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# Thyroid function disorders - Guidelines of the Netherlands Association of Internal Medicine

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## ABSTRACT

Thyroid function disorders are common with a female to male ratio of 4 to 1. In adult women primary hypothyroidism and thyrotoxicosis have a prevalence of 3.5/1000 and 0.8/1000, respectively. This guideline is aimed at secondary care providers especially internists, but also contains relevant information for interested general practitioners and gynaecologists. A multidisciplinary working group, containing delegates of professional and patient organisations, prepared the guideline. According to principles of 'evidence-based medicine' available literature was studied and discussed. Considering the availability and quality of published studies a practical advice was formulated. For a full overview of the literature and considerations the reader is referred to the original version of the guideline (accessible through NIV-net). In this manuscript we have aimed to provide the practicing internist with practical and 'as evidence-based as possible' treatment guidelines with respect to thyroid function disorders.

## KEYWORDS

Hyperthyroidism, hypothyroidism, thyroid function, thyroxine

## INTRODUCTION

Thyroid function disorders are common with a female-to-male ratio of 4 to 1. In adult women primary hypothyroidism and thyrotoxicosis have a prevalence of 3.5/1000 and 0.8/1000, respectively.<sup>1</sup>

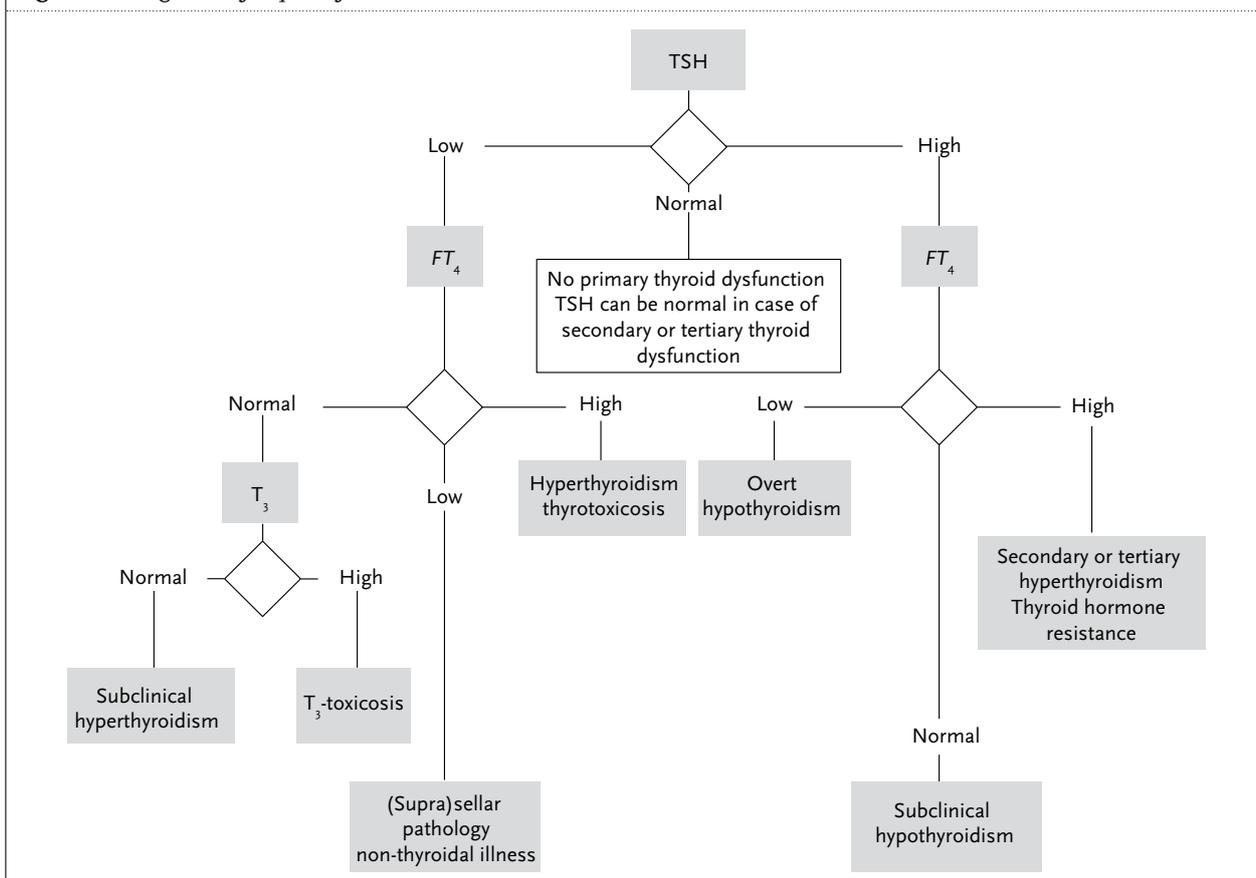
This guideline is aimed at secondary care providers, especially internists but also contains relevant information for interested general practitioners and gynaecologists. A multidisciplinary working group prepared the guideline. The members of the working group were delegates of their respective professional organisations and a delegate of the patient organisations was also a full member of the working group.

According to principles of evidence-based medicine available literature was studied and discussed. Considering the availability and quality of published studies, a practical advice was formulated. For a full overview of the literature and considerations, the reader is referred to the original version of the guideline (accessible through NIV net). In this manuscript we have aimed to provide the practising internist with practical and 'as evidence-based as possible' treatment guidelines with respect to thyroid function disorders.

## DIAGNOSIS OF THYROID FUNCTION DISORDERS

With regard to thyroid *function* disorders determination of the plasma thyroid-stimulating hormone (TSH) level is the single most important measurement.<sup>2</sup> *Figure 1* shows the algorithm for the diagnosis of thyroid function disorders. It is important to recognise that analytical problems can occur, most frequently due to concomitant medication (*table 1*). The algorithm is most useful in an ambulant setting. In case of a serious – nonthyroidal – illness thyroid function measurements are frequently abnormal and normalise during recovery of the underlying illness.<sup>3</sup> Therefore, in patients with (severe) illness, thyroid function should be determined only in cases with a very high index of suspicion.<sup>3</sup>

**Figure 1.** Diagnosis of thyroid function disorders



**Table 1.** Analytical problems due to concomitant medication

Inhibition of TSH secretion	Dopamine, glucocorticoids, somatostatin analogues
Inhibition of T4 secretion	Amiodarone, lithium
Stimulation of T4 secretion	Iodide, amiodarone
Impaired T4 absorption	Biliary salts, iron, antacids, calciumcarbonat, aluminium hydroxyde, sucralfate
Stimulation of TBG synthesis	Oestrogens, opioids
Inhibition of TBG synthesis	Androgens, glucocorticoids
Inhibition of 5' deiodinase	Amiodarone, β-blockers, glucocorticoids
TBG-T4 dissociation	Frusemide, heparin

After a descriptive diagnosis of a thyroid function disorder determination of thyroid autoantibodies or thyroid scintigraphy can be helpful in establishing the exact cause of the thyroid function disorder. This is especially prudent in case of thyrotoxicosis.

## TREATMENT OF THYROTOXICOSIS

There are three main causes of thyrotoxicosis: Graves' disease, toxic uni- or multinodular goitre and thyroiditis.

Available treatment options are medical therapy, radioactive iodine and surgical treatment. Because the preferred treatment differs according to the cause of the thyrotoxicosis, it is important to establish a causal diagnosis. Unless the cause of the thyrotoxicosis is obvious – e.g. in case of severe Graves' orbitopathy – thyroid scintigraphy is thus advised in all cases of thyrotoxicosis.

### How to do it box 1

#### Thyrotoxicosis: treatment options

- Graves' disease: medical, radioactive iodine, surgery<sup>4</sup>
- Toxic nodular goitre: radioactive iodine, surgery<sup>5</sup>
- Destructive thyrotoxicosis (subacute granulomatous thyroiditis, postpartum thyroiditis): wait and see, symptomatic treatment<sup>6</sup>

#### Graves' disease - treatment of thyrotoxicosis

Unless the thyrotoxicosis is very severe or a very large goitre is present, medical therapy is preferred for most patients.<sup>7</sup> Surgery can be especially useful in case of a very large goitre or if severe orbitopathy is present.<sup>8</sup> A high thyrotropin antibody titre is associated with a lower chance of permanent remission.<sup>9,10</sup>

Based upon the available literature propylthiouracil (PTU) and methimazole seem equally effective as antithyroid

drugs and no difference in the incidence of common adverse reactions (rash, arthralgia, gastrointestinal disturbances and altered taste) has been reported.<sup>11-14</sup> However, more severe and uncommon side effects such as hepatitis and ANCA-positive vasculitis are more frequently associated with PTU than with methimazole.<sup>15</sup> Also, methimazole can be dosed once daily improving compliance.<sup>13</sup> It should be noted here that both PTU and methimazole can lead to life-threatening agranulocytosis; therefore, in case of sore throat in combination with fever the use of these drugs should be postponed until agranulocytosis is excluded. Taken together we advise methimazole as antithyroid drug of choice in nonpregnant adults.

A recent meta-analysis concluded that with respect to reaching euthyroidism a block-and-replace (high-dose antithyroid) regimen is as effective as a titration (low-dose antithyroid) regimen.<sup>16</sup> After a treatment period of six to 18 months the relapse rates were 51% after a block-and-replace regimen and 54% after a titration regimen.<sup>16</sup> The incidence of adverse reactions is only marginally higher for block-replace regimens; surprisingly, this was found for minor but not for major adverse reactions.<sup>16</sup> We advise – based upon a more predictable lowering of thyroid hormone levels – a block-and-replace regimen for 12 to 18 months above a titration regimen in the treatment of Graves' disease in nonpregnant adults.

#### How to do it box 2

##### *Graves' disease: medical therapy of thyrotoxicosis*

- Methimazole starting dose 30 mg once daily<sup>15,17,18</sup>
- Check free thyroxine after 4-6 weeks, if in normal range add L-thyroxine full replacement dose
- Adjust L-thyroxine dose on the basis of thyroid function test results every 6-8 weeks. If test on two consecutive visits stable check thyroid function every 3 months
- Stop methimazole and L-thyroxine after 12-18 months<sup>19-22</sup>

A relapse of Graves' disease – after previous medical treatment – should preferably be treated with radioactive iodine.<sup>23</sup> In young patients with no cardiovascular history and a mild thyrotoxicosis, radioactive iodine can be given without previously rendering the patient euthyroid. In elderly patients and in those with a cardiovascular history it is advised to pretreat with antithyroid drugs until euthyroidism is achieved before treatment with radioactive iodine. Methimazole should be stopped three to five days and PTU at least 15 days prior to radioactive iodine treatment.<sup>24-28</sup> After treatment with radioactive iodine, antithyroid drugs should not be restarted within four days after treatment.<sup>29</sup> In order to prevent a worsening of symptoms – due to destruction of thyroid tissue – antithyroid treatment should be continued until at least three months after radioactive iodine treatment.<sup>30</sup> The risk of permanent hypothyroidism depends on the administered radioiodine dose.<sup>31</sup> In about 10% of patients the hypothyroidism that

ensues after treatment with radioactive iodine is transient; therefore, it is advised that this is stopped six months after starting thyroxine supplementation for determination of TSH.<sup>32</sup> Radioactive iodine should be considered as primary therapy for Graves' disease in case of a large goitre or an unusually severe thyrotoxicosis.<sup>7</sup>

#### How to do it box 3

##### *Graves' disease: radioactive iodine treatment*

- In elderly patients and in those with a cardiovascular history pretreat until euthyroidism is achieved
- Stop methimazole 3-5 days and PTU at least 15 days prior to radioactive iodine treatment<sup>24-28</sup>
- In case of post-I<sup>131</sup> hypothyroidism stop thyroxine 6 months after starting in order to diagnose transient post-I<sup>131</sup> hypothyroidism<sup>32</sup>

Surgical therapy for Graves' disease should be considered in case of severe allergic reactions on antithyroid drugs, if malignancy of the thyroid is suspected and if restoration of euthyroidism needs to be achieved very quickly (e.g. in case of severe mechanical complaints).<sup>8</sup> Operative management should consist of subtotal or near total thyroidectomy.<sup>8</sup> Preoperatively, the patient should be rendered euthyroid. Typical complications – depending on the surgeons experience – are hypoparathyroidism and damage to the laryngeal recurrent nerve.<sup>8</sup>

#### How to do it box 4

##### *Graves' disease: preoperative treatment*

- Standard: usual antithyroid therapy until euthyroidism is restored (see box 2)
- Allergic to antithyroid drugs:
  - $\beta$ -blocker until heart rate during exercise  $<80$  /min: propranolol 80-240 mg daily
  - Iodide: start 10-14 days preoperatively: KI 50-250 mg thrice daily (1-5 drops solutio iodi spirituosae) or solutio iodi aquosa (Lugol's solution) 0.1-0.3 ml thrice daily (3-5 drops)

#### Graves' disease - treatment of orbitopathy

Graves' orbitopathy (GO) is associated with hyperthyroidism in 87% of patients.<sup>33</sup> Three percent of patients with GO are hypothyroid and 10% are euthyroid. TSH-receptor antibodies are usually present and hyperthyroidism develops in about 25% within years.<sup>33</sup> In those with hyperthyroidism GO presents before thyrotoxicosis in 20%, during thyrotoxicosis in 40% and after thyrotoxicosis in 40%.<sup>33</sup> Conversely, of all patients with Graves' thyrotoxicosis only 5 to 15% develop serious GO and 30 to 40% mild GO.<sup>33</sup> GO is usually bilateral; however, in 15% the orbitopathy is unilateral. Indeed, GO is the most prevalent cause of unilateral exophthalmos.<sup>33</sup> In patients with GO quality of life is severely impaired.<sup>34,35</sup> Restoration of euthyroidism generally leads to improvement of GO.<sup>36,37</sup> Considering the effects on GO, medical and

surgical treatment of the thyrotoxicosis are equally safe; radioactive iodine treatment, however, may exacerbate GO in 15% of patients.<sup>38,39</sup> Such exacerbation occurs in the first few months after <sup>131</sup>I treatment; fortunately, in two-thirds of patients eye symptoms are mild and transient. Steroids can prevent exacerbation of GO after radioactive iodine treatment and is advised in patients with pre-existent active GO, serious thyrotoxicosis (TT<sub>3</sub> >5 nmol/l), high TSH-receptor antibody titres and smokers.<sup>38,40,41</sup>

#### How to do it box 5

*Graves' disease: radioactive iodine treatment – preventive treatment with steroids*

- Week 1-4: Prednisone 30 mg once daily
- Week 5-8: Prednisone 20 mg once daily
- Week 9-12: taper prednisone with 5 mg weekly

With respect to lifestyle, all patients with GO should be advised to quit smoking as this is associated with – more severe – GO and treatment failure.<sup>38,42,43</sup>

In order to further tailor immunosuppressive and surgical treatment, it is important to classify the severity and activity of GO. To this aim use of the clinical activity and NO-SPECS score is advised. For practical guidance and visual support see [www.eugogo.org](http://www.eugogo.org).

#### How to do it box 6

*GO activity: Clinical Activity Score (amended from Mourits et al. Br J Ophthalmol 1989;73:639-4)*

- Spontaneous orbital pain
- Gaze evoked orbital pain
- Eyelid swelling that is considered to be due to active (inflammatory phase) GO
- Eyelid erythema
- Conjunctival redness that is considered to be due to active (inflammatory phase) GO (ignore 'equivocal' redness)
- Chemosis
- Inflammation of caruncle or plica
- Increase of  $\geq 2$  mm in proptosis
- Decrease in uniocular excursion in any one direction of  $\geq 8^\circ$
- Decrease of acuity equivalent to 1 Snellen line

#### How to do it box 7

*GO severity: NO SPECS score*

0. No symptoms or signs of GO
1. Only signs, no symptoms
2. Soft tissue involvement (aperture in mm)
3. Proptosis (Hertel in mm)
4. Extraocular muscle involvement (motility, double vision)
5. Corneal involvement
6. Sight loss (visual acuity, colour vision)

Mild GO can be treated with retrobulbar radiotherapy. This is especially effective in pain control and improving motility but has no effect on proptosis.<sup>44,45</sup> GO of intermediate severity can be treated with immunosuppressants (preferably with intravenous steroids).<sup>44,45</sup> Severe GO characterised by optical neuropathy and corneal ulceration represents the most severe manifestation of GO and should be treated with either high-dose steroids or orbital decompressive surgery.<sup>44,45</sup> It is strongly advised to refer patients in whom immunosuppressive or orbital decompression surgery is contemplated to specialist centres.

#### Iodine-induced thyrotoxicosis

Iodine excess can lead to thyrotoxicosis. Iodine intake in the Netherlands is adequate (i.e. 150 to 300  $\mu\text{g}/\text{day}$ ).<sup>46</sup> In vulnerable people such as those with a history of Graves' disease or with nodular goitre, excess iodine can lead to thyrotoxicosis: iodine-induced thyrotoxicosis (IIT).<sup>47</sup> Common sources of excess iodine are: iodine-containing radiographic contrast agents, amiodarone, kelp, iodine-containing multivitamins and large quantities of Japanese food.<sup>47</sup> IIT due to iodine-containing radiographic contrast agents and amiodarone will be discussed in more detail.

IIT after administration of radiographic contrast agents occurs in 0 to 1.2% of patients without underlying thyroid disease.<sup>48</sup> In patients with an underlying thyroid disorder the incidence is 5.2%.<sup>48-51</sup> Risk factors are higher age, nodular goitre and suppressed TSH.<sup>48</sup> The thyrotoxicosis is usually mild and resolves spontaneously. Prevention is possible with methimazole (20 mg once daily) and sodium perchlorate (300 mg thrice daily).<sup>52-54</sup> Despite treatment thyrotoxicosis is not preventable in all patients and side effects are common.<sup>52,54</sup> Therefore preventive treatment should be considered only in those patients at high risk for serious cardiac arrhythmia.

#### How to do it box 8

*Prevention of contrast agent induced thyrotoxicosis*

Methimazole once daily 20 mg and sodium perchlorate three times daily 300 mg

Amiodarone administration has several effects on parameters of thyroid function. Amiodarone consists for 39.3% of iodine. A dose of 200 to 400 mg daily therefore leads to a substantial iodine excess. Such an excess leads to inhibition of thyroid iodine organification (Wolff-Chaikoff effect) resulting in an increase in TSH (resulting in a TSH of about 5 to 15 mU/l) which – due to escape of Wolff-Chaikoff effect – normalises after approximately three months. Peripheral effects of amiodarone on thyroid hormone metabolism collectively lead to higher T<sub>4</sub> and fT<sub>4</sub> levels while TSH remains normal. During amiodarone use the upper limit of normal for T<sub>4</sub> and fT<sub>4</sub> should be increased by about 25%.

In the Netherlands amiodarone-induced thyrotoxicosis (AIT) occurs in 12.1% of amiodarone-treated patients.<sup>55</sup> The clinical picture shows a wide variety; often the presenting symptom is worsening of cardiac arrhythmia.<sup>56,57</sup> Development of AIT is not associated with cumulative dose. It occurs unpredictably and in a short period of time.<sup>55</sup> There are two types of AIT: type I and type II. As treatment differs it is important to carefully evaluate patients with AIT.

Type I is a thyrotoxicosis with hyperthyroidism occurring in patients with nodular goitre or Graves' disease. Thyroid antibodies are frequently present. As a result of increased thyroid hormone synthesis radioactive iodine uptake can still be increased and the thyroid is hypervascularised.<sup>56</sup> Type II is a destruction-mediated thyrotoxicosis that results from the cytotoxic effect of amiodarone on thyroid follicular cells.<sup>56</sup>

Treatment can be difficult.<sup>56,57</sup> Type I AIT is preferably treated with methimazole 30 mg daily in combination with potassium perchlorate 500 mg twice daily.<sup>56,58</sup> As excess iodine renders methimazole less effective, methimazole alone does not significantly shorten the period of thyrotoxicosis in most patients. It is advised to stop administration of amiodarone if possible; unfortunately most patients are still thyrotoxic six to nine months after discontinuation of amiodarone. Radioactive iodine uptake is sometimes high enough to make radioactive iodine therapy possible. In case of type II AIT the treatment of choice is prednisone: 30 mg daily for two weeks and thereafter tapering to zero in three months.<sup>59</sup> In type II AIT continuation of amiodarone is usually possible.<sup>60</sup> In extremely therapy resistant cases thyroidectomy can be an option.<sup>61</sup>

#### How to do it box 9 Treatment of AIT

- Type I: methimazole 30 mg daily in combination with potassium perchlorate 500 mg twice daily. If possible stop amiodarone
- Type II: prednisone: 30 mg daily for two weeks and thereafter tapering to zero in 3 months. Continuation of amiodarone usually possible

#### Subclinical hyperthyroidism

Subclinical hyperthyroidism is a biochemical diagnosis characterised by suppressed TSH and normal free T<sub>4</sub> and T<sub>3</sub> concentrations.<sup>62</sup> When other causes of suppressed TSH – medication (steroids, dopamine), nonthyroidal illness, (supra) sellar disease – are excluded a suppressed TSH is indicative of a T<sub>4</sub> concentration that is above the individually determined setpoint.

The prevalence of endogenous subclinical hyperthyroidism is 0.7 to 1.9%, of exogenous hyperthyroidism 1.3 to

2.0%.<sup>63,64</sup> Causes are nodular goitre, Graves' disease and thyroiditis.

Subclinical hyperthyroidism is statistically associated with atrial fibrillation: in subjects in the Framingham heart study with a TSH <0.1 the cumulative ten-year incidence for atrial fibrillation was 28% compared with 11% in those with normal TSH levels.<sup>64</sup> These findings were recently confirmed by Capolla *et al.* who found in persons with a TSH <0.4 mU/l during a period of 13 years a twofold increased incidence of atrial fibrillation compared with euthyroid subjects.<sup>65</sup> Besides rhythm disturbances subclinical hyperthyroidism also leads to adverse changes in echocardiographic measurements.<sup>66</sup> In postmenopausal women subclinical hyperthyroidism is associated with osteoporosis.<sup>67</sup> With regard to fractures it can be said that women with a suppressed TSH have a higher fracture incidence than women with a normal TSH.<sup>68</sup> Finally, the risk of dementia seems threefold increased in subclinical hyperthyroidism.<sup>69</sup> However, whether there is an increased mortality in patients with subclinical hyperthyroidism is controversial.

Based on the above it is advised to treat patients with subclinical hyperthyroidism if there are toxic symptoms, atrial fibrillation or osteopenia.<sup>70</sup> Regardless of signs and symptoms it should be considered to treat persons older than 60 years, postmenopausal women especially if TSH is <0.1 mU/l.

#### Thyroiditis

Thyroid inflammation can be caused by physical stimuli, micro-organisms and autoimmunity.<sup>6</sup> Subacute granulomatous thyroiditis and subacute lymphocytic thyroiditis will be discussed here. Postpartum thyroiditis will be reviewed separately.

Subacute granulomatous thyroiditis (Quervain's thyroiditis)<sup>71</sup> has an incidence that is one-fifth to one-eighth of that of Graves' disease and is more common in women.<sup>72,73</sup> It is assumed that it is caused by a virus or by post-viral inflammation.<sup>6</sup> Thyroiditis presents with pain in the thyroid region often radiating to the ear accompanied by muscle pain, fatigue and symptoms of thyrotoxicosis.<sup>74-76</sup> Physical examination reveals a painful goitre.<sup>74,76</sup> In the acute phase the erythrocyte sedimentation rate is elevated (typically >40 mm) with slight anaemia and leucocytosis.<sup>74,77</sup> Thyroid function shows a thyrotoxicosis lasting two to ten weeks that resolves spontaneously.<sup>74,77,78</sup> The thyrotoxicosis is destruction mediated and is therefore self-limiting, treatment is symptomatic with aspirin (600 mg three to six times daily) and  $\beta$ -blockers.<sup>74,77,79</sup> In rare cases treatment with steroids (one week of prednisone 40 mg daily, then 30 mg to be tapered by 5 mg weekly) is needed to control pain.<sup>77,80</sup> There is no increased risk for development of permanent overt hypothyroidism.<sup>6</sup>

### How to do it box 10

#### *Symptomatic treatment of subacute granulomatous thyroiditis*

- Aspirin 600 mg three to six times daily
- $\beta$ -blockers e.g. propranolol 40-120 mg or atenolol 25-50 mg daily

Subacute lymphocytic thyroiditis and postpartum thyroiditis are generally considered to be variants of Hashimoto's thyroiditis.<sup>6</sup> It is an autoimmune destructive thyrotoxicosis.<sup>6</sup> Contrary to subacute granulomatous thyroiditis it is painless and classically has a biphasic course: a thyrotoxicosis followed by a hypothyroid period.<sup>6</sup> As in subacute granulomatous thyroiditis the thyrotoxic phase is destruction mediated and self-limiting.<sup>6</sup> However, unlike subacute granulomatous thyroiditis permanent hypothyroidism develops in 6%. Importantly, hypothyroidism can develop after a prolonged period of euthyroidism. Therefore, yearly assessment of thyroid function is advised.<sup>6</sup>

## TREATMENT OF PRIMARY HYPOTHYROIDISM

### Primary overt hypothyroidism

Primary hypothyroidism is caused by a thyroid disorder and biochemically characterised by an elevated TSH and a lowered fT<sub>4</sub>.<sup>81</sup> Symptoms are usually vague and nonspecific, frequently occurring symptoms are cold intolerance, constipation, dry skin, low heart rate, hoarse voice and impaired mental performance.<sup>82</sup> In its most extreme form heart failure and coma can occur.<sup>82</sup> In children hypothyroidism can cause mental retardation; indeed, worldwide hypothyroidism caused by iodine deficiency is the single most prevalent cause of mental retardation.<sup>83</sup>

The prevalence of hypothyroidism is 0.3 to 0.4%, increasing with age and with a female predominance.<sup>63,84,85</sup> Usually it is on autoimmune basis. Other causes are iatrogenic (after previous treatment for hyperthyroidism), medication (amiodarone, lithium) and congenital.<sup>82,86</sup> Worldwide, iodine deficiency is by far the most prevalent cause of hypothyroidism.<sup>82</sup>

Treatment is substituting the deficient hormone, i.e. L-thyroxine.<sup>82,87</sup> Dose is dependent on underlying cause and weight, around 1.8  $\mu$ g/kg for autoimmune hypothyroidism and about 2.0  $\mu$ g/kg after (near) total thyroidectomy.<sup>82</sup> However, interindividual variance is large. In young and healthy patients full-dose substitution can be given at once.<sup>82</sup> However, in the elderly (arbitrarily defined as >60 years) and those with cardiovascular morbidity it is advised to start more slowly (25  $\mu$ g with dose adjustments based on TSH every four to six weeks). Importantly, there are no differences in quality of life between a fast and slow titration schedule.<sup>88</sup>

Thyroid hormone dose is adjusted on the basis of TSH – not fT<sub>4</sub> – aiming for a TSH in the normal range.<sup>87</sup> L-thyroxine should be taken either in the morning on an empty stomach or in the evening at bedtime, in the last instance the required dose to reach euthyroidism is generally lower.<sup>89</sup>

Several drugs such as biliary salts, iron, antacids, calcium carbonate, aluminium hydroxide and sucralfate interfere with thyroxine uptake.<sup>90-95</sup> It is advised to take these medications two to four hours apart from thyroxine. Phenytoin, carbamazepine, fenobarbital and rifampicin lead to an increased clearance of thyroxine, thus the need for thyroxine increases.<sup>96-99</sup>

### Persistent symptoms after biochemically optimal substitution: T<sub>4</sub>/T<sub>3</sub> combination therapy

A substantial number of treated patients have persistent symptoms despite biochemically optimal substitution.<sup>100,101</sup> Possibly this is because of a lack of T<sub>3</sub> produced by the thyroid.<sup>82</sup>

In a recent meta-analysis of 11 studies with a total of 1216 randomised patients no significant differences with respect to body pain, depression, fear, quality of life and lipids were noted between T<sub>4</sub>/T<sub>3</sub> combination therapy and T<sub>4</sub> therapy.<sup>102</sup> In a large Dutch study patients preferred T<sub>4</sub>/T<sub>3</sub> combination therapy in a 5:1 ratio.<sup>103</sup> Surprisingly this preference was not reflected in a battery of neurocognitive tests. What was related to this patient preference was weight loss. In the dose the patients preferred (T<sub>4</sub>/T<sub>3</sub> in a ratio 5:1) 51% of the patients had a suppressed TSH, a higher heart rate and elevated bone markers. Based on the above T<sub>4</sub>/T<sub>3</sub> combination therapy is not advised as standard therapy for primary hypothyroidism.<sup>103</sup>

In case of persistent symptoms after biochemically optimal substitution it is reasonable – albeit not supported by evidence – to increase the substitution dose until the TSH is low normal. Also, it is important to exclude other diseases that are associated with primary – autoimmune – hypothyroidism, such as type I diabetes mellitus, adrenal insufficiency, vitamin B<sub>12</sub> deficiency and celiac disease.

### How to do it box 11

#### *Treatment of primary hypothyroidism*

- Young and healthy patients: L-thyroxine full dose substitution: 1.8  $\mu$ g/kg for autoimmune hypothyroidism and about 2.0  $\mu$ g/kg after (near) total thyroidectomy
- Elderly (arbitrarily defined as >60 years) patients and those with cardiovascular morbidity: titrate more slowly: 25-50  $\mu$ g starting dose
- Dose adjustments based on TSH every 4-6 weeks, aim for TSH in normal range
- When stable check TSH once yearly
- In case of persistent symptoms titrate TSH to low normal levels, exclude diseases that are associated with autoimmune hypothyroidism

### Subclinical hypothyroidism

Subclinical hypothyroidism is defined as the situation in which TSH is elevated and fT<sub>4</sub> is normal.<sup>70</sup> Alternative causes for such a biochemical profile are nonthyroidal illness, recovery from thyroiditis and treatment with recombinant TSH.<sup>104</sup> The prevalence varies between 4 and 8.5%.<sup>70</sup>

The risk for development of overt hypothyroidism is positively associated with TSH and the presence of TPO antibodies. If TSH is <6.0 mU/l the cumulative risk for development of overt hypothyroidism is close to zero, if TSH is between 6 and 12 mU/l this is 42.8%, and with a TSH >12 mU/l the cumulative incidence of overt hypothyroidism is 76.9%.<sup>105</sup> The presence of TPO antibodies can add in assessing the risk for development of overt hypothyroidism, especially if the TSH is between 6 and 12 mU/l; in this range the risk for development of overt hypothyroidism increases by 80%.<sup>105</sup> Outside this range the risk for development of overt hypothyroidism increases by 40%.<sup>105</sup>

There is one study on cardiovascular morbidity and mortality that shows no increased cardiovascular risk in patients with subclinical hypothyroidism followed for 20 years.<sup>106</sup> However, two recent meta-analyses did show that subclinical hypothyroidism is associated with coronary heart disease.<sup>107,108</sup>

Unfortunately there are no intervention studies of sufficient quality that show a positive effect of treatment.<sup>109-113</sup> Despite this shortcoming it seems defensible to start a trial of treatment of at least three months in case of otherwise unexplained fatigue or cognitive dysfunction in patients with subclinical hypothyroidism. It should be noted that in those older than 85 years the presence of subclinical hypothyroidism is associated with a lower mortality.<sup>114</sup>

### Lithium-induced hypothyroidism

In about 50% of lithium-treated subjects a goitre develops.<sup>115-118</sup> This is most likely caused by elevated TSH levels as subclinical and overt hypothyroidism are seen in 20 to 30% and 4.4% of cases respectively.<sup>66,115,119</sup> Therefore, in case of lithium use we advise checking TSH every six to twelve months;<sup>119</sup> and – in order to prevent goitre formation – prescribe thyroxine if the TSH is >4.0 mU/l.

## THYROID DYSFUNCTION DURING PREGNANCY AND POSTPARTUM

During pregnancy maternal thyroid hormone metabolism changes considerably.<sup>120</sup> There is an increase in iodine demand due to placental transport to the foetus.<sup>83</sup> Daily iodine intake during pregnancy and lactation should therefore be at least 250 µg.<sup>83</sup>

Under the influence of oestrogen, thyroxine-binding globulin (TBG) levels increase considerably; this leads to an increase in TT<sub>4</sub> and TT<sub>3</sub> concentrations.<sup>120</sup> In the first trimester hCG levels rise sharply and – due to the structural homology of hCG and TSH and their respective receptors – lead to a lowering of TSH (<0.4 mU/l in 10% of pregnancies).<sup>120</sup> Also, there is considerable placental thyroxine transport which adds to the increased thyroid hormone requirement during pregnancy.<sup>120</sup>

As the foetal pituitary-thyroid axis becomes functional around week 12 of gestation it follows that before this period the foetus is completely dependent upon maternal supply of thyroid hormone.<sup>121</sup>

Hyperthyroidism during pregnancy is most often due to gestational transient hyperthyroxinaemia. This occurs in 2 to 3% of European women and in 11% of Asian women. Graves' disease is seen in 0.01 to 0.02% of pregnancies.<sup>122</sup> As untreated or poorly treated hyperthyroidism is associated with obstetric complications (miscarriage, low birth weight, (pre)-eclampsia and possibly congenital malformations) and – in case of Graves' disease – with foetal and neonatal thyrotoxicosis adequate diagnosis and treatment are essential.<sup>123-126</sup>

Gestational transient hyperthyroidism occurs in the first trimester and is associated with hyperemesis in 50% of cases.<sup>127,128</sup> Women with gestational transient hyperthyroidism usually have no goitre, lack signs of thyroid eye disease and TSH receptor antibodies (TRAb) are negative. The thyrotoxicosis is usually mild, and resolves spontaneously by week 18 in most cases.<sup>127,128</sup>

Graves' disease should be suspected in the presence of a diffuse goitre, ophthalmopathy, thyroid dermopathy and the presence of TRAb. In women with known Graves' disease who are contemplating pregnancy the disease should preferably be treated by thyroid ablation either with radioactive iodine or surgery before pregnancy. It should be noted that for six months after radioiodine treatment pregnancy is contraindicated and euthyroidism is not always restored after one treatment.

Graves' disease diagnosed during pregnancy should be treated medically. Medical treatment of Graves' disease during pregnancy consists of monotherapy with antithyroid drugs in the lowest possible dose to achieve a fT<sub>4</sub> concentration in the high normal range.<sup>120</sup> Because there are reports linking methimazole use with aplasia cutis, choanal atresia and oesophagus atresia there is a preference for the use of PTU.<sup>129,130</sup> It is advised to perform thyroid function tests every six to eight weeks.<sup>120</sup> Often it is possible to stop treatment in the third trimester.<sup>120</sup> In exceptionally resistant cases thyroidectomy should be considered in the second trimester. During lactation it is safe to use methimazole (<20 mg daily) or PTU (<300 mg daily).

The risk of foetal and neonatal thyrotoxicosis can and should be assessed by the measurement of maternal serum TRAb.<sup>131</sup> It is advised to measure these antibodies in all women with (a history of) Graves' disease. This is especially relevant in women rendered hypothyroid as a result of ablative therapy for Graves' disease.<sup>131</sup> TRAb can be measured in the first or second trimester and if positive should be measured again in the third trimester.<sup>131</sup> If TSH-receptor antibodies are present in the third trimester adequate monitoring for foetal thyrotoxicosis is mandatory.<sup>131</sup>

Relevant literature suggests that even relatively mild and often unrecognised maternal hypothyroxinaemia (i.e. low fT<sub>4</sub> and normal TSH) is associated with significant and persistent impairment of neuropsychological performance in the offspring.<sup>132,133</sup> Unfortunately there are no prospective studies available on the effects of thyroxine supplementation regarding the long-term neurodevelopment of the infant. Moreover, determining free thyroxine levels in pregnancy has serious analytical shortcomings.<sup>120</sup> So, it is at present unclear how to proceed when the fT<sub>4</sub> is low but TSH is normal.

In case of an elevated TSH – i.e. >4.0 mU/l – a significantly increased rate of obstetrical complications has been described.<sup>134,135</sup> Therefore, it is advised to treat subclinical hypothyroidism (TSH >4.0 mU/l) in pregnancy. Whether in case of otherwise unexplained infertility or habitual abortion, treatment of subclinical hypothyroidism has favourable results is unknown. However, based on the above it seems reasonable at least to consider thyroxine treatment.

Overt hypothyroidism (raised serum TSH and decreased free thyroxine) diagnosed during pregnancy should be immediately treated with full replacement doses of T<sub>4</sub>.<sup>120</sup> In women preconceptionally treated, T<sub>4</sub> requirements during pregnancy increase on average by 50%.<sup>120,136</sup> Women with subclinical hypothyroidism should be advised to have thyroid function tests as soon as they have a positive pregnancy test. Women who are already using thyroxine should be instructed to increase their dosage by 30%; thereafter, dosage should be adjusted based upon thyroid function tests.<sup>136,137</sup> As in the treatment of hyperthyroidism it is advised to perform thyroid function tests every six to eight weeks aiming for a TSH between 1 and 2 mU/l.<sup>136,137</sup>

#### How to do it box 12

##### *Treatment of Graves' disease during pregnancy*

- Monotherapy with PTU in the lowest possible dose
- Aim for a normal TSH and a fT<sub>4</sub> concentration in the high normal range
- Adjust dose every 4-6 weeks
- Check TSH-receptor antibodies in mother

#### How to do it box 13

##### *Treatment of hypothyroidism during pregnancy*

- In pregnancy treat subclinical hypothyroidism (TSH cut-off >4.0 mU/l)
- Treat overt hypothyroidism diagnosed during pregnancy immediately with full replacement doses of T<sub>4</sub>
- If hypothyroid preconceptionally: instruct to increase dosage by 30% if pregnancy is diagnosed
- Aim for a normal TSH and a fT<sub>4</sub> concentration in the high normal range
- Adjust dose every 4-6 weeks

## POSTPARTUM THYROIDITIS

Postpartum thyroiditis is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery, based on an autoimmune inflammation of the thyroid.<sup>138</sup> In the Netherlands the incidence is reported from 5.2 to 7.2%.<sup>138</sup> Postpartum thyroiditis classically runs a biphasic course: a thyrotoxic phase is followed by a hypothyroid phase. 'Postpartum' thyroiditis can also occur after loss of pregnancy at 5-20 weeks gestation.<sup>138</sup>

The thyrotoxic phase of postpartum thyroiditis is due to leakage of thyroid hormones from destroyed thyrocytes and is therefore self-limiting. The most important differential diagnosis is Graves' disease, thus a thyroid scintigraphy or determination of TSH-receptor antibodies is advised.<sup>138</sup> The hypothyroid phase, developing approximately four to eight months postpartum and usually lasting four to six months, is clinically more important.<sup>138</sup> After a period of postpartum thyroiditis permanent hypothyroidism occurs in 12 to 61%. This can also occur after a previous period of euthyroidism, so yearly TSH determination is advised in all women after a period of postpartum thyroiditis.<sup>138</sup>

## THYROID EMERGENCIES

### Thyrotoxic crisis

Thyrotoxic crisis is a clinical syndrome characterised by a life-threatening thyrotoxicosis. Critical for diagnosis is a high level of clinical suspicion. Burch and Wartofsky have proposed a scheme that can facilitate diagnosis. Tachycardia, fever, gastrointestinal dysfunction and central nervous system dysfunction are the most prominent features.<sup>139</sup>

Mortality is high (10 to 75%) and therefore treatment should be instituted immediately in an intensive care unit.<sup>139,140</sup> Treatment should be supportive and thyroid-specific. Supportive treatment consists of correction of hyperpyrexia with acetaminophen (aspirin can elevate T<sub>4</sub> and T<sub>3</sub> levels), cardiovascular support, treatment of infection and other underlying/precipitating conditions.<sup>139,140</sup>

Thyroid-specific treatment is aimed at reducing thyroid hormone production and action. Thyroid hormone synthesis is blocked by antithyroid drugs; both PTU and methimazole can be used (PTU 200 to 250 mg every four hours or methimazole 30 mg every six hours).<sup>139,140</sup> Thyroid hormone release is inhibited by iodine: Lugol's solution 10 to 15 drops every eight hours or sodium iodide or potassium iodide which can be given intravenously 0.5 to 1 gram every 12 hours.<sup>139,140</sup> In order to prevent iodine from being used as a substrate for thyroid hormone synthesis it should be given at least one hour after the first dose of antithyroid drugs.<sup>139,140</sup> Inhibition of peripheral T<sub>4</sub> to T<sub>3</sub> conversion is produced by giving high-dose intravenous glucocorticoids, e.g. hydrocortisone 200 to 300 mg as a loading dose followed by 100 mg every eight hours.<sup>139,140</sup> Blocking the effects of T<sub>4</sub> and T<sub>3</sub> on peripheral tissues is achieved by  $\beta$ -blockers; propranolol is the classic drug for this indication: 0.5 to 1.0 mg intravenously in ten minutes followed by 1 to 3 mg every hour until concomitantly administered oral propranolol (60 to 80 mg every six to eight hours) is effective.<sup>139,140</sup>

#### How to do it box 14

##### *Treatment of thyrotoxic crisis*

- Block thyroid hormone synthesis: PTU: 200 to 250 mg every 4 hours or methimazole 30 mg every 6 hours
- Inhibit thyroid hormone release – only after administration of antithyroid drugs: Lugol's solution 10 to 15 drops every 8 hours or sodium iodide or potassium iodide intravenously 0.5 to 1 gram every 12 hours
- Inhibit T<sub>4</sub> to T<sub>3</sub> conversion: glucocorticoids, e.g. hydrocortisone 200 to 300 mg as a loading dose followed by 100 mg every 8 hours
- Block the effects of T<sub>4</sub> and T<sub>3</sub> on peripheral tissues:  $\beta$ -blockers, e.g. propranolol: 0.5-1.0 mg intravenously in 10 minutes followed by 1-3 mg every hour until concomitantly administered oral propranolol (60-80 mg every 4 to 6 hours) is effective

#### Myxoedema coma

Myxoedema coma is a severe state of hypothyroidism that presents with altered mental status, respiratory insufficiency and hypothermia besides other common

hypothyroid symptoms.<sup>141</sup> It is commonly precipitated by an acute event (e.g. infection, myocardial infarction, hypothermia, sedatives) on the background of a long-standing untreated – or insufficiently treated – hypothyroidism.<sup>141</sup> Laboratory investigation shows hyponatraemia, anaemia, hypoglycaemia, hypercholesterolemia, elevated LDH and creatinine kinase.<sup>141</sup> If secondary hypothyroidism is suspected hydrocortisone should also be given.<sup>141</sup> However, to establish the diagnosis determination of TSH and fT<sub>4</sub> are essential; in this respect it is important to be aware that TSH levels can be only slightly elevated as a result of nonthyroidal illness. Treatment should take place in an intensive care unit.<sup>141</sup> Thyroid hormone substitution should not be delayed until results of thyroid function tests are known. We advise supplementation of T<sub>4</sub> and T<sub>3</sub>. T<sub>4</sub>: a loading dose of 200 to 250  $\mu$ g intravenously followed by 100  $\mu$ g after 24 hours and thereafter 50  $\mu$ g daily (preferably oral otherwise intravenously). T<sub>3</sub>: 10  $\mu$ g every eight hours until normalisation of vital function.

#### How to do it box 15

##### *Treatment of myxoedema coma*

- T<sub>4</sub>: a loading dose of 200 to 250  $\mu$ g intravenously followed by 100  $\mu$ g after 24 hours and thereafter 50  $\mu$ g daily preferably orally
- T<sub>3</sub>: 10  $\mu$ g every 8 hours until normalisation of vital functions

#### NOTE

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