

UK Guidelines for the Use of Thyroid Function Tests



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Contents

Guidelines development group	4
Notes on the development and use of the guidelines	5
Types of evidence and the grading of recommendations	7
Abbreviations	8
Presentation conventions	9
Acknowledgements	10
1. Introduction	
1.1 Thyroid disease	11
1.2 Thyroid function tests	11
1.3 The patient perspective	11
1.4 The physician perspective	12
1.5 The laboratory perspective	12
1.6 The need for national guidelines	12
2. Indications for thyroid function testing	
2.1 Introduction	15
2.2 Screening for thyroid dysfunction	15
2.2 Surveillance of thyroid function	20
2.3 Monitoring of thyroid function	22
3. Hypothyroidism	
3.1 Primary hypothyroidism	24
3.2 Subclinical (mild) hypothyroidism	27
3.3 Secondary hypothyroidism	28
3.4 Congenital hypothyroidism	30
4. Hyperthyroidism	
4.1 Primary hyperthyroidism	32
4.2 Subclinical (mild) hyperthyroidism	36
4.3 Inappropriate TSH	37
5. Thyroid function in pregnancy	
5.1 Introduction	39
5.2 Hypothyroidism	39
5.3 Hyperthyroidism	40
5.4 Post-partum thyroiditis	42
5.5 Screening for thyroid disease during pregnancy	42
5.6 Neonatal thyroid assessment	43
6. Thyroid function testing in thyroid cancer	
6.1 Introduction	46
6.2 Differentiated thyroid cancer	46
6.3 Medullary thyroid cancer	49
6.4 Anaplastic thyroid cancer	51

Contents (continued)

7. Laboratory aspects of thyroid function testing	
7.1 Introduction	52
7.2 Biochemical investigations for thyroid function	52
7.3 Tests to establish if there is thyroid dysfunction	52
7.4 Selective use of thyroid function tests	54
7.5 Reference ranges	55
7.6 Quality control and quality assurance	56
7.7 Interpreting results of thyroid function tests	57
7.8 Follow-up of unusual test results	61
7.9 Laboratory tests used to determine the cause of thyroid dysfunction	61
7.10 Recommended protocol for determining functional sensitivity	66
7.11 Drugs that alter thyroid hormone synthesis, secretion & metabolism	66
8. Areas for further studies	68
Appendix 1 References	69

Use of thyroid function tests: guidelines development group

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Notes on the development and use of the guidelines

The guidelines development group

The Use of Thyroid Function Tests Guidelines Development Group was formed in 2002 under the auspices of the Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF).

Purpose of the guidelines

It is hoped that the document will provide guidance for primary care physicians, specialist physicians, endocrinologists, and clinical biochemists. The accompanying patient information sets have been especially designed to explain thyroid function testing and to summarise the main recommendations in the guidelines in everyday language. The purpose of the guidelines is to encourage a greater understanding of thyroid function testing amongst all stakeholders with a view to the widespread adoption of harmonised good practice in the diagnosis and management of patients with thyroid disorders. The guidelines are also intended to provide a basis for local and national audit and each section offers recommendations that are suitable for the audit process.

The document should be considered as guidelines only; it is not intended to serve as a standard of medical care. The doctors concerned must make the management plan for an individual patient. The focus of the document is thyroid function testing, and it is not intended to be a comprehensive text on thyroid disorders.

The process of development

The guideline development group met on several occasions. It was agreed to adopt the literature review accompanying the 2002 publication of The National Academy of Clinical Biochemistry entitled 'Laboratory support for the Diagnosis and Monitoring of Thyroid Disease' and to supplement this with publications occurring during and after 2001. Subgroups took responsibility for individual chapters and the whole group considered each draft. Patient representatives were full members of the development group throughout the development process.

After completion by the development group, the guidelines were subjected to external refereeing by individuals with a range of interests, including patients, GP's, physicians and laboratory specialists in district general hospitals and teaching centres as well as international experts. In addition the draft guidelines were posted on the websites of the ACB and BTA, with appropriate links, for a limited period, during which comments were invited and received. Subsequent to this the development group reviewed the comments and recommendations and appropriate revisions were made. All members of the group approved the guidelines.

Mechanism for updating

The guidelines were completed in June 2006. Comments on their accuracy and relevance are invited during the first year after publication and should be directed to gbeastall@gri-biochem.org.uk. It is intended that a full review will take place after three years.

Additional information

The format and style of the guidelines has been modelled on the complementary document entitled 'Guidelines for the Management of Thyroid Cancer in Adults', which was published in 2002 by The Royal College of Physicians.

The British Thyroid Foundation funded the project. No declarations of interest were received from any of the professional members of the development group.

These guidelines and the accompanying patient information sets may be downloaded from the ACB and BTA websites:

www.acb.org.uk

www.british-thyroid-association.org

Types of evidence and the grading of recommendations

The definition of types of evidence and the grading of recommendations used in the guidelines follows that of the Agency for Health Care Policy and Research (AHCPR), as set out below:

Type of evidence (based on AHCPR, 1992)

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of recommendations (based on AHRQ, 1994)

Grade	Evidence levels	Description
A	Ia, Ib	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B	IIa, IIb, III	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C	IV	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality
✓		Good practice point recommended by guideline development group

Abbreviations

AACE	American Association of Clinical Endocrinologists
ACB	Association for Clinical Biochemistry
ACTH	Adrenocorticotrophic hormone
AHRQ	Agency for Healthcare Research and Quality
ATA	American Thyroid Association
BTA	British Thyroid Association
BTF	British Thyroid Foundation
EQA	External quality assessment
FSH	Follicle stimulating hormone
FT4	Free thyroxine
FT3	Free tri-iodothyronine
GP	General practitioner
HAMA	Human anti-mouse antibody
HDU	High dependency unit
IMA	Immunometric assay
IQC	Internal quality control
ITU	Intensive therapy unit
LH	Luteinising hormone
MDL	Minimum detection limit
MTC	Medullary thyroid cancer
mU/L	Milliunits per litre
NACB	National Academy of Clinical Biochemistry
nmol/L	Nanomoles per litre
NTI	Non-thyroidal illness
pmol/L	Picomoles per litre
PRL	Prolactin
PTU	Propylthiouracil
rhTSH	Recombinant human TSH
RCP	Royal College of Physicians
RIA	Radioimmunoassay
SHBG	Sex hormone binding globulin
T4	Thyroxine, levothyroxine
T3	Tri-iodothyronine
TFT	Thyroid function tests
Tg	Thyroglobulin
TgAb	Thyroglobulin antibodies
TPOAb	Thyroid peroxidase antibodies
TSH	Thyroid stimulating hormone, thyrotrophin
TSHoma	TSH secreting pituitary adenoma
TSH-RAb	TSH receptor antibodies
TT4	Total thyroxine
TT3	Total tri-iodothyronine
UK NEQAS	UK National External Quality Assessment Schemes
µg	Microgram
WHO	World Health Organisation

Presentation Conventions

Convention for describing type of evidence and grade of recommendation

- The AHCPR level of evidence is included both in the main text and in the recommendations of Chapters 2-7 as bold roman numerals I – IV in parentheses. E.g. **(III)**.
- All recommendations in the guidelines are presented as bullet points with italic text. At the end of each recommendation the AHCPR level of evidence is included and the corresponding grade of recommendation is included as a bold capital letter A-C in parentheses. E.g. **(III,B)**

Convention for describing thyroxine and tri-iodothyronine

- Whenever the text refers to the administration of thyroid hormone replacement therapy the full words thyroxine and tri-iodothyronine are used.
- Whenever the text refers to the hormones synthesised and secreted by the thyroid gland the abbreviations T4 and T3 are used to describe thyroxine and tri-iodothyronine, respectively.
- Whenever the text refers to the measurement of thyroxine in serum or other body fluids the term FT4 has been adopted. In general this term is intended to signify that the form of hormone being measured is either free T4 (FT4) or total T4 (TT4); wherever this is not the case the text refers to the measurement of the specific form of thyroxine. In 2006, UK NEQAS returns indicate that the large majority of UK laboratories measure FT4 in preference to TT4.
- For the sake of consistency the term FT3 has been adopted to describe the measurement of either free tri-iodothyronine (FT3) or total tri-iodothyronine (TT3) in serum or other body fluids; wherever this is not the case the text refers to the measurement of the specific form of tri-iodothyronine. In 2006, UK NEQAS returns indicate that roughly equal numbers of UK laboratories measure FT3 and TT3.

Convention for recording numerical data

- At several points in the text numerical results are presented (e.g. ‘a TSH level of >10mU/L). These numerical results should be regarded as typical target figures rather than as absolute cut-offs. The historical nature of some of the evidence base together with uncertainty of the bias of the assays used in the older studies means that absolute cut-offs cannot be presented. Individual laboratories should use external quality assessment and other data to determine if bias-related cut-offs are appropriate for the methods that they use. However, in most cases it is unlikely that laboratories will have sufficient data to achieve an accurate adjustment of the TSH cut-offs quoted in these guidelines.

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- The Association for Clinical Biochemistry for hosting the meetings of the guidelines development group
- The Executive Committee of the British Thyroid Association for helpful comments during the formulation of the guidelines
- The individuals behind the 33 responses that were received as a result of the consultation exercise

1. Introduction

1.1 Thyroid disorders

Thyroid disorders are amongst the most prevalent of medical conditions, especially in women. Disorders of the thyroid include both overt and mild/subclinical hypothyroidism and hyperthyroidism, goitre and thyroid cancer.

Hypothyroidism is an insidious condition with significant morbidity and the subtle and non-specific symptoms and signs may be mistakenly attributed to other illnesses, particularly in post-partum women and the elderly. In iodine-replete communities the cause is normally either chronic autoimmune disease (atrophic autoimmune thyroiditis or goitrous autoimmune thyroiditis (Hashimoto's thyroiditis)) or destructive treatment for hyperthyroidism, which may account for up to one-third of cases of hypothyroidism in the community. The prevalence of spontaneous hypothyroidism is 1-2%; it is more common in older women and ten times more common in women than in men.¹

Hyperthyroidism has a significant short-term morbidity and long-term morbidity and mortality. The most common causes of hyperthyroidism in iodine-replete communities are autoimmune Graves' disease and toxic multinodular goitre and whilst rarer causes include excessive thyroxine replacement, an autonomously functioning thyroid adenoma, or thyroiditis. The prevalence of hyperthyroidism in women is 0.5-2% and is also ten times more common in women than in men.¹

1.2 Thyroid Function Tests (TFT)

Thyroid disorders are common and so thyroid function testing in blood samples is also common with approximately 10 million requests each year in the UK at an estimated cost of £30 million.² The most commonly performed tests in serum are used to establish if there is thyroid dysfunction or to monitor the response to therapy. These tests include thyroid stimulating hormone (TSH), free thyroxine (FT4), and free tri-iodothyronine (FT3). A range of other tests is also available to determine the specific causes of thyroid disease.

The majority of thyroid disorders present to and are managed initially within General Practice. Specialist thyroid physicians, who are usually hospital-based Clinical Endocrinologists, and surgeons are involved at a later stage in many cases. Virtually all thyroid function testing currently takes place in hospital laboratories in departments of Clinical Biochemistry. Therefore, there are three main stakeholders in thyroid function testing:

- The patient
- The physician (GP and specialist)
- The laboratory

1.3 The Patient Perspective

Patients are becoming more informed about their health and any disorders from which they suffer. They obtain this information from doctors, from patient support organisations and from the Internet. There is a huge amount of information available about thyroid disease but it can be confusing and it is not always consistent in terms of content or implementation. Patients find it difficult to understand that the diagnosis of thyroid disease is not always clear-cut or that individual patients respond differently to treatment. They have an expectation that thyroid function testing across the UK is uniform in terms of the tests performed, the results obtained and the interpretations made. Some of the questions most frequently asked by patients are listed in Table 1.1.

1.4 The Physician Perspective

The symptoms of thyroid disease can be relatively non-specific and one of the first challenges for the GP is to consider thyroid disease in the differential diagnosis of the symptoms of the individual patient. Once this consideration has been made the GP would like TFT either to exclude or confirm the diagnosis of thyroid disease. For borderline cases the GP expects the laboratory to provide the combination of TFT that provide the maximum information and they welcome an interpretation of the results in difficult cases. For patients known to have thyroid disease GPs expect TFT to provide information that assists with the optimisation of therapy. Some of the questions most frequently asked by GPs are listed in Table 1.2a. Many laboratories provide interpretive comments to GPs on all abnormal TFT results and user surveys indicate that this service is appreciated.

The specialist thyroid physician receives referrals from GPs and from other sources. In all cases the job of the thyroid physician is made much easier when the referral notes include results of appropriate TFT performed at appropriate times. The thyroid physician expects the laboratory to deliver a comprehensive range of TFT with analytically valid results and finds it difficult to understand why laboratories offer different test profiles and why results are not always transferable between laboratories. Some questions most frequently asked by thyroid physicians are listed in Table 1.2b.

1.5 The Laboratory Perspective

Thyroid function testing is relatively expensive and laboratory budgets have struggled to cope with the rapidly rising number of TFT over the last few years. Clinical biochemists wish to work with physicians to ensure that all requests for TFT are justified on clinical grounds and that there is not unnecessary repetition. They also strive to obtain sufficient clinical information with each request to ensure that they provide the optimal combination of TFT for each patient without performing unnecessary or misleading tests. Some of the questions most frequently asked by clinical biochemists are listed in Table 1.3.

1.6 The Need for National Guidelines

It is clear from the previous sections that the different stakeholders are uncertain about many aspects of thyroid function testing. Therefore, the need for national guidelines for something as common as thyroid function testing is self-evident. However, such guidelines do not exist in the UK, the nearest being the references given to testing as part of the consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism.³ In the USA the American Thyroid Association (ATA) has published guidelines for detection of thyroid dysfunction⁴; the ATA and the American Association of Clinical Endocrinologists (AACE) have published guidelines on subclinical thyroid disease⁵; and the National Academy of Clinical Biochemistry (NACB) has published practice guidelines on the laboratory support for the diagnosis and monitoring of thyroid disease.⁶ However, none of these two sets of guidelines addresses the subject of thyroid function testing from the perspective of all three stakeholders and neither uses the rules of evidence based medicine⁷ to support the recommendations.

As a result, the Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF) agreed to take the initiative to produce a set of evidence-based guidelines that meet the requirements of all three stakeholders. The model used for guidelines production has been that employed by the BTA and the Royal College of Physicians (RCP) in the recently published guidelines for the management of thyroid cancer.⁸

Table 1.1 Questions Frequently Asked by Patients

- What is a thyroid function test?
- Why should I have a thyroid function test?
- What do the results of thyroid function tests show?
- What is the difference between a normal range and a reference range?
- I didn't have any tests until after I had thyroid disease, how does my doctor know what is the normal range for me?
- Why do blood tests and ranges differ throughout the country?
- If my test results are abnormal will I be referred, and to whom?
- Can I arrange to have a private blood test?
- Can I buy a kit to do my own thyroid function testing?
- Why don't thyroid function tests always give clear-cut answers?
- What do the terms sub-clinical and borderline mean?
- Will I get treated if my results are borderline?
- How does pregnancy/menstruation/the pill/HRT affect my test results?
- Can my diet affect my test results and should I fast before testing?
- Does the number of hours after my thyroxine tablet affect my test result?
- Are test results influenced by general illness?
- Is it possible to have a normal test result and still have thyroid disease?
- Is the basal temperature an alternative to thyroid function testing?
- Are there other alternatives to the blood tests?
- There is a family history of thyroid disease, should my children be tested?
- My identical twin sister has a thyroid disorder, should I be tested?
- My son has Down syndrome, should he be tested?
- What do thyroid antibody tests measure and why don't all patients have them?
- How do test results help to optimise the dose of thyroxine?
- The test results suggest that I am taking the correct dose of carbimazole/thyroxine but I don't feel right. Can the dose be adjusted?

Table 1.2 Questions Frequently Asked by Physicians

a) General Practitioners

- What is the difference between total T4/T3 and free T4/T3 and which is better?
- Why do you attach so much significance to the TSH result?
- Why don't you always give me the same combination of tests?
- How long should it take for me to get results back?
- How accurate and precise are your results?
- What is the typical biological variability of thyroid hormones?
- Do thyroid hormones have a diurnal or seasonal rhythm?
- Why do I have to wait two months after adjusting the dose of thyroxine before I can perform thyroid function testing?
- Should TSH always be 'normal' in patients taking thyroxine?
- What does a TSH result of 5-10mU/L mean?
- How should I interpret a positive thyroid antibody result?
- What is non-thyroidal illness (sick euthyroid syndrome)?

b) Specialist Thyroid Physicians

- Why don't all labs offer the same profile of tests?
- Why don't you always give me the tests that I request?
- Why do different labs have different reference ranges?
- What effect do different methods have on results and reference ranges?
- How accurate and precise are your results?
- How does your laboratory perform in external quality assessment?
- What is the minimum detection limit of your TSH method?
- Where can I get antibodies to T4/T3 measured?
- Do heterophilic antibodies influence your methods?
- Why do results sometimes take a long time to come back?
- How much do thyroid function tests cost?

Table 1.3 Questions Frequently Asked by Clinical Biochemists

- What clinical question are you expecting to have answered with this request?
- Why have you asked for this combination of tests?
- What is the age/sex of this patient?
- Is the patient taking thyroxine / carbimazole?
- What medication is the patient taking?
- Why have you asked for thyroid function tests more than once this month?
- Why are you requesting thyroid function tests on all admissions?
- Do you really want thyroid function tests on this patient in ITU/HDU?
- Does this patient have non-thyroidal illness?

2. Indications for Thyroid Function Testing

2.1 Introduction

Hypothyroidism is an insidious condition with a significant morbidity and the subtle and non-specific symptoms and signs may be mistakenly attributed to other illnesses, particularly in postpartum women and the elderly. The earliest biochemical abnormality in hypothyroidism is an increase in serum TSH concentration associated with normal serum FT₄ and FT₃ concentrations (subclinical hypothyroidism), followed by a decrease in serum FT₄ concentration, at which stage most patients have symptoms and benefit from treatment (overt hypothyroidism). In the UK, the prevalence of spontaneous hypothyroidism is between 1% and 2%, and it is more common in older women and ten times more common in women than in men.¹ In a cross-sectional study of 2779 subjects of the community of Whickham, North East England, the prevalence of newly diagnosed overt hypothyroidism was 3 per 1000 women.² This is comparable with recent large US studies in which the prevalence of newly diagnosed hypothyroidism was 4 per 1000 and 3 per 1000 respectively.^{3,4} The cause is either chronic autoimmune disease (atrophic autoimmune thyroiditis or goitrous autoimmune thyroiditis (Hashimoto's thyroiditis)) or destructive treatment for hyperthyroidism which may account for up to one-third of cases of hypothyroidism in the community. In the original Whickham survey, 8% of women (10% of women over 55 years of age) and 3% of men had subclinical hypothyroidism². Community studies of elderly persons have confirmed the high prevalence of subclinical hypothyroidism in this age group, with approximately 10% of subjects over 60-years old having serum TSH values above the normal range.^{5,6} Subclinical hypothyroidism can progress to overt hypothyroidism, particularly if antithyroid antibody positive.⁷

Hyperthyroidism has a significant short-term morbidity and long-term morbidity and mortality. The prevalence of thyrotoxicosis in women is between 0.5 and 2%, and it is also ten times more common in women than in men.⁸ In the Whickham survey, the prevalence of undiagnosed thyrotoxicosis was 5 per 1000 women and none in men.² The most common causes of hyperthyroidism are Graves' disease, followed by toxic multinodular goitre, whilst rarer causes include an autonomously functioning thyroid adenoma, or thyroiditis. Subclinical hyperthyroidism is defined as a low serum TSH concentration and normal serum FT₄ and FT₃ concentrations. This pattern of biochemistry may reflect mild thyroid hormone excess but may also reflect hypothalamic or pituitary disease, non-thyroidal illness, or ingestion of drugs that inhibit TSH secretion. The available studies differ in the definition of a low serum TSH concentration and whether the subjects included were receiving thyroxine therapy. The reported overall prevalence ranges from 0.5% to 6.3%, with men and women over 65 years having the highest prevalence; approximately half of them are taking thyroxine.^{3-5,7,9}

2.2 Screening for Thyroid Dysfunction

2.2.1 Which Thyroid Function Test?

A strategy of first-line TSH may be cost effective for a wide range of clinical purposes including screening and case finding, but it may be inappropriate in patients being tested for the first time, and in some specific clinical settings. Throughout these guidelines we have highlighted the clinical situations where measurement of both serum TSH and FT4 is required; these are principally where the pituitary-thyroid axis is not intact or is unstable. These situations include relatively common situations such as optimising thyroxine therapy in newly diagnosed patients with hypothyroidism, diagnosing and monitoring thyroid disorders in pregnancy and monitoring patients with hyperthyroidism in the early months after treatment. Rare situations include diagnosis and monitoring treatment for central hypothyroidism, end-organ thyroid hormone resistance and TSH-secreting pituitary adenomas. It is the responsibility of the requesting physician to provide clinical information to guide the laboratory in the selection of the most appropriate TFT but if clinical details are not available that allow the identification of the above categories of patient, then it may be prudent for laboratories to measure serum TSH and FT4 on all specimens rather than embark on a first-line serum TSH testing strategy followed by a cascade to include FT4 and FT3 if indicated.

- *If laboratories are unable to identify those specimens that specifically require the measurement of both serum TSH and FT4 then it would be prudent to measure serum TSH and FT4 on all specimens rather than embark on a first-line serum TSH strategy. (IV,C)*
- *Measurement of serum TSH alone is appropriate after the first investigation in the sequential follow up of individuals who have not been treated for thyroid disorders and who may be at risk of developing thyroid dysfunction. (IV,C)*

2.2.2 Congenital Hypothyroidism

Congenital hypothyroidism affects about one newborn in 3,500-4,000 births and is the most treatable cause of mental retardation. There is an inverse relationship between age at diagnosis and intelligence quotient (IQ) in later life. In iodine-replete areas, 85% of the cases are due to sporadic developmental defects of the thyroid gland (thyroid dysgenesis) such as the arrested migration of the embryonic thyroid (ectopic thyroid) or a complete absence of thyroid tissue (athyreosis). The remaining 15% have thyroid dyshormonogenesis defects transmitted by an autosomal recessive mode of inheritance. Clinical diagnosis occurs in less than 5% of newborns with hypothyroidism because symptoms and signs are often minimal. As a result it is not possible to predict which infants are likely to be affected. Without prompt diagnosis and treatment most affected children gradually develop growth failure, irreversible mental retardation and a variety of neuropsychological deficits.^{10,11}

- *The value of screening for congenital hypothyroidism by measurement of serum TSH in heel-prick blood specimens is unquestioned, and it is now done routinely in many countries and should continue (IIb,B)*

2.2.3 Goitre and Thyroid Nodules

Testing of thyroid function should be performed as part of the routine assessment of all patients who present with a suspected goitre (diffuse, multi-nodular or single

nodule) at presentation to detect clinically unapparent hypothyroidism or hyperthyroidism.¹²

- *In any patient presenting with a suspected goitre, serum TSH should be measured (III,C)*

2.2.4 Atrial Fibrillation, Hyperlipidaemia, Osteoporosis, Subfertility

Thyrotoxicosis is a recognised cause of atrial fibrillation and about 5-10% of patients with thyrotoxicosis have atrial fibrillation, especially if older¹³ and hypothyroidism is a recognised secondary cause of dyslipidaemia.¹⁴⁻¹⁸ Hyperthyroidism is also a potentially correctable cause of osteoporosis.¹⁹ Hyperthyroidism and hypothyroidism can be associated with abnormal menstrual cycles, foetal loss and subfertility.²⁰

- *Patients with atrial fibrillation, dyslipidaemia, osteoporosis and subfertility should have an assessment of thyroid function by measurement of serum TSH at presentation (III,C)*

2.2.5 Women with Type 1 Diabetes

Women with type 1 diabetes are three times more likely to develop post-partum thyroid dysfunction.²¹

- *Women with type I diabetes should have their thyroid function, including serum TSH, FT4 and thyroid peroxidase antibody status, established pre-conception, at booking when pregnant and at 3 months post-partum (III,C)*

2.2.6 The Normal Healthy Adult Population Including the Elderly

The ageing UK population and the introduction of the General Medical Services contract are providing GPs with more opportunity to consider thyroid dysfunction in the normal community, especially in elderly subjects with few or no symptoms of thyroid disease. The prevalence of unsuspected overt thyroid disease is low, but a substantial proportion of subjects tested will have evidence of thyroid dysfunction, usually subclinical hypothyroidism. In the absence of the confounding effects of non-thyroidal illness or drugs, a normal serum TSH concentration has a high predictive value in ruling out thyroid disease in healthy subjects. In unselected populations, measurement of serum TSH has a sensitivity of 89 to 95% and specificity of 90 to 96% for overt thyroid dysfunction, as compared to cases confirmed by history, examination and additional testing.²² Normal serum TSH concentrations are found in some patients with hypothyroidism caused by pituitary or hypothalamic disease, but both these situations are rare. In nearly all populations screened a serum TSH value greater than 5mU/L is accepted as being raised. Different recommendations and position papers have been reported by various physician organisations as to whether subclinical thyroid disease is of sufficient clinical importance to warrant screening and therapy.^{8,11,23-32}

A cost-utility analysis using a computer decision model suggested that the cost-effectiveness of screening for subclinical hypothyroidism compared favourably with other preventive medical practices, such as screening for hypertension or breast

cancer, in women in the same age group, while providing a similar increase in quality adjusted life years.^{33,34} Over half of the presumed benefit in the latter was accounted for by preventing progression to overt hypothyroidism, 30% by improving associated mild symptoms and 2% by preventing cardiovascular disease. The cost of detecting subclinical hypothyroidism was \$9223 for women and \$22,595 for men per quality-of-life year gained, but this cost was heavily dependent on the cost of the serum TSH assay (\$10 to 50). The cost-benefit analysis did not allow for the extra costs of detecting, investigating and potentially treating subclinical hyperthyroidism. These data led the American Thyroid Association to recommend population-based screening for thyroid dysfunction by measurement of serum TSH, beginning at age 35 years and every five years thereafter.³⁵ Those organisations that assess screening programs, such as the US Preventive Services Task Force¹¹, have not recommended regular assessment of thyroid function in adults. A recent US expert consensus development conference recommended after review of the existing evidence that population screening for subclinical thyroid disease was not warranted.³⁰

There have been few trials to determine whether identification and treatment of subjects with thyroid dysfunction, which would mostly be subclinical hypothyroidism, results in any long-term benefit. A recent placebo- controlled double-blind intervention study has demonstrated no difference in neuropsychological function in subjects with subclinical hypothyroidism compared to controls, and thyroxine treatment for one year did not alter neuropsychological function in a cohort of the subjects with subclinical hypothyroidism.³¹ The potential benefits in terms of decreased symptoms or other systemic effects are generally small and may not enhance quality of life.³⁶ In a recent observational cohort 10-year study, a low serum TSH concentration (<0.5mU/L), but not a high serum TSH concentration, was associated with an increase in all-cause mortality and cardiovascular mortality.³⁷ Two further studies have also observed that in elderly groups of subjects low FT₄ and/or raised TSH were associated with reduced mortality and it has been speculated that this may reflect an adaptive mechanism to prevent excessive catabolism.^{38,39} Despite this growing evidence against thyroxine therapy it has recently suggested that individual patients with subclinical hypothyroidism may be offered a three month therapeutic trial of thyroxine as part of patient-centred care³².

- *Screening for thyroid dysfunction in a healthy adult population is not warranted. Case-finding in women at the menopause or if visiting a doctor in primary care with non-specific symptoms may be justified in view of the high prevalence of mild thyroid failure (IV,C)*
- *If screening is performed, and a high serum TSH concentration is found, and the FT₄ is normal, the measurement should be repeated 3-6 months later, along with measurement of serum FT₄, after excluding non-thyroidal illness and drug interference (IV,C)*
- *If the serum TSH is greater than 10mU/L and the serum FT₄ concentration is low, then the subject has overt hypothyroidism and should be treated with thyroxine (IV,C)*
- *If the serum FT₄ concentration is normal, but the serum TSH concentration is greater than 10mU/L, then treatment with thyroxine is recommended (II,B)*

- *If the serum TSH concentration is above the reference range but <10mU/L, then serum thyroid peroxidase antibodies should be measured. If the serum antibody concentration is high, then serum TSH should be measured annually or earlier if symptoms develop; thyroxine therapy should be started if the serum TSH concentration rises above 10mU/L. If the serum antibody concentration is not raised, then repeat measurement of serum TSH approximately every three years is all that is required (IV,C) (See also Chapter 3).*
- *There is no evidence to support the benefit of routine early treatment with thyroxine in non-pregnant patients with a serum TSH above the reference range but <10mU/L (II,B). Physicians may wish to consider the suitability of a therapeutic trial of thyroxine on an individual patient basis.*

Few subjects screened will have overt hyperthyroidism, but the consequences of finding subclinical hyperthyroidism have to be addressed.^{8,30} Patients with subclinical hyperthyroidism can be categorised into those with low but detectable serum TSH (0.1-0.4mU/L) and those with a clearly low serum TSH (less than 0.1mU/L). If a subject has a serum TSH value below the reference range but >0.1mU/L, and is not on thyroxine therapy, then the first step is to repeat the measurement together with FT4 and FT3 within one to two months to exclude overt hyperthyroidism (and also central hypothyroidism). In most circumstances serum TSH will have returned to within the reference range. If the repeat serum TSH measurement remains low but >0.1mU/L with normal FT4 and/or FT3, then repeat testing every 6-12 months is required. In those subjects with a serum TSH less than 0.1mU/L, FT4 and FT3 should be measured to exclude overt hyperthyroidism. Usually, subclinical hyperthyroidism will be confirmed. In addition to the risk of overt hyperthyroidism, the subject may be at risk for atrial fibrillation⁴⁰ and osteoporosis.⁴¹ No consensus exists regarding the treatment of subclinical hyperthyroidism³⁰ but any potential benefits of therapy must be weighed against the substantial morbidity associated with the treatment of thyrotoxicosis.^{30,42}

- *If a serum TSH concentration below the reference range but >0.1mU/L is found, then the measurement should be repeated one or two months later together with serum FT4 and FT3, after excluding non-thyroidal illness and drug interferences (IV,C)*
- *If the serum TSH is less than 0.1mU/L then the serum FT4 and FT3 must be measured to exclude overt hyperthyroidism (IV,C)*
- *If treatment is not undertaken, serum TSH should be measured every 6-12 months, with follow-up measurements of serum FT4 and FT3 if the serum TSH result is low. (IV,C) (See also Chapter 4)*

2.2.7 Hospital In-Patients

Isolated alterations in serum TSH concentrations (either slightly low 0.10-0.30mU/L or high 5-20mU/L) occur in about 15% of such patients due to altered TSH secretion in response to non-thyroidal illness or drugs.^{43,44} About 2-3% of hospitalized patients have

serum TSH concentrations that are suppressed ($<0.10\text{mU/L}$) or elevated ($>20\text{mU/L}$) but less than half will have an underlying thyroid disorder.⁴⁵ The reported point prevalence rates for previously undiagnosed hyperthyroidism, between 0.3 and 1%, are consistent with community surveys. An accurate diagnosis can be achieved if clinical indications for measuring thyroid function exist, an accurate drug history is taken, the abnormal serum TSH is subsequently confirmed and there is a reciprocal change in serum FT₄. The testing of hospital in-patients, predominantly elderly women, might be expected to reveal a higher proportion of unsuspected hypothyroidism, but this is not supported by the available studies, which confirm a prevalence of 2%.¹ Unless clinically indicated caution is also required in the investigation of thyroid function in acute psychiatric disturbances and clinical depression since non-thyroidal illness and medication that affects TFT are both common and may prompt inappropriate intervention.²⁷ (See also Chapter 7).

- *Routine testing of thyroid function in patients admitted acutely to hospital is not warranted unless specific clinical indications exist (III,B)*

2.3 Surveillance of Thyroid Function

2.3.1 Past History of Post-Partum Thyroiditis

Women with a past history of postpartum thyroiditis have a risk of long-term risk of permanent hypothyroidism and recurrence in subsequent pregnancies.⁴⁶ No consensus exists on whether healthy women should be screened for the risk postpartum thyroiditis pre-conception or during pregnancy.⁴⁷ (See also Chapter 5).

- *All women with a past history of postpartum thyroiditis should be offered an annual check of thyroid function and should also be screened prior to and at 6 to 8 weeks after future pregnancies (II,B)*

2.3.2 Patients with Diabetes

There is a high frequency of asymptomatic thyroid dysfunction in unselected patients with type-1 diabetes, it has been calculated that including an annual test of thyroid function in the annual review is cost-effective.⁴⁸

- *Patients with type-1 diabetes should have a check of thyroid function included in their annual review. Patients with type-2 diabetes should have their thyroid function checked at diagnosis but routine annual thyroid function testing is not recommended. (III,B)*

2.3.3 Down Syndrome and Turner's Syndrome

There is a high incidence of hypothyroidism in Down Syndrome^{49,50} and Turner's Syndrome.⁵¹

- *All patients with Down Syndrome and Turner's Syndrome should have an annual check of thyroid function (III,B)*

2.3.4 Patients receiving Amiodarone and Lithium

Amiodarone contains 75mg iodine per 200mg tablet and is frequently associated with iodide-induced thyroid dysfunction.⁵² Amiodarone-induced hyperthyroidism is particularly prevalent (10%) in areas of iodine-deficiency and in patients with underlying thyroid disease. Amiodarone-induced hypothyroidism is more common in iodine-replete communities (up to 20%) and related to the presence of thyroid autoimmunity. Lithium, used in the treatment of bipolar depression, is associated with mild and overt hypothyroidism in up to 34% and 15% of patients respectively, and can appear abruptly even after many years of treatment.⁵³ Lithium-associated thyrotoxicosis is rare and occurs mainly after long-term use. (See also Chapters 4,7).

- *All patients on amiodarone therapy should have thyroid function tested before commencing treatment and then should be routinely monitored every 6 months thereafter whilst on treatment and up to 12 months after cessation of therapy (III,B)*
- *All patients on lithium therapy should have thyroid function tested before commencing treatment and then should be routinely monitored every 6-12 months whilst on treatment (III,B)*

2.3.5 Post Neck Irradiation

The incidence of hypothyroidism after surgery, external radiation therapy of the neck, or both, in patients with head and neck cancer (including lymphoma) is as high as 50% within the first year after treatment, particularly in patients who underwent surgery and received high doses of radiation.⁵⁴⁻⁵⁸ The effect is dose-dependent, the onset is gradual, and subclinical hypothyroidism can be present for many years prior to the development of overt disease.

- *Thyroid function should be tested every 12 months in patients treated by external irradiation to the neck in view of the risk of hypothyroidism (III,B)*

2.3.6 Following Destructive Treatment for Thyrotoxicosis by either Radioiodine or Surgery

After destructive treatment of thyrotoxicosis with either radioiodine or surgery, the incidence of overt hypothyroidism is greatest in the first year.^{59,60} In an audit of 813 consecutive patients treated for thyrotoxicosis in Birmingham, UK, there was an increase in the incidence of hypothyroidism at one year in those given higher doses of radioiodine (61% among those given 10 mCi (370mBq) versus 41% among those given 5 mCi (185mBq).⁶¹ The incidence of hypothyroidism in patients with Graves' thyrotoxicosis was higher than that in patients with nodular goitre (55% vs. 32%). If the patient had subclinical hypothyroidism one year or more after radioiodine or surgical treatment, then the rate of progression to overt hypothyroidism after either treatment was 2-6% per year.^{59,60} (See also Chapter 4).

The recurrence of hyperthyroidism after radioiodine is rare and so surveillance is largely targeted at detecting hypothyroidism. In contrast, recurrent hyperthyroidism

occurs more frequently after partial thyroidectomy and follow-up should probe both for hypothyroidism and recurrent hyperthyroidism.

- *Indefinite surveillance is required following radioiodine or thyroidectomy for the development of hypothyroidism or the recurrence of hyperthyroidism. Thyroid function should be assessed around four to eight weeks post-treatment, then three monthly up to one year and annually thereafter (III,B)*

2.4 Monitoring of Thyroid Function

2.4.1 Treatment of Thyrotoxicosis with Anti-Thyroid Drugs

Antithyroid drugs, carbimazole and propylthiouracil, decrease thyroid hormone secretion and are used in the management of thyrotoxicosis.^{26,62} (See also Chapter 4).

- *It is recommended that thyroid function is tested every 1-3 months when initiating antithyroid drug therapy until stable and annually if used as a long-term treatment option (III,B)*

2.4.2 Patients on Thyroxine Therapy

Once hypothyroidism has been diagnosed and the appropriate dose of thyroxine has been established, the dose remains constant in many patients. In pregnancy there may be a need to increase the dose by at least 50µg daily to maintain a normal serum TSH.⁶³ Access to a computerised thyroid disease register improves the surveillance of patients treated for thyroid dysfunction⁶⁴ and a register may assist GPs to meet the targets in the General Medical Services contract. Patients with hypothyroidism who are taking thyroxine may become hypothyroid if given drugs which decrease thyroxine absorption, such as cholestyramine and iron salts, or increase its clearance, such as phenytoin and carbamazepine.⁶⁵ A recent report suggests that in women with hypothyroidism treated with thyroxine, oestrogen therapy may increase the need for thyroxine caused by an oestrogen-induced increase in the serum concentration of thyroxine-binding globulin.⁶⁶ (See Chapter 7). Poor compliance with thyroxine therapy or suboptimal treatment may also result in hypothyroidism. There is evidence from community studies that many treated hypothyroid patients have serum TSH levels outside the normal range.^{3,7,67} In the Colorado Thyroid Disease Prevalence Survey of 1525 subjects taking thyroid medication 17.6% had subclinical hypothyroidism, 0.7% were overtly hypothyroid, 20.7% had subclinical hyperthyroidism and over 90% had seen a health care provider in the previous year.³ Similar data are found in the UK community studies^{7,67}

- *Once thyroxine replacement is initiated, for whatever indication, then long-term follow-up with at least an annual measurement of serum TSH is required to check compliance and dosage and take account of variations in dosage requirement caused by concomitant drug treatment (III,B)*

- *In pregnancy there may be a need to increase the dose by at least 50 μ g daily to maintain a normal serum TSH, which should be measured in each trimester*
(III,B)

3. Hypothyroidism

3.1 Primary Hypothyroidism

3.1.1 Diagnosis

Hypothyroidism is associated with a number of classical symptoms and signs, which are described in many endocrinology textbooks. Some patients with severe hypothyroidism may exhibit several of these clinical features. However, many patients with milder forms of the disease exhibit few clinical features and some will exhibit none. This is especially true of the elderly. ¹⁻³ **(III)**.

Conversely, the symptoms of hypothyroidism are not specific for the disease; some are present in a significant proportion of euthyroid subjects. ⁴ Hypothyroidism cannot be diagnosed accurately on symptoms alone. ⁵ **(III)**. The diagnosis of hypothyroidism requires abnormal TFT results. A TSH greater than 10 mU/L combined with a FT4 below the reference range indicates the presence of overt primary hypothyroidism in ambulant subjects. ⁶⁻¹⁰ **(III)**.

A TSH concentration above the reference range together with FT4 within the reference range defines subclinical (mild) hypothyroidism (Section 3.2) (See also Chapter 2). Subclinical hypothyroidism requires to be confirmed 3-6 months after the initial results in order to exclude transient causes of a raised TSH. ¹¹ (see also Chapter 7). Subclinical hypothyroid patients who are TPOAb or TgAb positive are more likely to have higher serum TSH ¹²⁻¹⁵ and more likely to develop overt hypothyroidism ¹⁴⁻¹⁷ but do not have increased mortality or increased incidence of ischaemic heart disease. ¹³ **(III)**.

If the serum TSH is within the reference range and the patient is not taking any medication known to affect TSH (Chapter 7) then primary hypothyroidism is excluded. ⁶⁻¹⁰ **(III)**. Secondary hypothyroidism may still be considered if the clinical picture is suggestive (Section 3.3).

- *The diagnosis of primary hypothyroidism requires the measurement of both TSH and FT4 **(III,B)**.*
- *Subjects with a TSH of >10mU/L and FT4 below the reference range have overt primary hypothyroidism and should be treated with thyroid hormone replacement **(III,B)**.*
- *Subjects with subclinical hypothyroidism should have the pattern confirmed within 3-6 months to exclude transient causes of elevated TSH **(III,B)**.*
- *The measurement of thyroid antibodies in subjects with subclinical hypothyroidism helps to define the risk of developing overt hypothyroidism. **(III,B)**.*

3.1.2 Guiding treatment with thyroxine

Thyroid function tests have become the mainstay of optimising thyroxine replacement

therapy. The recommended approach in primary hypothyroidism is to titrate thyroxine therapy against the TSH concentration whilst assessing clinical well-being. The target is a serum TSH within the reference range.^{18,19} **(III)**. In the majority of patients 50-100µg thyroxine can be used as the starting dose, although a higher starting dose may be indicated in patients post-thyroidectomy. Thereafter alteration of the dose is achieved by using 25-50µg increments and repeat measurement of TSH 2-3 months after a change in dose. This will result in the majority of patients becoming clinically euthyroid with a 'normal' TSH and having thyroxine replacement in the range 75-150 µg/day (1.6ug/Kg on average).^{20,21} **(IIb)**. This strategy will prevent over-replacement in patients and decrease possible adverse effects noted in terms of cardiovascular outcome.^{22,23} In elderly patients and patients with with ischaemic heart disease consideration should be given to commence replacement with 25µg thyroxine and increase the dose in 25µg increments in an attempt to avoid cardiac complications.²³⁻²⁵ **(IIb)**.

Other published guidelines recommend that the serum TSH during thyroxine therapy should be targeted to be below 2.0mU/L²⁶. It has been suggested that in a minority of patients clinical well-being can only be achieved if the serum TSH is subnormal or suppressed and that this is of no detriment to the patient as long as the serum FT3 is unequivocally normal.²⁷ However, the guidelines development group could find no evidence to support a recommendation that in non-pregnant patients titrating the serum TSH to the lower half of the reference range results in improved outcomes.

Serum FT4 test results can vary immediately following the daily dose of thyroxine, but this is not clinically significant.²⁸⁻³⁰ **(IIb)**. An even greater variability of serum FT3 occurs in patients who are taking T3 therapy.³¹ It would, therefore, be ideal to standardise the timing of thyroid function testing in relation to the daily dose of T4 or T3 dose but clinic and surgery times make this ideal impracticable in most situations. A minimum period of 2 months, and in some patients up to 3 months, is required to restore stability in thyroid function tests after a change in dose.²⁰ **(IIb)**.

Measurement of TSH combined with FT4 is recommended when optimizing thyroxine replacement therapy. This is because of the misleading results that can be produced by patients who have intermittent or poor compliance with their treatment.³² **(IV)**. Once the patient is clinically stabilized on thyroxine serum TSH alone may be used to monitor therapy **(IV)**.

The lack of thyroidal production of T4 and T3 along with the dependence on peripheral conversion of T4 to T3 significantly alters thyroid hormone status in patients on replacement therapy such that the ratio of T4 to T3 is increased.³³ FT4 concentrations may exceed euthyroid reference ranges in patients on thyroxine when the TSH is normal whereas FT3 remains closer to euthyroid reference ranges.^{34,35} **(IIb)**.

- *The measurement of both TSH and FT4 is required to optimise thyroxine replacement therapy (IV,C).*
- *The primary target of thyroxine replacement therapy is to make the patient feel well and to achieve a serum TSH that is within the reference range*

(III,B). *The corresponding FT4 will be within or slightly above its reference range.*

- *The minimum period to achieve stable concentrations after a change in dose of thyroxine is two months and thyroid function tests should not normally be requested before this period has elapsed (IIb,B).*

3.1.3 Guiding treatment with tri-iodothyronine

If tri-iodothyronine is used as a replacement hormone increasing doses should be used until serum TSH is within the reference range. The measurement of FT4 is of no value in patients on tri-iodothyronine replacement and the measurement of FT3 is of limited value because of the variability after taking the replacement dose.

There has been considerable recent interest in using a combination of thyroxine and tri-iodothyronine therapy. This interest was stimulated by an initial small study that reported improved mood scores and self-reported wellbeing in the combined therapy group compared with the thyroxine only group.³⁶ However, a number of larger studies have failed to confirm the initial finding and there is currently no consistent evidence to suggest that combined therapy has advantages over therapy with thyroxine alone.³⁷⁻⁴² **(Ib).**

- *The measurement of TSH is required to optimise tri-iodothyronine replacement therapy (✓).*
- *There is no consistent evidence to recommend the use of combined therapy with thyroxine and tri-iodothyronine in comparison to thyroxine alone (Ib,A).*

3.1.4 Assessing response to thyroxine therapy

Most patients taking thyroxine will feel well when the serum TSH is maintained within the reference range. However, some surveys have indicated that up to 21-59% of patients receiving maintenance thyroxine therapy have TSH values below the reference range.^{16,22,43,44} There has been much debate regarding the possible consequences for these patients remaining on doses of thyroxine that reduce TSH to below the reference range²⁷ because suppression of TSH may result in cardiac problems.^{22,23} or bone loss^{45,46}. Therefore, it is recommended that a reduction in thyroxine dose is made to bring the TSH within the reference range.²³

Some patients on long term standard replacement doses of thyroxine, with thyroid hormone values within the range for patients on T4, report an apparent psychological benefit and general feeling of well being when TSH is undetectable.²¹ **(III)**, although this is not a universal finding. Although it may be difficult to reduce the thyroxine dose in such patients it is recommended that the dose should be reduced until the TSH is within the reference range, the use of small decremental changes of 25µg may make this possible.⁴⁷

Some patients will continue to show abnormal psychological well-being when receiving adequate thyroxine replacement with TFT within the reference range.⁴⁸ There is no evidence that increasing the thyroxine dose will improve psychological or

cognitive symptoms in these patients. Indeed a lack of benefit has been demonstrated from giving thyroxine to euthyroid patients with these symptoms.⁴⁹ **(Ib)**.

- *The optimal dose of thyroxine for long-term therapy is assessed from the results of thyroid function tests together with clinical findings. (✓). In determining the optimal dose of thyroxine the biochemical target is a TSH result that is detectable, not elevated, and preferably within the reference range (✓).*

3.1.5 Long-term follow-up of patients on thyroxine

Once stabilised on thyroxine all patients should have their serum TSH checked annually as a change in requirement for thyroid hormone can occur with ageing.^{50,51} **(III)**. In some parts of the UK computerised thyroid registers have been established and shown to be successful in ensuring excellent automated follow up for thyroid patients on replacement therapy.⁵²

- *Patients stabilised on long-term thyroxine therapy should have serum TSH checked annually **(III,B)**.*

3.2 Subclinical (Mild) Hypothyroidism

3.2.1 Diagnosis

Subclinical (mild) hypothyroidism is characterised by a TSH above the reference range with a FT4 measurement within the reference range. Depending on the age and gender of the population studied subclinical hypothyroidism is present in 1.3-17.5% of the UK or US populations.^{10-15, 53,54} **(III)**. Subclinical hypothyroidism should be confirmed by repeat thyroid function testing 3-6 months after the original result.¹¹

3.2.2 Guiding treatment

The decision on treatment of patients with subclinical hypothyroidism should be guided by repeated TSH measurements. When TSH is elevated but <10 mU/L there is no consistent evidence of an association with symptoms, secondary biochemical abnormalities (hyperlipidaemia), cardiac dysfunction or cardiac events.¹¹⁻¹⁵ In patients with TSH >10 mU/L there is increasing evidence of progression to overt hypothyroidism and deterioration in hyperlipidaemia with the passage of time particularly in patients with elevated TPOAb^{11,14-16, 55-58} **(Ib) (III)**. There is evidence of improvement in the lipid profile and symptoms when patients with modestly raised TSH (mean 11.7mU/L) were rendered euthyroid with thyroxine.⁵⁹ **(Ib)**.

The frequency of thyroid function testing in subjects with subclinical hypothyroidism and the influence of the TPOAb status on the frequency of testing is discussed in Chapter 2.

Factors that may prompt thyroxine therapy in a patient with subclinical hypothyroidism include pregnancy¹¹, goitre, or a rising TSH level.

- *If the serum FT4 concentration is normal but the serum TSH is >10mU/L, then treatment with thyroxine is recommended (II,B).*
- *If the serum FT4 concentration is normal and the TSH is elevated but <10mU/L then thyroxine therapy is not recommended as a routine therapy. However, thyroxine may be indicated in non-pregnant patients with goitre; also in patients who are seeking pregnancy (II,B).*

3.2.3 Assessing response to therapy

The aim of treatment should be to restore and maintain TSH within the reference range. Thyroxine should be given in doses increasing by 25-50µg daily titrated to bring the TSH within the reference range. TSH should be measured 2-3 months following a change in thyroxine dose.

3.2.4 Long-term follow-up

A number of studies have used long term follow up in the community to define the risk of progression from subclinical to overt hypothyroidism¹⁴⁻¹⁶ (III) Establishing treatment guidelines for individuals with elevated TSH or repeat testing protocols is still a subject of significant debate^{60,61} but it would appear prudent to measure TSH on an annual basis.

The requirement for thyroxine can increase in patients treated for subclinical hypothyroidism as they may develop overt hypothyroidism. TSH should be measured annually and the thyroxine dose altered to maintain TSH within the reference range.

In patients who do not receive thyroxine it is recommended that regular measurement of TSH and FT4 be performed to detect those patients who may develop overt hypothyroidism. For patients who are TPOAb positive an annual assessment is appropriate. For patients who are TPOAb negative less frequent assessment is required, perhaps every three years (IV).

- *Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody positive should have an annual thyroid function test. Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody negative should have repeat thyroid function testing approximately every 3 years. (IV,C).*

3.3 Secondary Hypothyroidism

3.3.1 Diagnosis

The biochemical diagnosis of secondary hypothyroidism necessitates the use of a combination of TSH with FT4. Plasma TSH can be low, within or mildly above the reference range in these patients⁶²⁻⁶⁴ but combined with a low thyroid hormone measurement is suggestive of secondary hypothyroidism (III).

A combination of TSH, FT4 and FT3, may be required to differentiate secondary hypothyroidism from NTI especially in older patients where symptoms are often

vague and non-specific. Referral to an endocrinologist for additional pituitary function tests (PRL, FSH, LH, ACTH/cortisol) may be required to make a diagnosis and tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism.. Very rarely a TRH test may help to establish the final diagnosis.

- *First line TSH and FT4 are required to identify secondary hypothyroidism (III,B).*
- *Secondary hypothyroidism can be distinguished from non-thyroidal illness on the basis of clinical history, measurement of FT3 and tests of other anterior pituitary hormones (✓).*

3.3.2 Guiding Treatment

Patients with secondary hypothyroidism usually also have a deficit of other anterior pituitary hormones and the degree of hypopituitarism must be established before commencing thyroxine replacement. This should include measurement of the appropriate sex steroid. In particular thyroid hormone replacement should not be commenced in patients with cortisol deficiency as this could provoke an Addisonian crisis.^{65,66} Treatment with an appropriate glucocorticoid should be initiated in such patients before commencing thyroxine therapy. (III).

In patients with secondary hypothyroidism, after a full diagnosis has been made and steroid treatment initiated, thyroxine should be given in increasing 25µg doses and optimised such that the thyroid hormone concentration is within the upper third of the reference range^{67,68} (III).

- *The extent of hypopituitarism should be established in all patients with secondary hypothyroidism before commencing thyroxine therapy (III,B).*
- *Some experts suggest that an appropriate target for adequate thyroxine replacement in patients with secondary hypothyroidism may be a FT4 concentration in the upper third of the reference range. (III,B).*

3.3.3 Assessing Response to Therapy

Measurement of TSH cannot be used in to assess the response to therapy in patients with hypopituitarism and it is essential to monitor treatment by estimating FT4 and maintain the thyroid hormone concentration within the reference range. These patients will also require regular monitoring of all hormone replacement therapy.

- *FT4 measurements should be used to help define the adequacy of thyroxine replacement in patients with secondary hypothyroidism. (III,B).*

3.3.4 Long-term Follow-Up

- *An annual check of thyroid hormone concentration should be performed in all patients with secondary hypothyroidism who are stabilised on thyroxine replacement therapy. (✓).*

3.4 Congenital Hypothyroidism (see also Chapter 5)

Congenital hypothyroidism (cretinism) is a common preventable cause of mental retardation. The prevalence of congenital hypothyroidism in the UK is 1:4000 live births. Approximately 85% of cases are sporadic, while 15% are hereditary. Unless thyroid hormone therapy is commenced shortly after birth the mental retardation will be irreversible.⁶⁹ Consequently most developed countries have instituted national screening programmes for congenital hypothyroidism with follow up procedures to facilitate the early administration of thyroid hormone replacement.

3.4.1 Diagnosis

Routine screening is required for all neonates. In the UK nationwide screening is based on using filter paper blood spot TSH measurements, which is sensitive for primary hypothyroidism but which will miss rare cases of secondary hypothyroidism⁷⁰. In parts of the USA screening is based on blood spot T4 measurement.⁶⁹ In order to maximize the quality of screening and outcome the testing procedure is restricted to specialist centres. An increase in TSH concentration occurs that can last up to 24h following birth thus to avoid false positive results it is best to perform the measurement on a sample taken at least 48h after delivery⁶⁹.

In neonates with an elevated TSH (>20 mU/L) formal clinical evaluation and testing with measurement of serum TSH and FT4 should be performed immediately after the TSH result is known (~2 weeks after birth).

It is important to perform TFT on the mother in cases with abnormal results; to ensure that no anti-thyroid medication was ingested during the pregnancy and to exclude the possibility of placental transfer of maternal antibodies that block the action of TSH.⁷¹

- *All newborn babies should be screened for congenital hypothyroidism by measurement of bloodspot TSH using a sample collected within 2-8 days after birth, as part of a national screening programme. (II,B).*
- *The measurement of thyroid related hormones as part of a neonatal screening programme should be restricted to specialist laboratories and should have a turnaround time of <5 days (✓).*
- *Confirmation of the diagnosis of congenital hypothyroidism involves measurement of serum TSH and FT4 in both mother and neonate and TSH receptor antibody in the mother. (III,B).*
- *All hypothyroid neonates should be treated as early as possible. Treatment must be started within the first 18 days of life. (Ib,A)*

3.4.2 Guiding Treatment/Follow Up

Thyroxine is the replacement hormone of choice. The goals of treatment are to raise the serum FT4 as rapidly as possible into the normal range, adjust the thyroxine dose with growth to keep the serum FT4 in the upper half of the reference range and the

TSH normal, and maintain normal growth and development while avoiding overtreatment.⁷¹ Monitoring of thyroxine replacement should take place 1-2 monthly during the first year of life and 3-6 monthly thereafter until growth has been completed. All infants should be re-evaluated at 3 years with a period of at least 2 weeks off thyroxine replacement therapy prior to repeat estimation of TSH and FT4 to exclude the possibility of a transient effect of maternal antibodies.⁶⁹

- *The measurement of both TSH and FT4 are required to optimise thyroxine replacement in infants. Age-related reference ranges should be used. (II,B).*

4. Hyperthyroidism

4.1 Primary Hyperthyroidism

4.1.1 Diagnosis

The classical symptoms and signs of hyperthyroidism (thyrotoxicosis) are reported in all textbooks of endocrinology. Some or all of these findings may be present in the individual patient depending on the severity and duration of hyperthyroidism. In elderly subjects the clinical picture is often different with predominance of weight loss and depression – so-called “apathetic” hyperthyroidism. In the elderly, cardiovascular problems are common, especially presentation with atrial fibrillation and deterioration in pre-existing heart disease.¹

It is essential that any clinical suspicion of thyrotoxicosis is confirmed or refuted by biochemical testing before further investigation or treatment is contemplated.²⁻⁴ The single most important biochemical test is serum TSH. If the serum TSH concentration is within the reference range then a diagnosis of hyperthyroidism is effectively ruled out.⁵ Exceptions to this rule are rare TSH-dependent causes of hyperthyroidism, such as TSH-producing tumours of the pituitary and syndromes of thyroid hormone resistance. (see Section 4.3).

The finding of a serum TSH concentration below the reference range (in a reputable second or third generation TSH assay) is not, however, specific for the diagnosis of hyperthyroidism. Low serum TSH, especially if low but >0.10 mU/L, often reflects “non-thyroidal illness” or therapy with a variety of commonly prescribed drugs^{2,6} (Chapter 7).

The presence of a low serum TSH should prompt measurement of circulating thyroid hormones (FT4 and FT3 concentrations).⁷ In most cases of hyperthyroidism a typical biochemical picture of elevated FT4 and FT3 with associated undetectable serum TSH will be evident. If FT4 is clearly elevated, then a diagnosis of thyrotoxicosis is confirmed; in such circumstances measurement of FT3 may not provide clinically useful additional information. If FT4 is not above the reference range in a patient with low serum TSH, FT3 should be measured since in some cases the biochemistry indicates a diagnosis of “T3-toxicosis” characterised by elevation of serum FT3 in the absence of a rise in FT4. This biochemistry is typically observed in mild cases of toxic nodular hyperthyroidism and early in the course of Graves’ disease (either primary presentation or relapse).⁴ In a few cases the converse is true in that a rise in FT3 is absent despite elevation of FT4 and suppression of TSH in a patient thought clinically to have thyrotoxicosis. The lack of rise in FT3 may reflect the presence of “non-thyroidal illness”, especially in elderly subjects; the explanation becoming evident on re-testing once other morbidity is eliminated⁸.

Once a biochemical diagnosis of hyperthyroidism has been made, other tests may be needed to indicate the cause and specialist referral should be sought⁹. Most cases of hyperthyroidism in the UK are due to Graves’ disease or toxic nodular goitre. In most cases the clinical picture indicates the cause (e.g. ophthalmopathy, diffuse goitre in Graves’ disease, nodular goitre in toxic nodular hyperthyroidism), in which case further investigations are not essential. If such clinical signs are absent, the presence

of thyroid peroxidase antibodies (TPOAb) is suggestive, but not diagnostic of, Graves' disease.^{2,4} The presence of TSH-receptor antibodies (TSH-RAb) is a more specific indicator of the diagnosis.¹⁰ Thyroid auto-antibodies are usually negative in toxic nodular hyperthyroidism. Radioisotope scanning, using ^{99m}technetium or ¹³¹iodine, typically shows a diffuse pattern of uptake in Graves' disease, in contrast to the presence of one or more "hot" nodules in toxic nodular hyperthyroidism^{2,4}. It is not mandatory to differentiate between Graves' hyperthyroidism and toxic nodular hyperthyroidism if the treatment plan is not altered (i.e. if ¹³¹iodine therapy is considered the treatment of choice).

In some cases, other causes of hyperthyroidism should be considered, particularly the diagnosis of thyroiditis in which there is thyroid cell destruction and release of pre-formed hormones, rather than increased synthesis and subsequent release of thyroid hormones. "Subacute" thyroiditis is suspected if there is thyroid pain/tenderness, often with a history suggestive of a viral illness. The finding of a raised ESR is helpful in confirming the diagnosis. Silent thyroiditis can occur in the post-partum period. All types of thyroiditis are associated with reduced or absent uptake of radioisotope (especially ¹²⁵iodine or ¹³¹iodine) into the thyroid. It is important to identify cases of thyroiditis since standard treatment with thionamides/radioiodine is ineffective and contraindicated¹¹. Thyroiditis is generally short-lived and self-limiting (and often followed by a hypothyroid phase).

Amiodarone-associated hyperthyroidism should be diagnosed only if high circulating FT4 is associated with high or high/normal FT3 and undetectable TSH since even in euthyroid subjects amiodarone therapy often causes modest elevation in serum FT4 (and reduction in FT3) because of its effect on peripheral deiodination of T4 to T3.¹² A diagnosis of amiodarone-associated hyperthyroidism should prompt specialist referral since management may be complex and involve further investigations.

- *The measurement of TSH using an assay with a functional sensitivity of <0.02 mU/L is a desirable early stage in the diagnosis of hyperthyroidism (II,B)*
- *In patients suspected of having hyperthyroidism all subnormal TSH results should trigger the measurement of FT4 (II,B)*
- *If FT4 is not elevated in the patient with subnormal TSH, FT3 should be measured to identify cases of T3-thyrotoxicosis (II,B)*
- *The co-existence of hyperthyroidism and non-thyroidal illness may result in the finding of a 'normal' FT3 (III,B)*
- *It is important to identify cases of thyroiditis since standard treatment with thionamides/radioiodine is ineffective and contraindicated⁹ (II,B)*
- *The measurement of TSH-receptor antibodies and thyroid peroxidase antibodies is not routinely required to determine the cause of hyperthyroidism if this is indicated by clinical features but they may be helpful in certain cases (III,B), especially if knowledge of the cause will influence treatment (II,B)*

- *Patients with confirmed hyperthyroidism should be referred for specialist care in order to establish the diagnosis and optimal management plan (III,B)*
- *Particular care is required in the diagnosis of hyperthyroidism in patients taking amiodarone. The measurement of TSH, FT4 and FT3 is required (II,B)*

4.1.2 Guiding Treatment

Patients with a confirmed biochemical diagnosis of hyperthyroidism should generally be commenced on a thionamide (carbimazole or propylthiouracil); this is not essential in those with mild disease if prompt definitive treatment with radioiodine is planned (II). Thionamides may be used short-term in preparation for definitive treatment with radioiodine or surgery or medium-term in the hope of inducing remission in cases of Graves' disease. Occasionally, thionamides are prescribed long-term (e.g. in elderly frail subjects with limited life expectancy) in whom definitive treatment is relatively contraindicated.²⁻⁴

If the patient has marked adrenergic symptoms e.g. tremor, tachycardia, then administration of beta-adrenergic blockers may be indicated for rapid relief of symptoms (II). Propranolol is often used but beta-adrenergic blockers requiring only once daily administration (e.g. atenolol, bisoprol) may be preferable. Beta-adrenergic blockers are usually the sole form of treatment indicated/required in cases of thyroiditis, although severe persistent symptoms/signs in "subacute" thyroiditis may require additional therapy with salicylates and/or glucocorticoids.²

Most patients with hyperthyroidism require definitive treatment with ¹³¹Iodine (II). This reflects the low remission rate with thionamides alone in Graves' disease (<50%, especially in cases with severe biochemical disease, large goitre and possibly in men)¹³ and lack of curative effect of these drugs in toxic nodular hyperthyroidism.

In mild clinical/biochemical disease, then prompt treatment with ¹³¹Iodine (without preceding thionamides) is often appropriate³; in severe clinical or biochemical disease thionamides should be administered (typically for 2-3 months) until the serum FT4 is normal or near normal.^{2,4,14} Propylthiouracil, but not carbimazole, may induce relative radioresistance determining the need for larger or repeated doses of radioiodine.^{15,16}

All patients proceeding to surgery should be rendered euthyroid (normal FT4 and FT3) with thionamides^{3,4} (II). Preparation with beta adrenergic-blockers, iodine or similar agents alone is considered inadequate unless thionamides are contraindicated.

- *The degree of elevation of serum FT4 and FT3 provides an indication of the severity of hyperthyroidism and should be interpreted in the context of clinical symptoms and signs to direct first-line therapy (III,B).*

4.1.3 Assessing Response to Therapy

a) Thionamide therapy. In patients being treated with thionamides, regular measurement of FT4 and TSH is essential in order to adjust drug doses to allow control of disease and avoidance of iatrogenic hypothyroidism.²⁻⁴ Measurement of

serum TSH alone is not adequate since TSH may remain suppressed for weeks-months after initiation of thionamides, especially in Graves' disease², so drug doses should be titrated against measurements of FT4 (or FT3 in cases of T3-toxicosis).

Biochemistry should be checked every 4-6 weeks for the first few months after initiation of thionamides.^{2,4} Once doses have been reduced to maintenance levels, testing may be less frequent (approximately every 3 months). A fall in FT4 to low normal or to below the normal range should prompt reduction in thionamide dosage. A rise in serum TSH also indicates the development of hypothyroidism and the need for dose reduction. Persistent suppression of serum TSH should not, in itself, prompt an increase in thionamide doses.

Where patients are to be treated with a 'block and replace' regimen, a thionamide is given alone for the first 4-6 weeks (e.g. carbimazole 40mg daily). Thyroxine (e.g. 125µg daily) is added in when the FT4 concentration has normalised while continuing with the same dose of antithyroid drug. The TSH and FT4 should be checked 4-6 weeks thereafter and adjustments made to the dose of thyroxine if indicated. FT4 and TSH should be checked again after 4-6 weeks; if the FT4 is in the reference range and TSH not elevated, the same dose is continued and tests checked again after 3 months. The serum TSH may remain suppressed for several months after initiation of antithyroid drug treatment and decisions about adjustment of medication should be influenced largely by the FT4 concentration. Once the FT4 and TSH have normalised the required dose of antithyroid drug and thyroxine is unlikely to vary and TFT may be checked less frequently (e.g. six monthly). Systematic review has shown that the use of a 'block and replace regimen' is not superior to a dose titration regimen in terms of remission rate in Graves' disease and may be associated with more adverse events.^{17,18}

Persistent elevation in serum FT4 despite apparent adequate prescription of thionamides usually indicates poor compliance (**III**). Persistent biochemical hyperthyroidism after weeks-months of therapy makes induction of remission in cases of Graves' disease very unlikely. Persistent suppression of TSH while on thionamides may also indicate poor likelihood of Graves' diseases entering remission, although evidence is conflicting.^{19,20}

- *Serum FT4 and TSH should be measured in all patients receiving thionamides. In most cases the FT4 result will be the marker of choice to guide therapy (II,B)*
- *Thyroid function tests should be performed every 4-6 weeks after commencing thionamides. The frequency of testing should be reduced to every ~3months once a maintenance dose is achieved (II,B)*

b) Radioiodine therapy. Serum FT4 and TSH should be checked every 4-6 weeks for several months after administration of ¹³¹I iodine. A fall in serum FT4 to below normal or rise in TSH should prompt reduction in dose or withdrawal of any thionamide administered post-radioiodine therapy. In those not receiving thionamides, a mild and transient rise in serum TSH may be observed in the first 6 months after ¹³¹I iodine and does not necessarily indicate the need for commencement of thyroxine replacement therapy.²¹ A more marked or persistent rise in serum TSH (>20 mU/L for more than

one month), especially if associated with symptoms, should prompt thyroxine prescription. Persistent elevation of FT4 six months after radioiodine therapy indicates lack of cure and need for consideration of re-dosing.²² Suppression of serum TSH may persist for weeks-months after radioiodine and does not, at present, indicate the need for re-treatment (see Section 4.2). If FT4 is normal (off thionamides) approximately 6 months after radioiodine, the frequency of testing may be reduced to 3 monthly and then 6 monthly. After an interval of euthyroidism (normal serum FT4) of more than 12 months after radioiodine therapy, the patient may be transferred to annual testing (see Section 4.1.4).

- *Serum FT4 and TSH should be measured in all patients treated with radioiodine. In most cases the FT4 result will be the marker of choice to guide therapy (II,B)*
- *Thyroid function tests should be performed every 4-6 weeks for at least six months following radioiodine therapy (II,B). The frequency of testing may be reduced when the FT4 remains within the reference range, although an annual TFT is still required (III,B).*
- *A fall in FT4 to below the reference range or a rise in TSH to above the reference range should prompt reduction in thionamide dosage or drug withdrawal in subjects prescribed these agents following radioiodine therapy, followed by re-assessment off thionamide therapy (III,B)*
- *A serum TSH result of >20mU/L following radioiodine therapy in a patient not receiving thionamides in the previous 4-6 weeks should trigger thyroxine therapy (II,B)*

4.1.4 Long-Term Follow Up

All patients who have received radioiodine therapy for hyperthyroidism or surgery (partial thyroidectomy) require life-long follow-up to identify development of hypothyroidism. Using a computerised recall system and testing of thyroid function (TSH plus FT4) approximately every 12 months most efficiently achieves this.²³ Measurement of serum TSH is the most sensitive and specific indicator of onset of hypothyroidism. Follow-up may also indicate recurrence of hyperthyroidism; this is rare in those previously rendered euthyroid by radioiodine but relatively common in those previously treated by partial thyroidectomy.²⁴ Regular thyroid function tests should also be undertaken in any patient treated long-term with thionamides (testing every 6-12 months).

- *Life-long thyroid function testing is required for all patients who have received radioiodine therapy or surgery for hyperthyroidism (II,B)*
- *Regular thyroid function testing is required for all patients being treated with long-term thionamides (II,B)*

4.2 Subclinical (Mild) Hyperthyroidism

4.2.1 Diagnosis

This is essentially a biochemical diagnosis based on the finding of low serum TSH in association with normal serum concentrations of FT4 and FT3. Clinical symptoms and signs are typically absent or mild/non-specific.²⁵

It should be noted that a low serum TSH (especially if reduced but >0.1mU/L) can reflect 'non-thyroidal illness' and various drug therapies (see Chapter 7). This is a frequent finding in hospitalised patients. In primary care a serum TSH of <0.1mU/L is more likely to indicate mild thyroid hormone excess²⁵.

- *Subclinical hyperthyroidism is defined as a low serum TSH in the presence of normal concentrations of FT4 and FT3 (II,B)*

4.2.2 Guiding treatment/follow-up

The finding of a low serum TSH should prompt consideration of the cause. If non-thyroidal illness and relevant drug therapies have been excluded then repeat measurement of TSH (with serum FT4 and FT3) should be performed, to exclude progression to overt hyperthyroidism and to determine if the biochemical abnormality is persistent. The timing of repeat assessment should be based on the clinical picture; more frequent testing may be appropriate if the subject is elderly or has underlying vascular disease, otherwise repeat biochemical testing after 3-6 months may be appropriate.²⁵

Growing evidence suggests subclinical hyperthyroidism in elderly subjects is associated with increased risk of development of atrial fibrillation²⁶ and increased vascular mortality.²⁷ Persistent subclinical hyperthyroidism should prompt specialist referral (III). The thyroid specialist may seek evidence for underlying nodular or Graves' disease (on the basis of clinical, immunological or imaging findings) and consider treatment with ¹³¹I iodine or thionamides.²⁵

If treatment is not given, long-term follow-up of undetectable TSH is important because of risk (albeit low) of progression to overt disease (characterised by a rise in serum thyroid hormones).²⁸

- *Patients with subclinical hyperthyroidism that cannot be explained by non-thyroidal illness or drug therapy should have repeat thyroid function testing with a frequency initially determined by the clinical findings (III,B)*
- *Persistent subclinical hyperthyroidism should prompt specialist referral (III,B)*
- *Untreated subclinical hyperthyroidism should be followed into the long term by testing thyroid function every 6-12 months (III,B)*

4.3 **Inappropriate TSH**

4.3.1 Diagnosis

This is a biochemical diagnosis in which elevation in circulating FT4 and/or FT3 is associated with an “inappropriately” detectable or elevated serum TSH concentration.³ If this biochemical picture is observed then assay artefact/laboratory error should be considered first (**III**). Common explanations are binding protein abnormalities leading to apparent elevation of FT4 (e.g. familial dysalbuminaemic hyperthyroxinaemia) or antibody interference with measurements of FT4, FT3 or TSH, although these problems are assay dependent.

Once the laboratory has excluded such explanations (Chapter 7) then the cause of “true” inappropriate TSH should be considered (**III**). The major diagnoses are a TSH-secreting pituitary tumour (TSH-oma) or a syndrome of thyroid hormone resistance.^{29,30} The finding of an elevated serum sex hormone binding globulin (SHBG) and circulating free alpha subunit may support the diagnosis of TSH-oma, as may the finding of hyper- or hypo-secretion of other pituitary hormones. Pituitary imaging usually confirms the diagnosis but should not be undertaken until the appropriate biochemical confirmation has been made. A syndrome of thyroid hormone resistance can be confirmed by family history; sequencing of the beta thyroid hormone receptor (available through the Supraregional Assay Service <http://www.sas-centre.org/>) confirms the diagnosis.

- *The finding of an inappropriate TSH in the presence of elevated FT4 and/or FT3 should stimulate the laboratory to consider errors or assay artefacts (**IIIB**). Confirmation by repeat, including another assay is good practice (✓).*
- *The measurement of serum SHBG, alpha subunit and other anterior pituitary hormones can help to distinguish TSH-oma from thyroid hormone resistance (**III,B**)*

4.3.2 Guiding treatment

TSH-secreting pituitary tumours require treatment in a specialist centre. Therapy should be monitored by serial measurement of FT4, FT3 and TSH.³¹ Patients with thyroid hormone resistance often require no therapy or only symptomatic treatment with beta adrenergic blocking agents. Treatment with radioiodine or thionamides is contraindicated. An important consequence of the diagnosis is thus avoidance of such treatments through incorrect interpretation of thyroid function tests.³²

5. Thyroid Function Testing in Pregnancy and Neonates

5.1 Introduction

During pregnancy oestrogen production increases and TBG concentrations rise, leading to an increase in TT4 and TT3. There is also a fall in serum TSH during the first trimester^{1,2} as a result of the mild thyrotrophic effect of HCG. Depending on the method used there may be a modest decrease in FT4 in the first trimester, but in the second and third trimesters the serum FT4 and FT3 levels decrease and may fall below the reference range derived from non-pregnant women. The magnitude of this fall in free thyroid hormones is method dependent. After delivery levels of thyroid hormones and TSH normally return to the pre-pregnant state. Trimester-related reference ranges should be applied for TSH and for total and free thyroid hormones; for free hormones these ranges should be appropriate to the method used by the laboratory.³ **(III)**.

In pregnancy there is an increased requirement for thyroxine, the reasons for which are incompletely understood.⁴ In the first trimester of pregnancy the foetus is dependent for normal development of the brain on maternal thyroid hormones; hence it is vitally important that adequate maternal levels of thyroid hormones are maintained. There is also an increased requirement for iodine through pregnancy, which becomes clinically significant in areas of iodine deficiency. A daily intake of 200µg in pregnancy is recommended by the WHO; nutritional surveys indicate that iodine deficiency is not generally a problem in the UK.

Changes in the immune system take place during and after pregnancy which influence the course of existing autoimmune thyroid disease and also predispose to the relapse or de novo development of autoimmune thyroid disease.

- *Both TSH and FT4 (and FT3 also when TSH is below the detection limit of a reputable assay) should be used to assess thyroid status and monitor thyroxine therapy in pregnant patients. **(III,B)***
- *Trimester- and method-specific reference intervals should be used when reporting thyroid test values for pregnant patients **(III,B)***

The role of TFT in hypothyroidism and hyperthyroidism are described in detail in Chapters 3 and 4, so only aspects relating specifically to pregnancy are included here.

5.2 Hypothyroidism

Maintenance of a true euthyroid state is particularly important during pregnancy. In the early stages of gestation, before the foetal thyroid gland becomes active (about 12 weeks gestational age), maternal thyroid hormone is required for normal foetal neurological development. There is an increased need for thyroxine during pregnancy in women with hypothyroidism^{1,4,5} and absorption of thyroxine may be diminished.⁶ Several recent studies report both increased foetal loss as well as IQ deficits in infants born to mothers with either undiagnosed or inadequately treated hypothyroidism^{7,8}

and it is also suggested that early identification and treatment of mild (subclinical) hypothyroidism may prevent the long-term effects of low thyroid hormone levels on the psychomotor and auditory systems of the neonate. The impairment appears to relate to the level of T4 rather than hypothyroidism per se⁹ and even mild degrees of hypothyroidism or presence of TPO-Ab are also incriminated.¹⁰

- *The thyroid status of hypothyroid patients should be checked with TSH + FT4 during each trimester (II,B). Measurement of T3 is not appropriate.*

The FT4 level should be maintained at the upper end of the non-pregnant reference range in the first trimester, with the TSH at the lower end of the reference range or a little below (0.4 – 2.0mU/L would be appropriate as this is normal for pregnancy). Results should ideally be monitored against trimester-related reference ranges.

- *Normal TSH and FT4 concentrations for the gestational age should be maintained. (II,B)*

Patients receiving thyroxine replacement therapy who become pregnant usually require an increased dose (an extra 25 or 50 ug/day) at diagnosis of pregnancy to maintain normal serum TSH levels.^{2,4,5,11}

- *In hypothyroid patients the TSH should be checked and the thyroxine dose should be adjusted as soon as pregnancy is diagnosed (II,B)*
- *The dose of thyroxine will usually require a small increase, to ensure that the FT4 level is in the (upper) reference range and the TSH in the low/normal range (0.4 – 2.0mU/L would be appropriate as this is normal for pregnancy) (II,B)*
- *An increase in the dose of T4 is especially important for women who have been treated for thyroid cancer, to ensure that the TSH remains fully suppressed (IV,C)*
- *After delivery the TSH should be checked (eg at 2 to 4 weeks post-partum, at which time the dose of thyroxine can usually be reduced back to the pre-pregnancy level (III,C)*
- *Ideally, the following sequence of TFT should be performed in the hypothyroid woman during pregnancy:*
 - *before conception if possible*
 - *at time of diagnosis of pregnancy*
 - *at antenatal booking*
 - *at least once in second and third trimesters and again after delivery (e.g. 2-4 weeks post-partum)*
 - *the newly diagnosed hypothyroid patient will need to be tested frequently (e.g. every 4-6 weeks) until stabilized (✓)*

5.3 Hyperthyroidism

Patients being treated with antithyroid drugs will require the dose to be revised at the diagnosis of pregnancy, as these drugs cross the placenta. The dose of anti-thyroid drug is kept to the minimum consistent with maintaining euthyroidism.^{12,13} Patients on a 'block and replace' regimen should be changed immediately to a maintenance dose of anti-thyroid drug only¹⁴. Patients on carbimazole may be switched to PTU which it is claimed has some advantages in the pregnant patient^{14,15} and is preferable during breast feeding.

The FT4 level should be maintained at the upper end of the reference range.¹⁵ This is particularly important in the first trimester, when even mild hypothyroidism must be avoided, because of both the risk to the foetus, and also increased rates of spontaneous miscarriage and premature delivery. Results should be monitored against trimester-related reference ranges.

Previous successful treatment of hyperthyroidism does not guarantee absence of thyroid related problems during pregnancy. Relapse is more likely to occur after delivery. There is also the possibility of intrauterine or neonatal thyrotoxicosis developing in the mature foetus or newborn if there is a high maternal titre of TSH-RAb¹⁶ even in women requiring T4 replacement therapy after thyroid surgery and/or ¹³¹I therapy. Graves' disease may present de novo after delivery.

- *In hyperthyroid women taking anti-thyroid drugs thyroid function tests should be performed prior to conception if possible, and therapy modified if appropriate (IV,C)*
- *Hyperthyroid women taking anti-thyroid drugs should have thyroid function tests checked at the time of diagnosis of pregnancy or at antenatal booking, when the therapy may need to be modified (eg to PTU) and the dose reduced (II,B)*
- *Pregnant women who are hyperthyroid should be seen by a specialist (III,B)*
- *The newly diagnosed hyperthyroid patient will require frequent testing during pregnancy (e.g. monthly) until stabilised (II,B). FT4 rather than TSH is the result that will guide therapy.*
- *Pregnant women receiving anti-thyroid medication should be tested frequently (perhaps monthly) and the dose reduced to the minimum required to maintain a euthyroid state (i.e. FT4 normal), or discontinued toward term if the patient is euthyroid. (II,B)*
- *Women who have been successfully treated previously for hyperthyroidism and are euthyroid at antenatal booking may be checked again once in the second and third trimesters. (IV,C)*
- *All previously hyperthyroid women should be retested after delivery, as there is a significant chance of relapse at this time. (II,B)*

- *Measurement of TSH-RAb at antenatal booking can be useful and if negative or low need not be measured again. A very high titre can predict the chance of intrauterine or neonatal thyrotoxicosis developing. (IV,C)*
- *The obstetrician must enquire about past history of thyroid disease, as women who have had previous thyroidectomy for Graves' hyperthyroidism and are currently euthyroid or hypothyroid may still have high titres of TSH-RAb with concomitant risk of neonatal Graves' disease. (IV,C)*

5.4 Post-Partum Thyroiditis

Post-partum thyroiditis^{10,17,18} occurs in rather more than 5% of the population in iodine-replete areas, within 2 to 6 months after delivery or miscarriage. It gives rise to transient thyroid dysfunction, which is most frequently characterised by a brief thyrotoxic phase followed by hypothyroidism, usually with spontaneous resolution. The thyroid is painless and often there is no goitre; symptoms are often non-specific (eg tiredness, anxiety, depression), so awareness and use of TFT are important. TPO-Ab results are usually positive, and the presence of TPO-Ab in early pregnancy predicts a 30 – 50% chance of postpartum thyroiditis developing.

If the initial TFT show a thyrotoxic pattern, further tests are required to differentiate postpartum thyroiditis from Graves' disease. These would include an isotope uptake \pm scan using either ⁹⁹Tc or ¹²³I (but not ¹³¹I), both of which necessitate temporary cessation of breast feeding. Measurement of TSH-RAb may also be useful if available. If the thyrotoxicosis is secondary to postpartum thyroiditis treatment is not required but the TFT should be monitored to detect onset of hypothyroidism.

If the initial tests show hypothyroidism thyroxine treatment should be started in a symptomatic patient, but may be discontinued after about 6 months when the TSH should be checked to determine if further thyroxine treatment is required.

- *Post-partum patients should have TSH and FT4 measured at 6 – 8 weeks post-partum (or post-abortion) if they have any of the following: (II,B)*
 - *goitre*
 - *non-specific symptoms that may suggest thyroiditis*
 - *previous history of post-partum thyroiditis*
 - *previous history of autoimmune thyroid disease*
 - *positive TPO-Ab*
- *If the initial TFT show a thyrotoxic pattern, further tests are required to differentiate postpartum thyroiditis from Graves' disease (II,B).*
- *If the thyroid function tests show hypothyroidism thyroxine therapy should be started in a symptomatic patient (II,B)*

5.5 Screening for Thyroid Disease during Pregnancy

There is now substantial evidence that thyroid deficiency during pregnancy can result in problems in development of the young child.⁷⁻¹⁰ In the early stages of pregnancy the developing foetus is entirely dependent on the mother's thyroid hormone, so it is vitally important that the pregnant woman's thyroid hormone levels are adequate.

The question therefore is whether all pregnant women should be screened.^{19,20} The issues are well discussed¹¹ and the British Thyroid Association will be giving its attention to these, but currently the recommendations are as follows:

- *Pregnant women in the following categories should have thyroid function assessed either at diagnosis or at antenatal booking, or even before conception if feasible (IIb,B)*
 - *type-1 diabetes*
 - *previous history of thyroid disease*
 - *current thyroid disease*
 - *family history of thyroid disease*
 - *goitre*
 - *symptoms of hypothyroidism*
- *Thyroid function testing during pregnancy should comprise both TSH and FT4 (II,B). TPO-Ab should also be considered as this has predictive value for both post-partum thyroiditis and foetal impairment (IV,C)*

5.6 Neonatal Thyroid Assessment

5.6.1 Reference Ranges in Neonates

At delivery the normal full term neonate shows a marked and rapid increase in serum TSH as a consequence of cutting the umbilical cord. The peak TSH surge occurs within 30 minutes of birth reaching concentrations that would be diagnostic of primary hypothyroidism in an adult. Serum TSH then starts to fall after 1-2 hours so that by 2-3 days they have returned to concentrations typical of adults. Following the TSH surge there is release of T4 and T3 and a progressive increase in serum FT4 and FT3 during the first 24-36 hours of postnatal life followed by a gradual return over the next few days to concentrations typical of normal adults.²¹ Similar, though less pronounced changes occur in premature neonates such that premature neonates are in a state of relative hypothyroxinaemia.²² Premature neonates may be considered as having a specific form of non-thyroidal illness (NTI) (see Chapter 7) and as they mature the TSH, FT4 and FT3 mimic the recovery phase from NTI. Few laboratories will have definitive reference ranges for TFT in neonates and so there is reliance on literature values.

- *Unless there are compelling clinical reasons thyroid function testing should be avoided during the first three days of life. Where testing is performed TFT results should be interpreted with care and repeat testing after a few days is recommended before any firm diagnosis is reached. (III,B)*

5.6.2 Neonatal Screening for Congenital Hypothyroidism

This topic has already been addressed in Chapter 3. The recommendations are repeated here for the sake of consistency. Details of policies and standards for newborn blood spot screening in the UK are published ²³.

- *All newborn babies should be screened for congenital hypothyroidism by measurement of bloodspot TSH using a sample collected within 2-7 days after birth, as part of a national screening programme. (II,B).*
- *The measurement of thyroid related hormones as part of a neonatal screening programme should be restricted to specialist laboratories and should have a turnaround time of <5 days (III,B).*
- *Confirmation of the diagnosis of congenital hypothyroidism involves measurement of serum TSH and FT4 in both mother and neonate and TSH receptor antibody in the mother. (III,B).*
- *All hypothyroid neonates should be treated as early as possible. Treatment must be started within the first 18 days of life (Ib,A).*

5.6.3 Neonatal Hypothyroidism

Treatment for neonatal hypothyroidism should be started as soon as possible, without necessarily waiting for confirmatory TFT or thyroid scanning. Every day of delay may result in loss of IQ²⁴. Therefore, it is safer to start treatment that can be stopped than to delay the introduction of treatment. Investigations such as scintigraphy, ultrasonography and measurement of circulating thyroglobulin concentrations may help to determine the precise cause of neonatal hypothyroidism. If scintigraphy cannot be performed before or soon after thyroxine therapy is commenced it can be performed when the infant is 3 years old. At that time thyroxine can safely be discontinued for one month. Confirmation of hypothyroidism may be obtained at this time by measurement of TFT while off therapy.²⁵

Thyroxine is the replacement hormone of choice. The goals of treatment are to raise the serum FT4 as rapidly as possible into the normal range, adjust the thyroxine dose with growth to keep the serum FT4 in the upper half of the reference range and the TSH normal, and maintain normal growth and development while avoiding overtreatment.²⁶ For a term neonate a high starting dose of 50µg per day (10-15 µg/kg) is typical and this dose may not need to be changed for many months.²⁵ Smaller doses of 25-37.5µg per day may be more appropriate if the biochemical abnormality is more subtle.

A neonate born to a mother with Graves' disease may have primary hypothyroidism on biochemical testing because of the transfer of antithyroid drug or 'blocking' TSH-RAb to the fetus.

Monitoring of thyroxine replacement should take place 1-2 monthly during the first year of life and 3-6 monthly thereafter until growth has been completed.

- *The measurement of both TSH and FT4 are required to optimise thyroxine*

replacement in infants. Age-related reference ranges should be used. (II,B).

- *Serum TSH and FT4 should also be measured in the mother of a neonate with suspected congenital hypothyroidism. Measurement of maternal TSHRab is also helpful when transient hypothyroidism is a possibility (✓)*

5.6.4 Neonatal Hyperthyroidism

Hyperthyroidism is rare in neonates, accounting for at most 1% of the cases of hyperthyroidism in childhood. Nearly all cases of neonatal hyperthyroidism are associated with maternal Graves' disease where the cause is transplacental passage of TSH-RAb. Hyperthyroidism is likely only in neonates of mothers that have appreciably elevated TSH-RAb but these women may themselves be hypothyroid as a result of previous treatment. It is possible for neonatal hyperthyroidism to be masked in the first few days of life by transplacental passage of antithyroid drugs being taken by the mother with Graves' disease. A very high titre of TSH-RAb in mid-or late pregnancy can predict a risk of intrauterine or neonatal thyrotoxicosis ²⁷.

The diagnosis of neonatal hyperthyroidism should be confirmed by measurement of serum TSH and FT4. This diagnosis may be made in cord blood from a woman with a history of Graves' disease. Treatment with antithyroid drugs should be initiated promptly with FT4 being used to guide therapy. In most neonates improvement is rapid and treatment can be withdrawn in several weeks or months, according to the clinical findings and measurements of serum TSH and FT4.²⁷

Hyperthyroidism in most neonates subsides spontaneously over 3-12 weeks after birth as the maternal TSH-RAb disappears from the infant's serum. However, a rarer form of persistent neonatal hyperthyroidism is caused by germ line mutations in the TSH receptor and the condition may also be associated with McCune Albright syndrome ²⁶.

- *The diagnosis of neonatal hyperthyroidism requires measurement of serum TSH and FT4. Both TSH and FT4 should be measured at regular intervals to guide treatment with antithyroid drugs. (III,B)*

6 Thyroid Function Testing in Thyroid Cancer

6.1 Introduction

Thyroid cancer may be differentiated (papillary or follicular), medullary or anaplastic. The use of thyroid function tests differs with the type of thyroid cancer. Details of the diagnosis and general treatment of thyroid cancer can be found in "Guidelines for the management of thyroid cancer in adults" published by British Thyroid Association and the Royal College of Physicians.¹

6.2 Differentiated Thyroid Cancer

6.2.1 The Role of TSH and Thyroid Hormones

a) Diagnosis. Patients with thyroid cancer usually present with a nodule or goitre. Thyroid function tests should be performed to aid the diagnosis of conditions such as toxic nodular goitre or goitrous hypothyroidism. Thyroid function tests do not directly aid the diagnosis of thyroid cancer, as patients are generally euthyroid.

b) Monitoring treatment. After surgery for thyroid cancer an important aspect of treatment is the long-term suppression of TSH with exogenous thyroid hormone. Thyroxine is used in preference to tri-iodothyronine for this purpose and the dose should be sufficient to suppress the TSH to $<0.10\text{mU/L}$ in a reputable second or third generation TSH assay (**III**). The serum FT4 is usually elevated on this dose and does not need to be within the 'reference range'; however clinical features of over treatment should be noted. The dose of thyroxine should be adjusted by $25\mu\text{g}$ (about every 6 weeks) until the serum TSH is adequately suppressed (**III**). Most patients will require 175 or 200 μg daily.

c) Long term follow-up. After surgery the supervision of the replacement treatment is best done by an endocrinologist. The aim of treatment is to maintain the serum TSH at a level $<0.1\text{mU/L}$ (**III**). General practitioners should be advised of the need for this suppression and of the target TSH level.

- *After thyroidectomy for thyroid cancer the TSH should be suppressed to and maintained at a level of $<0.1\text{ mU/L}$ in a reputable assay (**III,B**)*

6.2.2. Thyroglobulin and Thyroglobulin Antibodies

Details of the assay methodology for the measurement of thyroglobulin can be found in Chapter 7 and also in Appendix 2 of "Guidelines for the management of thyroid cancer in adults".¹ A recent article has reviewed the clinical impact of method differences for the measurement of thyroglobulin (Tg) and thyroglobulin antibody (TgAb) on the management of patients with differentiated thyroid carcinomas².

Although Tg is a specific and extremely useful tumour marker for differentiated thyroid cancer it has no role in the diagnosis of the condition. Thyroglobulin is

secreted by both normal and cancerous thyroid cells, therefore in patients who have not had a total thyroidectomy and ¹³¹I iodine ablation, the interpretation of serum Tg measurements is limited by the inability to differentiate between tumour and thyroid remnant.

- *The measurement of serum thyroglobulin has no role in the diagnosis of thyroid cancer (✓)*

b) Assessing response and monitoring treatment. In patients who have been treated with total thyroidectomy and ¹³¹I iodine ablation, detectable serum Tg (>2ug/L) is highly suggestive of residual or recurrent tumour, but could also indicate persistence of a remnant of normal thyroid tissue.³ The sensitivity of serum Tg measurements for detecting recurrence is enhanced by an elevated TSH concentration. Therefore, Tg should preferably be measured when the serum TSH is more than 30 mU/L, usually in conjunction with a whole-body radioiodine scan; this can be achieved by either withdrawal of thyroxine or administering recombinant TSH. To assess TSH status TFT should be performed whenever Tg is being measured. The profile of the TFT will be determined by the nature of thyroid hormone replacement (thyroxine or tri-iodothyronine).

Endogenous TgAb may interfere in Tg assays, causing either falsely elevated or falsely lowered results, making interpretation difficult. Therefore, it is recommended that TgAb be measured at the same time as Tg. However, the absence of elevated TgAb in one assay does not entirely exclude their presence² nor exclude the possibility of interference in Tg assays. Discrepancy of Tg results measured by radioimmunoassay and immunometric assay may indicate interference by TgAb. There is evidence that TgAb themselves have some value in monitoring response to treatment.⁴

c) Long term follow-up. There is normally no need to measure serum Tg more frequently than 3 monthly during routine follow-up, and for patients in remission annual measurement should suffice. For routine follow-up of patients in remission serum Tg can be measured while the patient is taking TSH suppressive therapy. If the serum Tg is detectable while on suppressive therapy there is no need for TSH stimulation.

Different assays for Tg can give different results depending on the assay antibody specificity and the degree of interference from endogenous antibodies (Chapter 7). Therefore, to ensure continuity in monitoring, clinicians should use the same laboratory and Tg assay on a long-term basis. Laboratories should not change methods without prior consultation with clinical users of the service².

- *Samples for thyroglobulin assay should not be collected for at least 4-6 weeks after thyroidectomy, or ¹³¹I iodine therapy. (II,B)*
- *In a sensitive assay (RIA or IRMA) detectable thyroglobulin usually indicates the need for further investigation to identify the source. (II,B). The laboratory should advise of the cut-off level for a particular assay method.*

- *Thyroid function tests should be performed whenever thyroglobulin and thyroglobulin antibodies are measured (II,B). The requesting clinician should indicate on the form whether the patient is on thyroxine or tri-iodothyronine therapy.*
- *Thyroglobulin antibodies should be measured at diagnosis and simultaneously with measurement of thyroglobulin. (IV,C)*
- *If TgAb are detectable, measurement should be repeated at regular (~6 monthly) intervals. If undetectable they should be measured at follow-up when thyroglobulin is measured. The development of increasing TgAb may indicate recurrence of tumour. (II,B)*
- *For best sensitivity Tg should be measured when the serum TSH is >30 mU/L. (after thyroxine withdrawal or the use of recombinant human TSH) (II,B). There is no need for TSH stimulation if the serum Tg is already detectable.*
- *For routine follow-up of patients in remission, serum Tg can be measured while the patient is taking TSH suppressive treatment. (II,B)*
- *The frequency of Tg measurement during follow-up of thyroid cancer will be determined by the clinical condition of the patient, whether the tumour has been deemed high risk or low risk and on previous results.*
- *Thyroglobulin assays are difficult and continuity of availability and use is recommended (✓)*
- *Laboratories should not change methods without prior consultation with clinical users of the service (✓)*

6.2.3 Recombinant Human TSH (rhTSH)

Detailed recommendations for the use of rhTSH in the management of differentiated thyroid cancer can be found in Appendix 3 of "Guidelines for the management of thyroid cancer in adults".¹

a) Assessment of response to treatment. RhTSH (thyrogen) is used as a provocative test to assess if any thyroid cancer cells remain after ablative therapy. It is not currently available for therapeutic use. Withdrawal of thyroxine treatment is not necessary prior to the administration of rhTSH. The rhTSH test is used only in patients:

- who have had total thyroidectomy and remnant ablation
- who have no clinical evidence of residual or recurrent disease
- when the basal Tg is <2ug/L and TgAb are negative

The rhTSH test is specifically indicated for patients who are unable to mount a TSH response to thyroxine withdrawal, and those for whom a period of hypothyroidism may be dangerous; however its use need not be restricted to the latter groups.

Although the rhTSH test has only recently been introduced, the evidence which is evolving suggests that the test is probably as reliable as thyroxine withdrawal⁵, and that measurement of the thyroglobulin response may be adequate without the need for ¹³¹iodine scan, particularly in low-risk patients.^{3,5,6}

- *The measurement of Tg stimulated by the administration of recombinant human TSH is a sensitive probe of recurrent thyroid cancer and does not require thyroxine withdrawal (III,B)*

b) Protocol. RhTSH must only be used in accordance with the manufacturer's instructions. After administration of rhTSH the presence of tumour tissue is detected by measurement of serum thyroglobulin with or without a ¹³¹iodine scan. The protocol is as follows:

- On each of days 1 and 2 rhTSH 0.9 mg is administered by deep IM injection
- A tracer dose of ¹³¹iodine is given on day 3 and the scan performed on day 5. (The tracer dose of ¹³¹iodine should be approximately 150 MBq; a minimum of 30 minutes scanning time or a minimum of 140,000 counts per minute should be obtained)
- Serum Tg is measured on day 5. If a ¹³¹iodine scan has been performed as part of the protocol the laboratory should be informed since the presence of residual radioactivity has implications for sampling handling and transport and for the method used to measure Tg.

c) Interpretation of test result.

- *A thyroglobulin level of >2µg/L after recombinant human TSH indicates the need for further investigation⁵ (III,B)*
- *If the thyroglobulin is stimulated by rhTSH and ¹³¹iodine scan is either negative or not done, then further tests are required to localise the presumed tumour tissue. (IV,C)*
- *A newly detectable Tg level or a Tg level rising over time after rhTSH stimulation, or a high index of suspicion of metastatic disease, even in the setting of a negative radioiodine scan, should prompt further evaluation with thyroid hormone withdrawal. (IV,C)*

6.3 Medullary Thyroid Cancer (MTC)

Details of the diagnosis and management of MTC can be found in "Guidelines for the management of thyroid cancer in adults".¹

6.3.1 Calcitonin

Details of the analytical considerations for the measurement of serum calcitonin can be found in Chapter 7 and Appendix 2 of "Guidelines for the management of thyroid cancer in adults".¹

a) Diagnosis. Calcitonin is a useful tumour marker for medullary thyroid cancer. Pre-operative diagnosis should include baseline values for calcitonin. There is a positive correlation between the calcitonin level and the tumour mass. A stimulation test with calcium/pentagastrin may also be indicated in the following situations:

- To confirm a diagnosis of MTC pre-operatively when calcitonin levels are only mildly elevated (<100ng/L)
 - To detect C-cell disease in RET positive gene carriers (see Section 6.3.3)
 - For pre-surgical assessment of RET positive children
 - For post-operative monitoring for tumour recurrence
-
- *A pre-operative value for plasma calcitonin (preferably fasting) should be measured in patients with medullary thyroid cancer to establish a baseline for the longer-term follow up. (✓)*
 - *A stimulation test with calcium/pentagastrin may be indicated in some patients (✓)*

b) Monitoring treatment. Patients with MTC will require lifelong follow-up, including regular measurement of plasma calcitonin. The response to primary surgery can be assessed both clinically, and by the measurement of calcitonin. The finding of an elevated calcitonin level post-operatively requires further investigation and progressively rising concentrations of calcitonin should trigger imaging for further staging.

- *Response to primary surgery can be assessed both clinically, and by the measurement of calcitonin. (II,B)*
- *A post-operative plasma calcitonin level is required to aid the longer-term follow-up. Post-operative samples should be collected at least ten days after thyroidectomy and should be fasting samples if possible (✓).*
- *The finding of an elevated calcitonin level post-operatively requires further evaluation. (II,B)*
- *Progressively rising levels of calcitonin should trigger imaging for further staging. (II,B)*
- *Lifelong calcitonin measurement is recommended for patients with medullary thyroid cancer. The frequency of measurement will be determined both clinically and by the previous calcitonin result (✓).*

6.3.2 Thyroid Function Tests in Medullary Thyroid Cancer

Thyroid function tests have no place in the diagnosis of MTC. However, TFT should be monitored during follow-up in patients who have had thyroid ablation in order to optimise thyroid hormone replacement. TSH suppression is not appropriate for the treatment of MTC and so thyroid hormone replacement should follow the guidelines for treating hypothyroidism.

6.3.3 Genetic Testing in Medullary Thyroid Cancer

Detailed recommendations for genetic investigation can be found in "Guidelines for the management of thyroid cancer in adults".¹

- *All new patients with MTC should be referred to a Clinical Genetics Service for RET mutation testing, whether or not there is an evident family history (II,B)*
- *RET mutation testing includes exons 10, 11, 13, 14,15 and 16; failure to screen of exons 13-16 is an incomplete test. (III,B)*

6.4. Anaplastic Thyroid Cancer

Thyroid function tests have no place in the diagnosis of anaplastic thyroid cancer. However, TFT should be monitored during follow-up in patients who have had thyroid ablation and the dose of thyroxine adjusted accordingly.

7. Laboratory Aspects of Thyroid Function Testing

7.1 Introduction

This chapter concerns itself with identifying the various hormone measurements that are widely available for thyroid function testing and outlining the general principles of how such tests should be selected, performed, reported and interpreted. The pitfalls of thyroid function testing are discussed and recommendations given regarding how such problems may be recognised or avoided. These recommendations have been formulated from a number of sources but in particular from the detailed “Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease” guidelines published by the National Academy of Clinical Biochemistry.¹

7.2 Biochemical Investigations for Thyroid Dysfunction

7.2.1 Provision of Laboratory Tests

In the majority of cases there is no urgency for receipt of routine TFT but all laboratories should be capable of issuing results for these tests within 48 hours from receipt of the specimen.

In some circumstances a more rapid response is desirable. For example a turnaround time of less than 24 hours should be provided for hospitalised patients who have been admitted with thyroid disease as a cause of their presenting symptoms.

Thyrotoxic crisis and myxoedema coma are medical emergencies with significant morbidity and mortality if not treated promptly and adequately. Because of their rarity few clinicians have first-hand experience of their diagnosis and management and therefore rely heavily on biochemical proof of clinical suspicion. In these two situations rapid provision of TFT is desirable but such requests should be supported by an endocrinologist.

7.2.2 Grouping of Thyroid Function Tests

The tests used to investigate thyroid dysfunction can be grouped into:

- Blood tests which establish if there is thyroid dysfunction (TSH, FT4, FT3)
 - Tests to elucidate the cause of thyroid dysfunction, *i.e.* thyroid auto-antibodies to determine if the thyroid dysfunction has an autoimmune component and occasionally alpha subunit when a differential diagnosis of TSHoma or end organ resistance is being considered.
-
- *Measurement of TSH and thyroid hormones should be performed to determine the patient's thyroid status before invoking the more demanding tests that seek to determine the cause of the thyroid dysfunction. (✓)*

7.3 Tests to Establish if there is Thyroid Dysfunction

7.3.1 Thyrotrophin

- *The measurement of TSH in a basal blood sample by a sensitive immunometric assay provides the single most sensitive, specific and reliable test of thyroid status in both overt and subclinical primary thyroid disorders.*^{2,3} **(B)**.

In primary hypothyroidism TSH is increased whilst in primary hyperthyroidism TSH is below 0.1mU/L. There are exceptions to this generalisation, abnormal TSH concentrations may be found in some euthyroid patients (see Section 7.8.2) **(IIa)**. TSH alone is not a reliable test for detecting thyroid dysfunction arising from hypothalamic-pituitary dysfunction and in other specific instances⁴ (see section 7.8.2) **(III)**.

- *It is essential that laboratories use a reliable and sensitive method for TSH that meets the following conditions:*
 - *The functional sensitivity should be used to define the lowest concentration of TSH that can be determined in routine use*⁵. **(C)**
 - *Functional sensitivity is defined from the 20% between-run coefficient of variation (CV) determined by a recommended protocol*⁵ (Section 7.11) **(C)**
 - *Laboratories should use a TSH method with a functional sensitivity of <0.02 mU/L*⁵ **(C)**
 - *Prior to the introduction of a TSH method, the laboratory should validate the functional sensitivity quoted by the manufacturer. Quality assurance procedures should be in place to ensure that the functional sensitivity of the assay is regularly monitored* (✓)

7.3.2 Free T4 (FT4) and Free T3 (FT3)

Free (unbound) thyroid hormones are regarded by many as the biologically active fraction of the total circulating thyroid hormone pool and are unaffected by changes in the concentration and affinity of thyroid-hormone binding proteins. Free hormones thus theoretically provide a more reliable means of diagnosing thyroid dysfunction than measurement of total hormone concentrations.⁶⁻⁹ **(III)**. Free hormones are normal in patients with mild (subclinical) thyroid disorders.²

Several assay techniques have been developed to measure free hormone concentrations and these are usually given names which relate to the methodology used e.g. one-step, two-step, analogue, labelled antibody etc. These methods produce results that show good agreement in most ambulant patients and are superior to the use of urinary thyroid hormone measurements^{7,13}. However, because of inadequacies in method design and construction, the free hormone results for these methods do not always correlate well in some circumstances. These include samples where the thyroid hormone capacity is low such as may occur in TBG deficiency, severely ill patients, and patients taking certain drugs that interfere with hormone binding to the plasma binding proteins.⁶⁻¹² Equilibrium dialysis, using undiluted serum, is widely held to be a reference method¹ but cannot be performed in large numbers on a routine basis. When measured by equilibrium dialysis, normal euthyroid serum shows little change in FT4 concentration at final dilutions of up to approximately 50-fold; in

contrast many routine methods for FT4 show a marked decreases in the measured FT4 concentration on dilution.⁶⁻¹³

- *The nomenclature given to a method for free hormone measurement in no way predicts its validity or agreement with equilibrium dialysis (IIa,B)*
- *Laboratories should obtain from kit manufacturers free hormone assay behaves when the sample is diluted (✓)*
- *Laboratories should be aware of how their assay performs in a variety of clinical situations including thyroid disorders, pregnancy, non-thyroidal illness, certain medications (e.g. heparin, phenytoin, frusemide, carbamazepine, salicylate) and familial binding protein abnormalities such as familial dysalbuminaemic hyperthyroxinaemia and TBG excess or deficiency (✓)*
- *Clinicians should be made aware, by the laboratory, of the expected assay performance in the clinical settings listed above (✓)*
- *Laboratories should obtain from kit manufacturers details of how their assay compares with equilibrium dialysis in the clinical situations stated above (✓)*
- *Free hormones can increase in some samples on storage^{8,9} but because of assay design (eg inclusion of albumin in reagents) not all free hormone methods detect such changes. Laboratories should be aware of how storage affects free hormone concentrations when measured by their own method. Appropriate action should be taken to minimise such sample deterioration. For example it may necessary to freeze samples that cannot be assayed within 48 hours of collection (✓)*
- *Interference from anti-thyroid hormone antibodies is method dependent and laboratories should know how the presence of such antibodies would affect their assay (✓)*

7.3.3 Plasma Total T4 (TT4) and Total T3 (TT3)

Total thyroid hormone concentrations are abnormal in patients with overt thyroid dysfunction and also in euthyroid subjects in whom the concentration or affinity of binding proteins are abnormal¹⁴. Changes in plasma thyroid hormone binding proteins may involve a change in concentration (e.g. as may occur in pregnancy) or changes in affinity for hormone (e.g. in non-thyroidal illness or in patients taking certain drugs such as salicylate).¹⁴ It is thus common to find abnormal TT4 and TT3 in some euthyroid patients.

7.4 Selective Use of Thyroid Function Tests

Many laboratories measure basal TSH as the initial test of thyroid function. This strategy is not infallible but a normal TSH usually excludes primary thyroid dysfunction.¹⁻⁴ (IIb). Initial measurement of both TSH and FT4 together can provide

a more satisfactory method of assessing thyroid status. However, it is essential to understand and appreciate the factors that can affect the results of thyroid function tests for correct interpretation. ⁴ **(III)**.

Throughout these guidelines we have highlighted the clinical situations where measurement of both serum TSH and FT4 is required; these are principally where the pituitary-thyroid axis is not intact or is unstable. These situations include relatively common situations such as optimising thyroxine therapy in the early months of treatment of newly diagnosed patients with hypothyroidism, diagnosing and monitoring thyroid disorders in pregnancy and monitoring patients with hyperthyroidism in the early months after treatment. Rare situations include diagnosis and monitoring treatment for central hypothyroidism, end-organ thyroid hormone resistance and TSH-secreting pituitary adenomas. If clinical details are not available that allow the identification of the above categories of patient, then it may be prudent for laboratories to measure serum TSH and FT4 on all specimens rather than embark on a first-line serum TSH testing strategy

- *The use of first-line TSH will fail to identify some patients with thyroid disorders **(III,B)***
- *Measurement of TSH with FT4 should allow the detection of almost all causes of thyroid dysfunction as long as the results of both tests are correctly interpreted **(III,B)***
- *Additional tests such as FT3 may be required in some circumstances **(III,B)***
- *If laboratories are unable to identify those specimens that specifically require the measurement of both serum TSH and FT4 then it would be prudent to measure serum TSH and FT4 on all specimens rather than embark on a first-line serum TSH strategy. **(IV,C)***

7.5 Reference Ranges

The secretion of TSH is pulsatile and night time concentrations are higher than during the day. The concentrations of FT4 and FT3 in blood change little during a single day but like TSH they do change throughout the year. Reference ranges for TFT are derived from a reference population that comprises a large group of subjects who do not have thyroid disease and are otherwise well. By convention, a reference range usually only comprises 95% of a reference population. Thus 2.5% of “normal” individuals will fall above the reference range and 2.5% will fall below the range. For TSH the reference population shows a log normal distribution and has a diurnal variation but for thyroid hormones a normal distribution is seen with no significant diurnal variation. ¹⁵⁻²²

For a number of reasons, reference ranges for TFT may show variation between laboratories. Firstly the reference population studied may have included subjects with subclinical hypothyroidism as indicated by the presence of thyroid antibodies. This would have the effect of falsely increasing the calculated upper reference limit for TSH. Secondly assays will have differences in standardisation, the matrix of the

calibrators and specificity of antibodies. These differences commonly give rise to method-related biases which should be compensated for by the use of method-related reference ranges. Thirdly, the measurement of free thyroid hormones is technically difficult and differences in assay design may lead to significant method related differences in hormone concentration even when measured in identical samples.

Recently, there has been a growing controversy about the upper limit of the reference range for serum TSH. This culminated in a published debate in which one set of authors argued in favour of reducing the upper limit of the reference range to 2.5mU/L²³ while the other set of authors argued to retain the upper limit of the reference range at 4.5mU/L²⁴. The Guidelines Development Group recognizes the controversy but it believes that the evidence in favour of narrowing the TSH reference range is not convincing and cannot justify the large increase in the number of subjects that would require regular investigation. This judgement is further influenced by the established log-linear relationship between serum TSH and FT4¹ and by the lack of evidence in favour of systematic thyroxine therapy in subclinical hypothyroidism (see Chapters 2 and 3).

Therefore, typical serum reference ranges in adults are:

TSH	0.4 – 4.5 mU/L	TT4	60 – 160 nmol/L
FT4	9.0 – 25 pmol/L	TT3	1.2 – 2.6 nmol/L
FT3	3.5 – 7.8 nmol/L		

- *Where possible manufacturers reference ranges should be confirmed locally using an adequate population size of at least 120 ambulatory subjects.*¹ **(IV,C)**
- *For TSH, reference ranges should be established using specimens collected between 0800h and 1800h and using 95% confidence limits from log transformed data. Alternatively, non-parametric methods of statistical analysis could be used to derive the reference range. The reference population should have no personal or family history of thyroid dysfunction, be on no medication known to alter TSH and have no thyroid antibodies detectable by a sensitive assay.*¹ **(IV,C)**
- *Since TSH, free and total thyroid hormones change during pregnancy, trimester related reference ranges should be available (see Chapter 5)* **(III,B)**

7.6 Quality Control and Quality Assurance

It is essential that a laboratory performs adequate checks on the performance of all thyroid assays.

7.6.1 Internal Quality Control (IQC)

- *All laboratories must run IQC that comprise human serum pools (✓)*
- *The analyte concentrations for the pools should be chosen to ensure that assay performance is monitored within the euthyroid, hyperthyroid and hypothyroid*

ranges **(IV,C)**. Laboratories should define allowable limits of error for each of these IQC pools.

- The minimum frequency with which IQC pools are run by laboratories will usually be based on that recommended by the manufacturer for a particular method. The laboratory should ensure that such recommendations are reasonable and if not the laboratory should modify the IQC frequency accordingly (✓)

7.6.2 External Quality Assessment (EQA)

- All laboratories must participate in an accredited EQA scheme **(IV,C)**
- Laboratories should ensure that assay performance meets the minimum performance specified by the EQA scheme (✓)
- If the laboratory appends interpretative comments to its thyroid function tests, then those responsible for making such comments should be professionally qualified to MRCPATH (or equivalent) or be supervised by a person with these qualifications (✓)

7.7 Interpreting Results of Thyroid Function Tests

7.7.1 Situations in which TSH Usually Provides the Correct Estimate of Thyroid Status.

- In overt primary hyperthyroidism TSH is nearly always below 0.10 mU/L. ¹⁻⁴ **(IIb,B)**
- In overt primary hypothyroidism plasma TSH is always increased. ¹⁻⁴ **(IIb,B)**
- In mild (subclinical) disorders, TSH will be the most sensitive indicator of failing thyroid function, and plasma FT4 and FT3 are often normal **(III,B)**. Before the diagnosis of subclinical thyroid disorders can be made, causes of an abnormal TSH other than thyroid disorders must be excluded **(IV,C)**. These include pregnancy, non-thyroidal illnesses, drug treatment, and assay interference (see Section 7.7.2). ^{4,22}
- In subjects without thyroid dysfunction TSH will be normal **(IIa,B)**

7.7.2 Situations in which TSH Results may be Misleading

a) Assay interference. All assays are prone to interference from a range of substances in blood including heterophilic antibodies. Heterophilic antibodies can interfere with immunoassays for TSH and produce clinically misleading results **(IIa)**. In most circumstances assay interference produces a result that is higher than the true result but the converse can also be found. ²⁵⁻²⁸

b) Pregnancy. In the first trimester a TSH of <0.10 mU/L may be found in up to 3% of patients. ²⁹⁻³¹ **(III)**.

- *Trimester-related reference ranges should be applied for TSH, total and free thyroid hormones (III,B)*

c) Situations in which Thyroid Status is Unstable.

i) Early months after treatment for hyperthyroidism TSH may be normal or low and thus misleading, when hypothyroidism has been induced during the early weeks or months after treatment of hyperthyroidism, due to delayed recovery of the previously suppressed thyrotroph. ³² At that stage measurement of FT4 is the more sensitive indicator of thyroid failure. If however, the hypothalamic-pituitary-thyroid axis has recovered, measurement of TSH is more meaningful in this respect (III).

- *The recovery of the thyrotrophs cannot be predicted for an individual patient, measurement of both FT4 and TSH is important for appropriate treatment (IV,C)*

ii) Following an episode of thyroiditis

iii) Early weeks of thyroxine therapy

iv) Poor compliance. Some patients who are poorly compliant with thyroxine therapy take excessive doses in the days prior to a clinic visit. These individuals can be identified by the seemingly anomalous combination of a raised TSH and FT4. Measurement of TSH alone is likely to lead to a recommendation for increasing the daily dose of thyroxine when diligent adherence to the previous drug regime is all that is required.

- *The use of TSH alone is thus only adequate for patients on replacement therapy once they are stable and compliant. (IV,C)*

d) Hypopituitarism. Normal TSH is found in about half of patients with central hypothyroidism, TT4 or FT4 are usually low ³³ and in occasional cases of hypopituitarism a raised TSH may be seen. ³⁴ (III).

e) TSH secreting adenoma. Very rarely, the cause of the hyperthyroidism is a TSH-secreting tumour. The persistent finding of hyperthyroid symptoms and elevated thyroid hormones is consistent with the diagnosis once the common problems of assay interference or non-thyroidal illness have been eliminated. ^{35,36} (III). (See also Chapter 4).

f) End organ resistance. Certain patients with end organ resistance to thyroid hormones may present with abnormal thyroid function tests. Some may have high concentrations of thyroid hormone but normal TSH and others will have raised TSH with normal thyroid hormones. ^{37,38}. Confirmation of the diagnosis can be made by the thyroid hormone receptor β -gene sequence analysis available through the Supraregional Assay Service (<http://www.sas-centre.org>). The decision to treat these patients is often made on clinical grounds rather than the biochemical abnormality (III). (See also Chapter 4).

g) "Non-thyroidal illnesses" and the "sick-euthyroid syndrome" Patients suffering from any of a wide range of chronic or acute non-thyroidal illnesses, may show abnormalities in thyroid function tests even though they are clinically euthyroid. This has been described as the "sick euthyroid syndrome".³⁹⁻⁴² **(III)**. In the majority of these sick patients TSH will be normal and thus provide the best guide of thyroid status. However in some patients, TSH concentrations may be suppressed in the acute phase and on recovery TSH concentrations may rise transiently into the hypothyroid range.⁴³ **(III)**. Total T3 and FT3 concentrations usually fall as a result of impaired tissue uptake of T4 and impaired conversion of T4 to T3.^{39-42,44,45} However using ultrafiltration or some commercial assays FT3 may be normal or sometimes raised.^{39,44} **(III)**.

Illness modifies both the concentration and binding capacity of the plasma thyroid hormone binding proteins^{39-42,46} which in turn tends to diminish the total thyroid hormone concentrations and raise the FT4 hormone fraction. When measured by a reference method, FT4 concentrations usually remain within the reference range or are modestly raised in the sick patient.^{8,10-13,47,48} However many routine methods for FT4 produce low values in the sick patient due to assay artefacts.^{8,10-13,47,48}

The contribution of each of the above mechanisms may vary with the severity and stage of the illness and thus the pattern of thyroid function tests may be extremely variable and may mimic the profile seen in primary or secondary thyroid disorders **(III)**.

- *In hospitalised patients a TSH <0.10 mU/L is at least twice as likely to be due to non-thyroidal illness as hyperthyroidism.*⁴³ **(III,B)**
- *In hospitalised patients an increased TSH is as likely to be associated with recovery from illness as hypothyroidism.*⁴³ **(III,B)**
- *Because of the poor predictive value of thyroid function tests in hospitalised patients, these tests should only be requested if there is a clinical reason for suspecting a thyroid problem* **(IV,C)**
- *Additional investigations such as FT3 may point strongly to non-thyroidal illness as a cause of the abnormal results. A repeat sample may show that the abnormal results have been transient and attributable to an acute illness or a specific treatment regimen.*⁴⁹ **(III,B)**
- *Although these procedures may clarify the cause of abnormal thyroid function tests for some patients, clinical assessment by an endocrinologist may be indicated* **(IV,C)**

h) Drug treatment. Drugs may interfere with TSH secretion or the production, secretion, transport and metabolism of thyroid hormones.^{50,51} Some drugs modify thyroid status whilst others produce abnormal thyroid function test results in otherwise euthyroid subjects. In general, serum TSH is less affected by medication than thyroid hormones, although glucocorticoids and dopamine in high doses inhibit TSH release.^{52,53}

Certain agents will impair the absorption of thyroxine from the gut and patients on thyroxine therapy should be advised to take their thyroxine at least 4 hours apart from these medications. Patients taking thyroxine are likely to require an increase in replacement dose if drugs such as phenytoin or carbamazepine are prescribed that increase hepatic metabolism of T4. Propranolol may decrease TT3 and increase TSH.⁵⁴ Phenytoin, carbamazepine, frusemide and salicylate compete with thyroid hormone binding to serum binding proteins and may increase FT4.⁵⁵⁻⁵⁸ In vivo administration of heparin liberates free fatty acids, which displace thyroid hormones from their binding proteins and also increase FT4. However it is important to note that the influence of drugs on modifying free thyroid hormone concentrations may be method specific. For example, depending on the method, FT4 may be measured as normal or low in patients given heparin or taking phenytoin or carbamazepine^{58,59} **(IIa)**. Amiodarone and lithium can alter thyroid status and are discussed below. Similarly the use of some cytokines such as interferon alpha for the treatment of chronic hepatitis C can induce hypothyroidism or hyperthyroidism.

Section 7.12 lists some of the drugs that may produce abnormal thyroid function tests.

- *For patients taking drugs known to modify thyroid function tests, the laboratory must be able to provide appropriate interpretative advice (✓)*
- *Certain drugs interfere with thyroid hormone absorption from the GI tract e.g. ferrous sulphate, cholestyramine, cholestapool, and aluminium hydroxide. Patients taking thyroxine should be advised against taking these drugs until at least 4 hours after taking thyroxine.⁶⁰ **(IIa,B)***
- *The dose of thyroxine may have to be increased in patients who are taking drugs that increase thyroid hormone metabolism. For example anticonvulsants induce drug metabolising enzymes (see Chapter 4) **(III,B)***

Lithium can cause hypothyroidism and hyperthyroidism in up to 10% of patients. Patients with positive TPOAb are particularly at risk.⁶¹⁻⁶³ **(III)**. Patients taking lithium should have their TFT measured at 6-12 month intervals or earlier if goitre develops.

The anti-arrhythmic drug amiodarone is an iodine-containing drug that has complex effects on thyroid metabolism⁶⁴⁻⁶⁷. These include inhibition of T4 to T3 conversion, inhibition of thyroidal iodine uptake and inhibition of T4 entry into cells. The drug may also induce a destructive thyroiditis. Patients may have an altered thyroid hormone profile without thyroid dysfunction but 14% -18% of patients taking amiodarone may develop clinically significant hypothyroidism or amiodarone induced thyrotoxicosis. Because of the long half-life of amiodarone, clinical problems may occur up to a year after stopping the drug.

- *Euthyroid subjects taking amiodarone for more than three months frequently have increased FT4, decreased FT3 but normal TSH. During the first three months of treatment, however, TSH may increase transiently (up to 20 mU/L) particularly in patients receiving higher doses of amiodarone.*⁶⁴⁻⁶⁷ **(IIa,B)**
- *It is important to evaluate patients before they commence therapy with amiodarone. This should include clinical examination and a basal measurement of TSH and TPOAb, together with FT4 and FT3 if TSH is abnormal. After starting treatment these tests should be repeated at 6 months and thereafter every six months including the year after the drug is stopped* **(III,B)**

The diagnosis of patients with amiodarone-induced type I or type II thyrotoxicosis is discussed in Chapter 4. Thyroxine replacement may be necessary in patients who develop hypothyroidism (see Chapter 3).

7.8 Follow-Up of Unusual Test Results

Unusual combinations of TSH and thyroid hormone results may have a pathological source but more commonly result from poor compliance or assay interference in one or more assays.^{68,69}

- *Laboratories should have protocols available to determine if results are analytically valid or due to assay interference (✓)*
Such protocols may include:-
 - *Dilution tests*
 - *Removal of heterophilic antibody and HAMA using commercial tubes (for total hormones only)*
 - *Remove of anti-thyroid antibodies using polyethylene glycol precipitation.*
 - *Confirmation by an alternative assay which if possible should have been validated against a reference method (✓)**Validated alternative procedures to the above would also be acceptable.*

7.9 Laboratory Tests Used to Determine the Cause of Thyroid Dysfunction

7.9.1 Thyroid Peroxidase Antibodies (TPOAb)

These are present in the serum of patients with a wide range of immunologically mediated thyroid disorders (e.g. Hashimoto's thyroiditis, Graves' disease). They may also be found in a small proportion of apparently healthy individuals but the appearance of TPOAb usually precedes the development of thyroid disorders.^{18,70}

- *The measurement of TPOAb is of clinical use:*
 - *In diagnosis of autoimmune thyroid disorders.*^{71,72} **(III,B)**
 - *As a risk factor for autoimmune thyroid disorders.*^{18,70} **(III,B)**
 - *As a risk factor for hypothyroidism during treatment with interferon alpha,*

*interleukin-2 or lithium.*⁷³⁻⁷⁶ **(III,B)**.

- *As a risk factor for thyroid dysfunction during lithium or amiodarone therapy.*^{64-66, 77} **(III,B)**

- *TPO results are method dependent and this should be recognised.* **(III,B)**
- *Functional sensitivity should be determined for the TPOAb method using the same protocol as for TSH (Section 7.10)* **(IV,C)**
- *A sensitive and specific immunoassay should be used to measure TPOAb, not an agglutination test* **(IV,C)**
- *A reference interval for TPOAb should be derived using at least 120 subjects who have no personal or family history of thyroid disorders and have no visible goitre and are on no medication. They should have no autoimmune or systemic disease. Young males <30 years with TSH between 0.5-2.0 mU/L may be a suitable source of subjects* **(IV,C)**

7.9.2 Thyroglobulin Antibodies (TgAb)

Antibodies to thyroglobulin (TgAb) are found in many patients with autoimmune thyroid disorders; however, in most circumstances TgAb measurements have no additional value over the measurement of TPOAb and need not be done if TPOAb is present **(IV)**. TgAb measurements may be helpful in patients with differentiated thyroid cancer **(IV)**. Because of marked differences in assay sensitivity it should be noted that the absence of TgAb in one assay does not absolutely exclude their presence.⁷⁸

- *In iodine sufficient areas it is of no value to measure both TgAb and TPOAb in non-neoplastic conditions.*^{16,79,80} **(III,B)**
- *The only reasons to measure Tg antibodies are i) in differentiated thyroid cancer to determine possible interference from these antibodies in immunoassays for thyroglobulin. ii) Serial measurements may prove to be useful as a prognostic indicator.*⁸⁰⁻⁸² **(II,B)**
- *Assays should be performed using a sensitive immunoassay not an agglutination method.*⁸³ **(✓)**
- *Functional sensitivity should be determined as given for TSH (Section 7.10).* **(IV,C)**
- *A reference interval should be derived using at least 120 subjects who have no personal or family history of thyroid disorders and have no visible goitre and are on no medication. They should have no autoimmune or systemic disease.* **(IV,C)**
- *Thyroglobulin and TgAb should be measured in the same specimen.* **(IV,C)**

- *If TgAb is being used for monitoring purposes the method should not be changed without consultation with the users. (IV,C)*

7.9.3 TSH Receptor Antibodies (TSH-RAb)

TSH-receptor antibodies are measured in most routine laboratories using commercial methods that quantify the inhibition of TSH binding to porcine or human TSH receptors. The antibodies measured in these assays are referred to by a number of names including Thyroid Binding Inhibiting Immunoglobulins (TBII) and TSH Receptor Antibodies (often abbreviated to “TRAbs”). These assays do not distinguish between stimulatory or blocking properties of these antibodies. A few specialist laboratories do offer assays that assess the stimulating ability of TSH-RAb by quantifying cyclic AMP production in cultured thyrocytes or cell lines that express the TSH receptor.⁸⁴⁻⁸⁷

In most patients the measurement of TSH-RAb is not an essential investigation for diagnostic purposes. (See also Chapter 5).

- *The measurement of TSH-RAb is particularly useful in pregnancy and may also be helpful in the following situations:*
 - *To investigate hyperthyroidism of uncertain aetiology (IV,C)*
 - *To investigate patients with suspected “euthyroid Graves’ ophthalmopathy (IV,C)*
 - *For pregnant women with a past or present history of Graves Disease (IV,C)*
 - *To identify neonates with transient hypothyroidism due to TSH blocking antibodies (IV,C)*

7.9.4 Thyroglobulin (Tg)

Many differentiated papillary and follicular carcinomas of the thyroid synthesise and secrete thyroglobulin. Detailed UK guidelines for the diagnosis and management of thyroid cancer have been published recently⁸⁸, (also see chapter 6) and problems with thyroglobulin assays have been widely reviewed.⁸⁹⁻⁹² It should be noted that marked bias differences occur between Tg assays with up to four fold differences being seen between the highest and lowest biased assays⁷⁸. It is important that the laboratory is consulted to determine the appropriate bias-adjusted cut-offs for use in clinical practice.

- *In patients with differentiated thyroid cancer measurement of serum Tg is used in monitoring, but is not of value in the initial diagnosis (III,B)*
- *Samples for Tg measurement should preferably be taken when the TSH is elevated either after withdrawal of T4 therapy or following administration of recombinant human TSH (Thyrogen). For patients in remission and under routine follow-up it is acceptable in the first instance to sample during T4 administration (see Chapter 6) (IV,C)*
- *There should be clear guidance on specimen requirements and sample stability (✓)*

- *The use of the Community Bureau of Reference standard for thyroglobulin (CRM 457) is recommended. (IV,C)*
- *The use of a reference range derived from normal subjects is not recommended. The laboratory should ensure that users are aware that patients on T4 suppressive therapy should ideally have a Tg <2µg/L or a bias-adjusted cut-off as advised by the laboratory. (IV,C)*
- *Laboratories and manufacturers should determine and quote the minimum detection limit (MDL) of their Tg assay based on functional sensitivity derived from patient samples. The MDL should ideally be in the order of $\leq 0.2\mu\text{g/L}$ (IV,C)*
- *Although a post-rhTSH (Thyrogen) serum thyroglobulin in the order of 2 µg/L has been suggested as a positive response justifying further investigations and treatment, this threshold may not be applicable for many of the currently available assays because of known differences in sensitivity, accuracy and precision. The laboratory should be able to advise on the appropriate bias-adjusted cut-off.⁷⁸ (IV,C)*
- *Laboratories and manufacturers should identify the analytical range of their Tg assay and adopt procedures to identify samples suffering from 'hook' effects (IV,C)*
- *Laboratories and manufacturers should inform clinicians of the possibility of interference due to endogenous TgAb and indicate the most likely nature of the interference (false elevation/false reduction in measured Tg) (IV,C)*
- *Identification of possible assay interference is best achieved using either TgAb measurements or discordance between Tg results obtained using immunometric assay and radioimmunoassay.⁹¹ Recovery experiments alone are not recommended to identify assay interference.⁹³ (IV,C)*
- *For a particular Tg method it is highly desirable that the results of a clinical assessment of the assay performance should be available. The clinical sensitivity and specificity (i.e. positive and negative predictive values) of the assays should be quoted (IV,C)*
- *Laboratories should run internal quality control samples, which encompass the range of results reported by the laboratory. A sample with a Tg concentration close to the minimum detection limit should also be run with each assay to ensure that the quoted MDL is being achieved (IV,C)*
- *Laboratories should participate in an accredited EQA scheme (IV,C)*

7.9.5 Calcitonin

Detailed UK guidelines for the diagnosis and management of thyroid cancer and the use calcitonin assays have been published recently.⁸⁸

The following recommendations apply to the measurement of calcitonin (IV,C)

Timing of specimen collection

- *Ideally a fasting morning specimen should be obtained to enable optimal comparison with reference values. [If this is not possible, specimens can be collected at any time of day.]*
- *Post-operative samples should be collected at least ten days after thyroidectomy and should also be fasting samples if possible*
- *For provocative testing samples are usually collected 5 minutes prior to administration of calcium /pentagastrin and then at intervals of 2,5 and 7 minutes after.*

Type of specimen

- *Serum or plasma requirements should be confirmed with laboratories and/or manufacturers' kit inserts. The effect of gel tubes should be known.*
- *Calcitonin results may be affected by visible haemolysis or lipaemia and assay of such specimens should be avoided if possible*

Specimen stability

- *Calcitonin in serum or plasma is unstable and blood specimens should be kept on ice. Red cells should then be separated within 30 minutes of collection and serum or plasma frozen immediately.*

Effects of other conditions, treatment and medication

- *Previous treatment with monoclonal antibodies should be noted because of the potential for interference with human anti-mouse antibodies in immunometric assays.*
- *Chronic renal failure may increase basal calcitonin levels.*
- *Mildly increased calcitonin may be observed in pregnancy, pernicious anaemia and during the neonatal period.*

Methodology

- *Assays should be standardised using WHO International Standard IS 89/620.*
- *Laboratories must decide whether to use a method that recognises primarily monomeric calcitonin (IMA) or a method with broader specificity (RIA).*

Assay sensitivity

- *Laboratories and/or manufacturers should determine and quote the minimum detection limit of their assay based on precision profiles derived from patient samples*

Assay interferences

- *Laboratories should have established protocols for identifying specimens that may have 'hooked' and specimens that may contain interfering antibodies*

Clinical assessment

- *For a particular calcitonin method the results of a clinical assessment of the assay performance should be available. The clinical sensitivity and specificity (i.e. positive and negative predictive values) of the assays should be quoted.*

Quality assurance

- *Laboratories should run internal quality control at concentrations appropriate for the range of results obtained. A pool with a calcitonin concentration close to the minimum detectable limit should also be run to ensure good baseline security.*
- *Laboratories should participate in a recognised and accredited external quality assessment scheme*

7.9.6 Alpha Subunit.

The majority of TSH-secreting adenomas secrete either TSH alone or in combination with the alpha subunit. The measurement of alpha subunit is helpful in distinguishing between a TSH-secreting pituitary adenoma and thyroid hormone resistance. In thyroid hormone resistance the concentration of alpha subunit and the molar ratio of alpha subunit to TSH is normal whilst in a TSHoma these are often elevated.⁹⁴ The interpretation of results is not straightforward and the concentrations of FSH, LH and TSH should be determined along with alpha subunit.

Assays for alpha subunit are performed in a few specialist laboratories in the UK. No external quality assessment scheme is available. The specialist laboratory performing the measurement should be consulted for interpretation of the results.

7.10 Recommended Protocol for Determining Functional Sensitivity and Between Run Imprecision

- Human serum pools should be used.
- For determining functional sensitivity, pools should be used that lie above and below the estimated functional sensitivity.
- For monitoring the long-term stability of an assay a pool should be selected that is 10% above the estimated functional sensitivity. Other pools should also be selected to ensure that the precision of the complete assay range is monitored.
- At least 10 runs spaced over approximately an 8-week period should be used to determine between-run precision.
- More than one reagent lot should be used during the testing period.
- The number of replicates used to determine precision should be the same as is used for patient samples.

7.11 Drugs that Alter Thyroid Hormone Synthesis, Secretion and Metabolism

Decrease in TSH Secretion	Decreased Thyroid Hormone Secretion	Increased thyroid Hormone secretion	Decreased thyroidal synthesis*	Displacement of Hormone from Plasma Proteins	Impaired T4 to T3 Conversion
Dopamine Dopaminergic agents Glucocorticoids Cytokines Octreotide	Lithium Iodide Amiodarone	Iodide Amiodarone Lithium (rare)	Methimazole Carbimazole Propylthiouracil Lithium	Frusemide Fenclofenac Salicylates Mefenamic acid Carbamazepine Non-steroidal AIDs	Beta antagonists Glucocorticoids Amiodarone Propylthiouracil Iopanoic acid Radiocontrast dyes
Increase TBG, TT3, TT4	Decrease TBG, TT3, TT4	Increased Hepatic Metabolism of T4	Impaired Absorption of Thyroxine **	Alter autoimmunity***	Modify Thyroid Hormone Action
Oestrogens Tamoxifen Heroin Methadone Clofibrate Raloxifene	Androgens Anabolic steroids Glucocorticoids	Phenytoin Carbamazepine Barbiturates Rifampacin	Cholestyramine Cholestapal Aluminium hydroxide Ferrous sulphate Sucralfate Calcium carbonate Soy protein Proton pump inhibitors	Interleukin 1 Interferon α Interferon β TNF α	Amiodarone

*Drugs listed as causing a decrease in thyroid hormone synthesis or secretion thus leading to altered thyroid status.

** Drugs interfere with thyroid hormone absorption from the GI tract. Patients on thyroxine therapy should be advised to take their thyroxine at least 4 hours apart from these medications.

***Treatment with these cytokines have been associated with cases of transient hypothyroidism and thyrotoxicosis. These usually resolve several months after treatment is stopped. The mechanism is unclear but the changes may be autoimmune

The other drugs listed are thought to produce abnormal thyroid function tests but patients maintain a euthyroid status. Amiodarone is an exception (see main text).

8. Areas for further studies

Routine thyroid function testing has been available for more than thirty years. Therefore, it may seem surprising that the quality of evidence to support the recommendations in these guidelines is generally poor. The main reason for this finding is that the early studies that were used to assess the value, validity and effectiveness of thyroid function tests in a variety of clinical situations were performed before the requirements for evidence based medicine were adopted. There is a real need to conduct new studies that conform to the rules of evidence based medicine in order to provide answers to some common but contentious issues in the use of thyroid function testing.

The guideline development group highlights the need for additional studies on:

- The definition of age-related and trimester-related UK reference ranges for serum TSH and FT4
- The appropriateness of using thyroid function tests in screening selected categories of the normal healthy adult population for thyroid disease
- The appropriateness of using thyroid function tests for case finding for thyroid disease in hospital inpatients
- The optimal use of thyroid function tests in the diagnosis, monitoring and treatment of patients with subclinical hypothyroidism and subclinical hyperthyroidism
- The use of thyroid function tests to optimise thyroxine replacement therapy in patients with primary hypothyroidism and secondary hypothyroidism
- The relative clinical outcome of patients on thyroxine therapy who have serum TSH concentrations maintained within and below the reference range
- The relative effectiveness of thyroid function tests and tissue markers of thyroid hormone action in the diagnosis and management of thyroid disorders

Appendix 1. References

References are numbered separately for each Chapter. Therefore, Reference 1.1 is reference 1 in Chapter 1 and reference 7.26 is reference 26 in Chapter 7.

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