have previously been very high or have been high for a long time. They agreed that healthcare professionals should take this into account when adjusting doses, to avoid large dose increases that could cause thyrotoxicosis.

The committee based recommendations about the timing of testing on their experience. They made

separate recommendations for children under 2 years because in this age group the impact of poorly treated hypothyroidism can be most severe, and the child is developing at such a rate that frequent dose changes may be needed.

The committee used their experience to agree which thyroid function tests are needed for monitoring. They followed the general principle that once TSH has stabilised in the reference range, TSH testing alone is enough if the person has no symptoms suggesting thyroid dysfunction.

They agreed that children should have more frequent monitoring to ensure that dose adjustments are made promptly and because in the very young, under-treatment can lead to serious neurodevelopmental consequences.

How the recommendations might affect practice

The committee agreed that generally the testing strategies are in line with current practice, although there may be some variation across the country. The recommendations should help patients (and their support groups) to advocate for their own monitoring and treatment. Doctors will have clear guidance on monitoring to assist with consultations.

Full details of the evidence and the committee's discussion are in evidence review F: monitoring thyroid disease.

Return to recommendations

Managing and monitoring subclinical hypothyroidism

Recommendations 1.5.1 to 1.5.10

Why the committee made the recommendations

Adults

There was little evidence on treatment for people with subclinical hypothyroidism, with most of the evidence relating to older adults. The committee agreed that as most studies used 65 years as a cut-off it was appropriate to define older adults as over 65 and make separate recommendations for this group.

The committee discussed the tendency to over-rely on TSH levels when making decisions about treatment. They agreed that factors suggesting underlying thyroid disease should also be taken

into account when deciding whether or not to treat subclinical hypothyroidism.

The committee noted that a TSH level of 5 to 10 mIU/litre might return to the reference range without treatment in around half of people, whereas a TSH level above 10 mIU/litre is less likely to do so and is more often associated with symptoms. They therefore agreed that levothyroxine should be considered for all adults with a TSH level of 10 mIU/litre or more because this may improve symptoms and may have long-term benefits including on cardiovascular outcomes. For people with a TSH level lower than 10 mIU/litre, the committee agreed based on their experience that treatment was less likely to have a benefit but that the balance of risks to benefits was most favourable for adults under the age of 65. The committee noted that for people over 65 there was less likely to be an improvement in symptoms and the potential for harms from suppressing TSH (such as atrial fibrillation) is greater. The committee agreed that the trial of levothyroxine treatment should be stopped if symptoms persist with TSH levels within the reference range, as they are likely to be due to causes other than hypothyroidism.

The committee also agreed that the recommendations on testing TPOAbs in overt hypothyroidism applied to subclinical hypothyroidism because testing would help to inform the decision on whether or not to treat.

Because of the small amount of evidence available on the treatment of subclinical hypothyroidism, the committee made recommendations for research on selenium and iodine.

Children and young people

In children and young people there are a number of different causes of a mild increase in TSH besides autoimmune thyroid disease. These include mild congenital hypothyroidism, a low iodine intake (for example, because of a special diet), intercurrent illness, adrenal insufficiency and the paradoxical 'increase' in TSH observed in children with secondary hypothyroidism. The committee agreed that there is no urgency to treat with levothyroxine if thyroid hormone levels are appropriate for age. It is important to make a diagnosis before offering any treatment. The committee recommended caution when considering levothyroxine for children and young people whose thyroid dysfunction was unexplained. However, they also noted that in the very young it would not be appropriate to wait as long as for adults (3 months) to confirm a raised TSH with a second test.

How the recommendations might affect practice

The committee highlighted that current practice for monitoring of subclinical hypothyroidism varies considerably, with unnecessary testing often being undertaken. They agreed that the

recommendations are likely to reduce the number of tests overall.

Full details of the evidence and the committee's discussion are in evidence review G: managing subclinical hypothyroidism.

Return to recommendations

Tests for people with confirmed thyrotoxicosis

Recommendations 1.6.1 to 1.6.4

Why the committee made the recommendations

The committee agreed that it is crucial to determine the cause of thyrotoxicosis because this affects management decisions. Antithyroid drugs are unlikely to cure toxic nodular disease but may induce remission in Graves' disease. TRAbs testing provides confirmation of clinical features that suggest Graves' disease. Getting an accurate diagnosis sooner benefits the patient because the appropriate treatment options would be offered first. If TRAbs levels are high it is unlikely that antithyroid drugs will induce remission of Graves' disease.

Evidence suggested that in adults, the diagnostic accuracy of TRAbs testing for Graves' disease was high across different cut-off values. Evidence also showed the accuracy to be high in children. However, the evidence was limited in terms of the number of studies and the study sizes. But it was in line with the committee's experience and current practice, so they agreed to recommend TRAbs testing for Graves' disease in both adults and children and young people.

Evidence on the diagnostic accuracy of TPOAbs testing was not available in either adults or children. The committee agreed that based on their experience, TPOAbs testing alone is not likely to be as useful as TRAbs testing for the diagnosis of Graves' disease, but it could be used in children and young people where the absence of TRAbs but presence of TPOAbs indicates that thyrotoxicosis is more likely to resolve spontaneously.

Evidence for the diagnostic accuracy of ultrasound was limited in both adults and children. Based on clinical experience, the committee agreed that ultrasound was useful for the diagnosis of Graves' disease but only when there were palpable thyroid nodules.

The committee agreed that technetium scanning may be useful when TRAbs are negative and Graves' disease is suspected because generalised uptake on the scan suggests Graves' disease.

How the recommendations might affect practice

Over recent years, TRAbs testing has become more widely available and more centres in the UK are using it to confirm the diagnosis of Graves' disease. However, some centres continue to use TPOAbs testing. If TRAbs testing allows more accurate differentiation between the different causes of thyrotoxicosis, there are likely to be reductions in unnecessary antithyroid treatment (including surgery) for people with transient thyroiditis and more timely and appropriate treatment choices for people with toxic nodular hyperthyroidism. The committee anticipates that TRAbs testing will become standard best practice for all UK centres leading to a correct diagnosis of Graves' disease for more people.

The use of technetium scanning for adults who are TRAbs negative reflects current practice in most centres.

Although thyroid ultrasound has only a limited role in the investigation of suspected Graves' disease, many healthcare professionals offer this investigation. This often results in incidental findings of doubtful clinical significance leading to further unnecessary investigations and interventions. The recommendation will discourage healthcare professionals from using thyroid ultrasound routinely in the investigation of suspected Graves' disease, which is likely to be cost saving.

Full details of the evidence and the committee's discussion are in evidence review H: tests for people with confirmed thyrotoxicosis.

Return to the recommendations

Initial management in primary/non-specialist care for people with thyrotoxicosis

Recommendations 1.6.5 and 1.6.6.

Why the committee made the recommendations

Based on their experience, the committee reminded healthcare professionals that transient thyrotoxicosis does not need definitive treatment. They recommended that short-term treatment with antithyroid drugs may be needed until decisions about the most appropriate treatment can be made in specialist care. The committee also agreed that treatment with antithyroid drugs before radioactive iodine would minimise the rise in circulating thyroid hormone levels following this

treatment and so reduce the symptoms of thyrotoxicosis. They acknowledged that it is important to render the patient euthyroid with antithyroid drugs before surgery to ensure patient safety.

How the recommendations might affect practice

The recommendations reflect current practice so the committee agreed there should be no change.

Full details of the evidence and the committee's discussion are in evidence reviews I, J, K, L: managing thyrotoxicosis.

Return to the recommendations

Treatment for adults with Graves' disease

Recommendations 1.6.7 to 1.6.14

Why the committee made the recommendations

The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs in terms of thyroid status, but with a greater risk of thyroid eye disease. There was no convincing evidence of a difference between radioactive iodine and surgery. The economic evidence showed that radioactive iodine offered a better balance of benefits and costs than surgery (total thyroidectomy) and was more cost effective than antithyroid drugs. Although exposure to radiation will always lead to some small increase in relative risk of cancer, the evidence showed that this did not translate into an absolute effect that was clinically important. The committee agreed nonetheless that continued follow-up of people who have undergone radioactive iodine treatment was important and the 'as low as reasonably practicable' (ALARP) principle applied. They also agreed to make a research recommendation on the long-term effectiveness and safety of exposure to radioactive iodine.

The committee agreed, based on the clinical and economic evidence, that radioactive iodine should be offered as first-line definitive treatment for most people with hyperthyroidism secondary to Graves' disease. However they noted a number of important exceptions and specified these in the recommendations. The committee acknowledged that circulating levels of thyroid hormones are likely to rise following radioiodine administration and pre-treatment with anti-thyroid drugs would make radioactive iodine safer and lead to reduced symptoms of thyrotoxicosis. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and a course of antithyroid drugs could be equally appropriate

options.

Some studies have suggested that some people are more likely to relapse after antithyroid drugs. These include males, younger people, people who smoke, people with a large goitre, people with high levels of thyroid hormones at the time of diagnosis and people with high levels of TRAbs. However, most of the studies were small and retrospective. The committee agreed that it would be very helpful to confirm these findings in large prospective multi-centre studies. They made a research recommendation to inform future guidance.

Calculated or fixed strategy for radioactive iodine

The evidence did not identify a clinically important difference between a calculated or fixed strategy in terms of radioactive iodine dosing. A calculated strategy has an increased cost because of the need for imaging (usually ultrasound) and uptake measurements. There are theoretical benefits from a calculated strategy to administer a more precise dose that could reduce potentially unnecessary additional radiation exposure, but the evidence did not indicate that this precision translated to clinically important benefits. The committee's experience is that, in the UK, radioactive iodine is usually given without calculating the absorbed dose. The committee agreed that there was too much uncertainty around the impact of the differing strategies to make a recommendation and chose to make a research recommendation.

Surgery options

The evidence suggested no clinically important difference between surgical options (total and hemithyroidectomy) for Graves' disease, but tended towards a benefit of total thyroidectomy in terms of relapse rates and harm in terms of increased risk of hypoparathyroidism. These findings were consistent with the committee's own experience. The committee agreed to recommend total thyroidectomy for adults with Graves' disease having surgery. This was based on their experience that people opting for surgery are generally seeking a definitive treatment.

How the recommendations might affect practice

The committee was aware that the recommendations would result in radioactive iodine being offered as first-line definitive treatment to more people than currently. This is likely to be cost effective as shown by the economic evidence.

Full details of the evidence and the committee's discussion are in evidence reviews: I, J, K, L: managing thyrotoxicosis.

Return to the recommendations

Treatment for adults with toxic nodular goitre

Recommendations 1.6.15 to 1.6.17

Why the committee made the recommendations

The committee used their experience and an extrapolation of the evidence from Graves' disease to recommend radioactive iodine as the first-line definitive treatment for hyperthyroidism secondary to multiple nodules. Surgery or life-long antithyroid drugs could be offered in some circumstances when radioactive iodine is inappropriate (for example, young mothers, people in nursing homes or people unable to adhere to radiation protection guidance) or surgery is likely to have additional benefits (for example, if malignancy is suspected). The committee used their experience to recommend that when surgery is chosen hemithyroidectomy should be considered for people with hyperthyroidism due to a single toxic nodule, and total thyroidectomy for people with hyperthyroidism and multiple toxic nodules. A hemithyroidectomy is a shorter procedure that removes less of the thyroid gland; this requires less time in hospital and leads to a lower risk of adverse effects like hypoparathyroidism and long-term hypothyroidism but has a greater risk of relapse of hyperthyroidism. The risk of relapse is greater for multiple toxic nodules, hence the different recommendations for different populations.

How the recommendations might affect practice

The recommendations broadly reflect current practice so the committee agreed there should be no substantial change.

Full details of the evidence and the committee's discussion are in evidence reviews I, J, K, L: managing thyrotoxicosis.

Return to the recommendations

Treatment for children and young people with Graves' disease or toxic nodular goitre

Recommendations 1.6.18 to 1.6.20

Why the committee made the recommendations

No evidence was identified for treatments in children and young people with hyperthyroidism. Based on their experience, the committee recommended that antithyroid drugs should be first-line definitive treatment for children and young people with Graves' disease or hyperthyroidism secondary to a single or multiple toxic nodules. The committee agreed that the risks of radioactive iodine and surgery may be greater than for adults so it is important to get input from the multidisciplinary team and discuss these options with the child and their family.

When surgery is chosen, the committee recommended that this should be total thyroidectomy for Graves' disease or bilateral thyroid nodules. They based this on their experience and evidence in adults.

How the recommendations might affect practice

The recommendations to offer antithyroid drugs as first-line treatment are broadly in line with current practice and are unlikely to have a substantial cost impact. The potential risks and benefits (and therefore cost effectiveness) of radioactive iodine treatment in children are uncertain.

Full details of the evidence and the committee's discussion are in evidence reviews I, J, K, L: managing thyrotoxicosis.

Return to the recommendations

Antithyroid drugs for people with hyperthyroidism

Why the committee made the recommendations

Recommendations 1.6.21 to 1.6.26

Evidence showed a clinically important benefit in terms of normalising thyroid hormone levels and minor drug-related adverse events for methimazole or carbimazole compared with propylthiouracil. However, hypothyroidism was more frequent with methimazole or carbimazole. The committee questioned whether this was a result of over-treatment and thought hypothyroidism unlikely to be permanent. Because carbimazole, and not methimazole, is currently licensed in the UK, the committee recommended carbimazole as the drug of choice when offering an antithyroid drug for treating hyperthyroidism. The committee noted that carbimazole is not recommended in children under 2 years. In view of the potential risk of liver failure the committee agreed that propylthiouracil should not be the first choice of antithyroid drug. However, the

committee noted the MHRA drug safety advice for carbimazole on contraception and the risk of acute pancreatitis and agreed that propylthiouracil is appropriate as an alternative for adults.

Duration of treatment

Evidence showed a clinically important benefit in terms of lack of relapse to hyperthyroidism and maintaining normal thyroid hormone levels with 12 to 18 months' treatment compared with 6 to 12 months' treatment. There was no clinically important difference in relapse following a longer treatment of more than 18 months.

The committee recommended that carbimazole should be offered for at least 12 to 18 months. They noted that this differed from the summary of product characteristics which advises 6 to 18 months, but agreed that the deviation was justified by the evidence. The committee agreed based on their experience and extrapolation from evidence in adults that the treatment duration for children should be reviewed every 2 years.

Treatment regimen

Evidence showed that block and replace (fixed high dose combined with levothyroxine) and titration (dose based on thyroid function tests) regimens of antithyroid drugs were similar in terms of minor drug-related adverse events (skin reactions). There were fewer relapses to hyperthyroidism with block and replace treatment compared with titration. But there was limited evidence suggesting more chance of agranulocytosis with block and replace regimens. The committee noted that block and replace treatment could theoretically provide greater stability and require fewer medical appointments than titration regimens. Therefore they recommended a choice of either regimen for adults with Graves' disease. Hyperthyroidism in children and young people should usually be managed with a dose titration regimen because of the increased risk of adverse events in this age group. The committee also made a recommendation for further research in this area.

The committee noted that people with hyperthyroidism secondary to a single or multiple toxic nodules will not go into remission and therefore discontinuing antithyroid drugs is not relevant. They agreed that titration regimens are generally more appropriate for this group.

How the recommendations might affect current practice

Current practice in the UK, in adults and children, is a mix of block and replace (approximately 40%) and titration regimens (approximately 60%). The recommendations are broadly in line with current practice and unlikely to have significant resource impact.

Full details of the evidence and the committee's discussion are in evidence review J: management of thyrotoxicosis – antithyroid drugs.

Return to recommendations

Follow-up and monitoring of hyperthyroidism

Recommendations 1.7.1 to 1.7.12

Why the committee made the recommendations

No evidence was identified on the most appropriate ways to monitor hyperthyroidism, so the committee made recommendations based on their experience. The precise timing of monitoring depends on the treatment chosen, but in general the committee aimed to minimise unnecessary testing while ensuring early treatment failures or adverse effects (for example, hypothyroidism) were identified. Regardless of treatment option chosen, the committee agreed that in the long term TSH alone is sufficient for monitoring, although TSH alongside FT4 and FT3 will be needed in the short term after treatment. Should TSH become abnormal, having been stable within the reference range for a prolonged period, further tests will be necessary. Short-term combined testing with TSH, FT4 and FT3 is needed to inform decisions about the need for additional courses of treatment or dose changes with antithyroid drugs. As no evidence was found to support a strategy of routinely monitoring full blood count and liver function tests, and these tests have a treatment burden for people with hyperthyroidism and a resource impact, the committee recommended that healthcare professionals do not test unless there is a clinical suspicion of specific adverse effects of treatment.

How the recommendations might affect practice

More people with Graves' disease are expected to have monitoring because radioactive iodine is more likely to be offered as first-line treatment. This extra cost is likely to be justified, because radioactive iodine is more cost effective than other treatments for hyperthyroidism. In general, these recommendations reinforce best practice, with earlier detection leading to earlier treatment, reduced costs of treating complications and improved quality of life. The recommendation that there is no need to monitor full blood count and liver function after antithyroid drug treatment unless liver dysfunction or agranulocytosis are suspected is likely to be cost saving.

Full details of the evidence and the committee's discussion are in evidence review F: monitoring thyroid disease.

Return to recommendations

Managing and monitoring subclinical hyperthyroidism

Recommendations 1.8.1 to 1.8.5

Why the committee made the recommendations

Treating subclinical hyperthyroidism

There was no evidence available on treating subclinical hyperthyroidism so the committee used their experience to develop the recommendations. They agreed that treatment might be suitable if subclinical hyperthyroidism is persistent and appears to be caused by intrinsic thyroid disease. However, the committee noted that there is currently no evidence that treatment offers benefits and it can have adverse effects. Overall the committee agreed that treatment decisions should be made with specialist advice. Treatment would be appropriate in those most likely to benefit, in other words those with very suppressed TSH and other features suggesting thyroid disease. The committee also agreed that they could not make specific recommendations about when to treat subclinical hyperthyroidism in children as specialist input would also be needed for this.

Several large population-based observational studies have shown that subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation, osteoporosis, dementia, and death, including death from cardiovascular disease. Although most people with subclinical hyperthyroidism have no symptoms, an important question is whether treatment could improve long-term outcomes (for example, atrial fibrillation and dementia). The committee agreed to make a research recommendation to inform future practice.

Monitoring subclinical thyroid dysfunction

There was no evidence available on monitoring subclinical thyroid dysfunction so the committee based the recommendations on their experience.

The overall aim of these recommendations is to ensure that if the subclinical thyroid dysfunction needs treatment, this will be identified in a timely manner but without subjecting a person to a lot of unnecessary tests.

The committee agreed that for children and young people monitoring may need to be more frequent.

How the recommendations might affect practice

Current practice in managing subclinical hyperthyroidism is variable. Some people are offered antithyroid drugs or radioactive iodine; surgery is very rare. Many people are offered no treatment. The recommendations are likely to reduce inappropriate treatment and to be cost saving.

The recommendations for monitoring subclinical thyroid dysfunction reflect good current practice.

Full details of the evidence and the committee's discussion are in evidence review M: management of subclinical thyrotoxicosis.

Return to recommendations

Investigating non-malignant thyroid enlargement with normal thyroid function

Recommendations 1.9.1 to 1.9.6

Why the committee made the recommendations

Imaging for fine needle aspiration

Evidence showed that ultrasound using established criteria is accurate for determining whether thyroid nodules need fine needle aspiration to investigate potential malignancy. The committee noted that many referrals for thyroid ultrasound are based on incidental findings of other types of imaging (for example, CT scans performed for other indications). They agreed that thyroid ultrasound should only be performed when a full assessment indicates a likelihood of malignancy. Thyroid ultrasound of incidental findings should not be the default option because most incidental findings are not malignant and further investigation may cause harms in terms of the adverse effects of testing and patient anxiety.

The evidence showed that different ultrasound criteria generally assessed the same features and had similar accuracy for detecting malignancy. Rather than recommending a specific set of criteria, the committee chose to list the essential features of any grading system (the lesion's echogenicity, border, shape, vascularity, presence of microcalcifications and cervical lymphadenopathy). Based on their knowledge that nodule size does not determine the likelihood of malignancy, and the observation that the criterion (SRU) that includes nodule size results in significantly lower sensitivity and specificity, they agreed not to include nodule size in the list.

Because healthcare professionals need to be able to re-visit ultrasound findings, the committee agreed that the grading system used for clinical decision making, including the specific nodule features examined to assess malignancy, should be specified in ultrasound reports. For the same reason, they agreed that ultrasound reports should also confirm that both lobes have been assessed and document the assessment of cervical lymph nodes.

The committee agreed that the recommendations should apply to children and young people as well as adults.

Ultrasound guidance for fine needle aspiration

Evidence indicated that performing fine needle aspiration under ultrasound guidance provides greater sensitivity and specificity for determining the malignancy of thyroid nodules compared with palpation guidance.

The evidence also showed that with ultrasound guidance an inadequate sample is less likely than with palpation. Inadequate sampling is likely to add to the overall cost of palpation-guided fine needle aspiration because samples may need to be repeated or require more extensive investigation. The committee also noted that there were additional benefits of ultrasound guidance because ultrasonographic characteristics identified by simultaneous imaging provide more information about the risk of malignancy before cytology results are obtained.

How the recommendations might affect practice

Imaging for fine needle aspiration

Ultrasound is currently already used to assess the likelihood of thyroid malignancy, so the recommendations are not likely to make a significant impact. In the UK, the most commonly used ultrasound criteria are those of the British Thyroid Association, which are in line with the recommendations in this guideline.

Ultrasound guidance for fine needle aspiration

The recommendation reflects current practice so the committee agreed that it should not have a significant impact.

Full details of the evidence and the committee's discussion are in evidence review N: imaging for fine needle aspiration and evidence review O: ultrasound guidance for fine needle aspiration.

Return to the recommendations

Managing non-malignant thyroid enlargement

Recommendations 1.9.7 to 1.9.12

Why the committee made the recommendations

Surgery

The committee noted that there was little evidence on the efficacy of surgery for nodules; this was related to the challenges of comparing surgical and non-surgical interventions. In general, the committee agreed that surgery would be appropriate for nodules or enlargement causing symptoms, if there has been no response with other options or if there is true compression of nearby organs (for example, tracheal narrowing).

Cystic nodules

Aspiration is routinely done before more intensive intervention for cystic nodules because it is simple and can be done in the same appointment as preliminary investigation by a radiologist (or endocrinologist). The evidence generally showed a benefit of ethanol ablation over levothyroxine and equivalence with radiofrequency ablation.

Non-cystic nodules/multinodular goitre

The evidence showed no clinically important effect of levothyroxine on non-cystic nodules and a benefit of radiofrequency ablation and laser ablation. There was no evidence identified on radioactive iodine ablation although the committee noted that it is very commonly used in the UK for diffuse goitres that are causing symptoms, particularly if there is demonstrable radionuclide uptake. The committee also noted that the more recently developed techniques for percutaneous thermal ablation (for example, high-intensity focused ultrasound and microwave ablation) may be appropriate for some people but are not widely available. They made a research recommendation on percutaneous thermal ablation to inform future practice. The committee agreed not to recommend the use of levothyroxine due to the evidence suggesting no clinically important benefit for most outcomes and their awareness of adverse effects (for example, TSH suppression and increasing cardiovascular risk).

Children and young people

The committee noted that there was no evidence in children. They agreed that a healthcare

professional should refer a child with thyroid enlargement to an appropriate multidisciplinary team, to ensure appropriate management as early as possible.

Monitoring thyroid enlargement

There was no evidence on monitoring thyroid enlargement but the committee agreed that, given the accuracy of ultrasound imaging, the risk of missing a malignancy or malignant transformation in an enlarged thyroid gland is low. However, they agreed that worsening symptoms or development of new symptoms may warrant repeating the ultrasound and TSH measurement. Suspicion of malignancy or compression would warrant repeating these tests.

How the recommendations might affect practice

The recommendations on surgical referral for goitre and non-malignant thyroid nodules are broadly in line with current clinical practice and therefore not expected to have significant impact.

The recommendations on managing non-malignant thyroid enlargement are also unlikely to have substantial resource impact. Radiofrequency ablation and laser ablation are not currently widely available. However it is current practice to only provide interventions to adults with nodules causing symptoms, as outlined in the recommendations. This limits the number of adults needing these interventions. Referral of children to a multidisciplinary team is not likely to occur often because thyroid enlargement is rare in this population.

Monitoring thyroid enlargement

The recommendation broadly reflects current practice. The committee recognised that there may be some centres in which routine monitoring is done, and the recommendation is likely to reduce this.

Full details of the evidence and the committee's discussion are in evidence review P: management of non-malignant thyroid enlargement, and evidence review F: monitoring thyroid disease.

Return to recommendations

[5] NHS England's specialist pharmacy service has produced advice on prescribing liothyronine.

Context

Key facts and figures

Thyroid disease includes thyroid enlargement and thyroid hormone dysfunction. Thyroid enlargement may be benign, resulting in nodules or goitre, or malignant in people with thyroid cancer. Conditions causing thyroid dysfunction can be broadly divided into those that result in thyroid gland underactivity (hypothyroidism) or overactivity (thyrotoxicosis).

Thyroid enlargement is common. About 15% of the UK population have clinically detectable goitres or thyroid nodules, and the lifetime risk of developing a thyroid nodule is around 5 to 10%. In many cases, thyroid glands harbouring malignancy are clinically indistinguishable from those that are not. Most people with a non-malignant enlarged thyroid gland and normal thyroid function need no treatment.

Hypothyroidism is a condition of thyroid hormone deficiency and is usually caused by autoimmune Hashimoto's thyroiditis. Primary hypothyroidism refers to conditions arising from the thyroid gland rather than the pituitary gland (secondary hypothyroidism). Hypothyroidism is found in about 2% of the UK population and in more than 5% of those over 60. Women are 5 to 10 times more likely to be affected than men. Long-term consequences of hypothyroidism include cardiovascular disease and an increase in cardiovascular risk factors, including hypercholesterolaemia.

Thyrotoxicosis is a disorder of excess circulating thyroid hormones caused by increased production and secretion (hyperthyroidism) or the release of (thyroiditis) stored thyroid hormones. In the UK, autoimmune hyperthyroidism (Graves' disease) is the most common form, accounting for 60 to 80% of cases. Thyrotoxicosis is a common endocrine disorder with a prevalence of around 2% in UK women and 0.2% in men. Graves' disease is caused by a genetic predisposition to developing stimulating thyroid autoantibodies and occurs mostly in women aged 30 to 60 years. Thyrotoxicosis affects 1 to 2 children per 10,000. Children may be severely affected, with poor educational performance often being an early feature. Long-term consequences of hyperthyroidism include increased cardiovascular morbidity and mortality and bone-related complications, including osteoporosis.

Subclinical thyroid dysfunction is a biochemical diagnosis where serum thyroid-stimulating hormone (TSH) levels are outside the reference range, and circulating thyroid hormone levels (thyroxine [T4] and tri-iodothyronine [T3]) are within the reference range. It is often detected

incidentally, although some people may have symptoms of hypothyroidism or hyperthyroidism. The prevalence of subclinical thyrotoxicosis is 0.5 to 10% and that of subclinical hypothyroidism is 4 to 20%; these wide ranges reflect differences in the studied populations. Data on the long-term consequences of subclinical thyroid dysfunction largely come from people over 65. They indicate increased cardiovascular morbidity and mortality, an increased risk of osteoporosis and potential links to dementia.

Current practice

This guideline covers investigating all suspected thyroid dysfunction and managing primary thyroid disease (related to the thyroid rather than the pituitary gland). There is variation in how thyroid disease is investigated and managed in primary and secondary care. There are currently no standardised diagnostic or referral criteria in the UK to guide decision making in primary care for people with structural thyroid abnormalities or enlargement. In secondary care, there is significant variation in the types of diagnostic tests and imaging used, as well as in surgical and non-surgical management and follow-up protocols. Standardisation in thyroid hormone replacement strategies for people with hypothyroidism is currently lacking. In addition, guidance on optimal treatment and follow-up strategies is needed for managing thyrotoxicosis, which is usually done by shared care between primary and secondary care. Opinions regarding the need to treat subclinical thyroid dysfunction, especially in older people, vary widely.

This guideline also aims to improve the diagnosis, management and follow-up of non-malignant thyroid enlargement associated with normal thyroid function.

Finding more information and resources

You can see everything NICE says on thyroid disease in our interactive flowchart on thyroid disease.

To find out what NICE has said on topics related to this guideline, see our web page on thyroid disorders.

For full details of the evidence and the guideline committee's discussions, see the evidence reviews. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting NICE guidelines into practice, see resources to help you put guidance into practice.

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