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CLINICAL QUESTION

Measuring TSH receptor antibody to influence treatment choices in Graves' disease

Asha Hesarghatta Shyamasunder and Prakash Abraham

Department of Diabetes and Endocrinology, Aberdeen Royal Infirmary, Aberdeen, UK

Summary

TSH receptor antibody (TRAb) plays a key role in the pathogenesis of Graves' disease (GD), and its levels correlate with the clinical course. The second- and third-generation TRAb assays have >95% sensitivity and specificity for the diagnosis of GD and have improved the utility of TRAb to predict relapse. TRAb levels decline with antithyroid drug (ATD) therapy and after thyroidectomy. Its level increases for a year following radioactive iodine (RAI) therapy, with a gradual fall thereafter. TRAb level >12 IU/l at diagnosis of GD is associated with 60% risk of relapse at 2 years and 84% at 4 years. The prediction of risk of relapse improves further to >90% with TRAb >7·5 IU/l at 12 months or >3·85 IU/l at cessation of ATD therapy. TRAb tests are not expensive, and hence, TRAb measurements at presentation, after 12 months and/or 18 months (at cessation) of ATD therapy, could potentially guide treatment choices in GD. Elevated TRAb favours definitive treatment in the form of RAI or thyroidectomy, depending on the presence or absence of moderate-to-severe Graves' ophthalmopathy (GO) and the ability to comply with radiation protection requirements. Use of ATDs in early pregnancy is associated with increased risk of congenital anomalies; early ablative treatment (RAI/surgery) should be considered in women of childbearing age at higher risk of relapse of GD. TRAb ≥5 IU/l in pregnant women with current or previously treated GD is associated with increased risk of foetal and neonatal thyrotoxicosis, and hence needs close monitoring. TRAb levels parallel the course of GO, and elevated TRAb is an indication for steroid prophylaxis to prevent progression of GO with RAI therapy.

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Correspondence: Prakash Abraham, Centre for Diabetes & Endocrinology, David Anderson Building, Aberdeen Royal Infirmary, Aberdeen AB25 2ZP, UK. Tel.: 01224-558121/558075(secretary); E-mail: p.abraham@nhs.net

Introduction

TSH receptor antibodies (TRAb) are implicated in the causation of Graves' disease (GD) due to prolonged stimulation of TSH receptors by these antibodies, leading to unsuppressed hypersecretion of thyroid hormones. Despite their well-known role in the pathogenesis of GD, and the availability of serological tests to measure TRAb,[1] several questions remain unanswered. This article aims to discuss the influence of TRAb measurements on treatment choices in GD.

How is TRAb generated?

The TSH receptor is a G protein-coupled receptor synthesized as a 764 amino acid polypeptide. It undergoes post-translational cleavage of a 50 amino acid C-peptide to form TSH receptor A and B chains, linked by disulphide bonds. The extracellular A subunit is shed resulting in the generation of self-antigens which are presented in the context of MHC class II molecules, leading to activation of nonself-tolerant CD4+ T cells, eventually resulting in the production of stimulatory antibodies. TRAb was discovered by Adams and Purves 60 years ago.[1,2]

What are the assays available to measure TRAb?

Rees Smith and Hall[3] developed the original receptor assay in 1974 using a simple competition method to quantitatively measure TRAb. The assays used particulate thyroid tissue from patients with GD and I-125-labelled bovine TSH to detect inhibition of binding of radiolabelled TSH to these membranes. Subsequently, liquid phase TRAb assays (first generation) with detergent solubilized recombinant human or porcine TSH receptors were developed, but these assays had low functional and diagnostic sensitivity. Solid-phase TRAb assays (second generation) were developed in the 1990s with better functional and diagnostic sensitivity. These used fluorescent read-outs in comparison to radioactive read-outs in the earlier assays.[4] In 2002, Sanders *et al.*[5] developed thyroid-stimulating monoclonal antibodies of human origin (TSMAb), named M22, from lymphocytes of a patient with GD to replace labelled bovine TSH for the competition assays. This has led to the introduction of third-generation TRAb assays with improved sensitivity because M22 and patients' TRAb bind to similar epitopes of the TSH

receptor.[4] The sensitivity and specificity of a fully automated electrochemiluminescence assay evaluated in a multicentre trial were 99% at a cut-off value of 1·75 IU/l for the diagnosis of GD, with positive and negative predictive values of 95% and 100% respectively.[6] A meta-analysis of TRAb immunoassays in the diagnosis of GD reported a very high sensitivity and specificity of the second- and third-generation assays of 97·1% and 97·4% and, 98·3% and 99·2% respectively. The difference between the second- and third-generation assays was small, indicating that both were equally useful.[7]

The bioassays measure cAMP production in human thyroid cell monolayers incubated with patients sera to quantify TSH receptor-stimulating antibodies (TSAb/TSI assays). These assays have undergone refinement over the years with the third-generation assay employing a luciferase reporter to detect increased cAMP production.[1] A study comparing the third-generation TRAb assay with a thyroid-stimulating immunoglobulin (TSI) assay to predict progression of Graves' ophthalmopathy (GO) showed comparable results with both assays.[8] It may be useful to test for TSI in patients with euthyroid GO.[1]

In a study comparing three TRAb assays (second and third generation) in 128 patients with GD after 18 months of ATD therapy, TRAb values from the different assays were not comparable. Despite the variability, the performance of second- and third-generation TRAb assays was similar in predicting relapse of GD. A higher prevalence of TRAb positivity was noted in patients who relapsed following withdrawal of methimazole.[9]

How do TRAb levels vary with treatment of GD?

Laurberg *et al.* evaluated the effect of treatment of GD on TRAb titres in a prospective study. They randomized 131 patients with GD to treatment with antithyroid drugs (ATD; n = 48), surgery (n = 47) or radioactive iodine (RAI; n = 36, if age ≥35 years). Serial measurements of TRAb were obtained from baseline to 5 years following initiation of treatment (every 3 months up to 3 years and then every 6 months). A gradual decline in TRAb was noted in patients treated with ATDs and surgery, with disappearance of TRAb in 70% to 80% of patients after 18 months. RAI therapy on the other hand led to increased TRAb levels for 1 year, followed by a gradual decline over the following years. About a third of patients treated with ATDs developed recurrence of hyperthyroidism after stopping medication. These patients had persistently positive TRAb levels 18 months after therapy, with a further increase in levels at the time of recurrence, but below the baseline value. The initial TRAb values and the fall in TRAb during therapy overlapped between patients who remained euthyroid and those who relapsed. Thus, TRAb levels paralleled the response to therapy except for those treated with RAI.[10]

Does TRAb predict relapse?

Relapse rates of GD following withdrawal of ATD therapy range from 50% to 67%[11] as compared to 15% with RAI and 10% following thyroidectomy.[12] With such high relapse rates with ATDs, it is prudent to identify patients at higher risk of relapse and consider definitive treatment. A meta-analysis evaluated studies from 1975 to 1991 to determine whether TRAb predicted long-term (i.e. at least 1 year) relapse after ATD. Twenty five per cent of patients who were TRAb positive at the end of ATD treatment remained in remission; while 25% of TRAb negative patients relapsed, indicating that TRAb had insufficient predictive value. The studies in this meta-analysis used either the first-generation assays for TRAb (with low sensitivity) or the TSI assays.[13] However, with better sensitivity and specificity of the second- and third-generation assays for TRAb, it has greater utility to predict relapse of GD.

Table 1 lists the predictive value of different TRAb cut-offs at diagnosis of GD, after 12 months or at cessation (≥18 months) of ATD therapy, and 4 weeks after cessation of ATDs to determine the risk of relapse. All the studies cited in the table used either the second- or third-generation assay to measure TRAb and had at least 1 year follow-up after withdrawal of ATDs.[14–18] A TRAb cut-off of 3·85 IU/l at the end of ATD treatment had the best sensitivity, specificity, positive and negative predictive values to determine the risk of relapse of GD (at a median follow-up of 15 months). About 20% of patients with TRAb <3·85 IU/l in this study had relapse; but they relapsed much later compared to those with TRAb ≥3·85 IU/l (median time to relapse 56 *vs* 8 weeks).[17] In a recent observational study, 70% of patients with GD treated with ATDs had relapsed by 4 years of follow-up. Higher TRAb levels at diagnosis (>12 IU/l) and at cessation of thionamide treatment (>1·5 IU/l) were associated with higher risk of relapse of 59% and 65% at 2 years and, 84% and 82% at 4 years respectively.[14] TRAb measurement 4 weeks after stopping ATDs also has good predictive value in determining the risk of relapse.[18]

Does a prediction model incorporating TRAb improve the assessment of risk of relapse?

Vos *et al.* assessed the utility of a prediction model to determine the risk of relapse of GD following a 12-months course of ATDs in a cohort of 178 newly diagnosed GD patients. Relapse of GD was noted in 37% of patients within 2 years of withdrawing ATDs. The Graves' recurrent events after therapy (GREAT score) incorporated clinical parameters including age (≥40 years, <40 years), goitre size (0–I and II–III), freeT4 (<40, ≥40 pmol/l) and serum TRAb (<6, 6–19 and ≥20 IU/l). They were divided into three classes of risk based on the total score. The GREAT plus score, in addition, included scores for PTPN22 C/T polymorphism and HLA subtypes DQB1 *02, DQ A1 *05 and DRB1*03. They were classified into four risk classes based on the total of clinical and genetic risk scores. Patients in the highest classes of GREAT and GREAT plus scores had increased risk of relapse of 68 and 84% respectively.[19] This model may serve to individualize treatment of newly diagnosed patients with GD, but due to limitations of cost and availability of genetic testing, its practical utility remains restricted.

Table 1. TSH receptor antibodies (TRAb) as a predictor of risk of relapse in studies with at least 1 year follow-up after withdrawal of ATDs

TRAb		Prediction of relapse			
Study	Cut-off (IU/l)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
At diagnosis					
Tun *et al.**	>12	34·5	80·9	59·4	60·4
Thyroid 2016 (n = 184)[14]	Relapse at 2 years				
	>12	32·3	85·7	83·7	35·8
	Relapse at 4 years				
TRAb after 12 months of ATD treatment					
Eckstein *et al.*	>7·5	46	97	97	44
Clin Endocrinol 2007 (n = 98)[15]					
TRAb at cessation of ATD therapy (≥18 months)					
Okamoto *et al.*†	>1	57·7	68·9	52	74
Endocr J 2006 (n = 71)[16]					
Tun *et al.**	>1·5	41·9	83·6	65·4	66
Thyroid 2016 (n = 184)[14]	Relapse at 2 years				
	>1·5	35·6	84·3	81·8	39·8
	Relapse at 4 years				
Carella *et al.*	>3·85	85·3	96·5	96·7	79·2
Thyroid 2006 (n = 58)[17]					
TRAb 4 weeks after cessation of ATD					
Quadbeck *et al.*	>1·5	87	14	49	54
Thyroid 2005 (n = 96)[18]	>10	40	92	83	62

PPV, positive predictive value; probability of relapse with a positive test.
NPV, Negative predictive value; probability of sustained remission with a negative test.
*Sensitivity, specificity and NPV calculated from information in the article.
†Sensitivity and specificity calculated from information in the article.

Does TRAb measurement influence treatment choices?

Measurement of TSH receptor antibodies before stopping ATDs improves the prediction of relapse to >90% from 50 to 67% without TRAb. The TRAb cut-offs of 7·5 IU/l and 3·85 IU/l at 12 and 18 months respectively have good specificity and positive predictive value (>96%) for relapse of GD.[15,17] Hence, a pragmatic approach (Fig. 1) would be to measure TRAb at diagnosis, and further after 12 and/or 18 months (at cessation) of ATD therapy to identify patients who are at higher risk of relapse, particularly those with persistently suppressed TSH on a carbimazole dose of over 5 mg per day. The 2016 American Thyroid Association (ATA) guidelines for diagnosis and management of hyperthyroidism recommend TRAb measurement before discontinuing ATD therapy. If TRAb remains persistently elevated, they suggest either ablative therapy (RAI or thyroidectomy) or to continue low-dose ATD with monitoring of thyroid functions and repeat TRAb test after further 12–18 months.[20]

The negative predictive value of the TRAb cut-offs at 12 and 18 months were 44 and 76% respectively.[15,17] Hence, a TRAb value below the cut-offs does not rule out the risk of relapse, but suggests a lower risk several months after stopping ATDs. Guidelines recommend a follow-up strategy of thyroid function tests every 2–3 months for 6 months, 4–6 monthly for the next 6 months and subsequently every 6–12 months. These patients should be counselled to report to their physician if they experience symptoms of thyrotoxicosis.[20]

Antithyroid drug treatment in pregnancy is associated with increased risk of birth defects (3·4%), and hence, early ablative therapy (RAI or thyroidectomy) should be considered in women of childbearing age with intent to cure GD before planning pregnancy.[21]

While considering long-term medical treatment with ATDs, we have to be mindful of the costs and adverse effects of long-term ATD treatment.[12] The cost of ATDs has increased exponentially in the UK over the last decade[22] (Table 2), while the cost of RAI and thyroidectomy has reduced. The cost of medical treatment is further escalated by the need for periodic thyroid function tests and specialist clinic visits. RAI treatment requires the patient to comply with radiation safety measures. The main challenge would be minimizing contact with children and pregnant women for up to 4 weeks.[23,24] RAI is associated with increased risk of worsening of GO. Prophylactic steroid therapy is indicated in patients with mild or inactive GO with risk factors for progression of eye disease (elevated TRAb, clinical activity score ≥1 and smokers). RAI is contraindicated in moderate-to-severe GO.[20,25]

The cost of TRAb measurement is about £47·04 (personal communication – local NHS lab); three measurements (at diagnosis, after 12 and 18 months) would cost about £141. This additional cost is negligible when compared with the cost of prolonged medical therapy. A cost–utility analysis comparing RAI, ATD and total thyroidectomy as first-line therapy for GD in England and

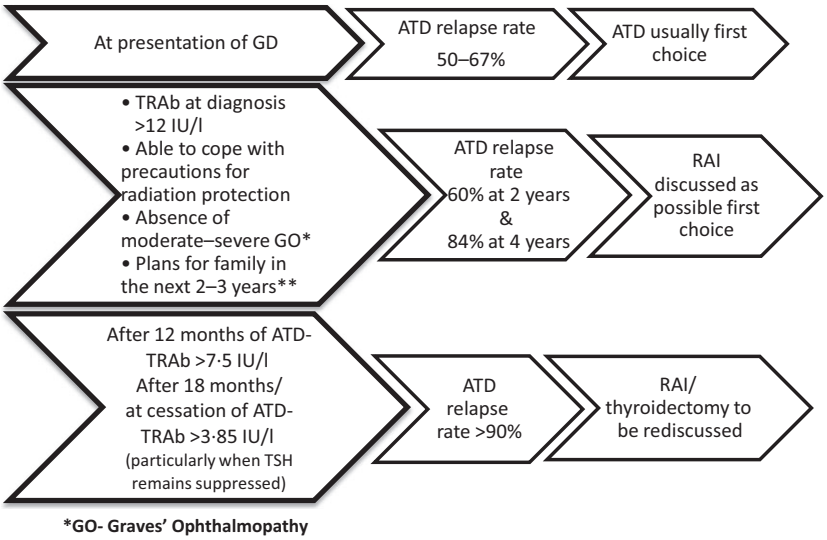

Fig. 1 Figure showing the utility of TSH receptor antibodies to influence treatment choices in GD. *GO, Graves' Ophthalmopathy; **Discuss definitive treatment to minimize ATD exposure during pregnancy.

Table 2. Changing costs (GBP) of treatments for hyperthyroidism in the UK

	2002[20]	2012	2014	2015	2016	Increase in the last 4 years (%)	Increase in the last 14 years (%)
CBZ 5 mg × 100*	2·87	4·53	23·20	64·79	84·8	1772	2855
CBZ 20 mg × 100*	10·65	16·83	56·88	160·09	208·17	1137	1855
PTU 50 mg × 100*	43·70	72·55	74·52	87·52	131·25	81	200
RAI	450				200†		−55·6
Surgery	5688				5150‡		−9·5

*Costs from BNF of the year.
†Nuclear medicine department;
‡Local private hospital.

Australia found RAI to be the least expensive choice. They calculated quality-adjusted life years (QALYs) in a model that included efficacy, rates of relapse and major complications associated with each treatment. The lifetime cost of treatment with RAI, ATDs and thyroidectomy were £5425, £16 866 and £7115 respectively, with corresponding QALYs 34·73, 35·17 and 33·93 respectively.[26]

What is the utility of TRAb in pregnancy?

TSH receptor antibody measurement helps differentiate gestational thyrotoxicosis from GD in women with hyperemesis gravidarum and clinical signs of thyrotoxicosis.[27] TRAb levels decline as pregnancy advances, especially after 20 weeks. Transplacental transfer of TRAb has been implicated in causing foetal and neonatal thyrotoxicosis. In a study of 47 TRAb positive pregnant women, TRAb ≥5 IU/l (greater than × 3 the upper limit of the reference range) in the second trimester had 100% sensitivity and 43% specificity in predicting neonatal hyperthyroidism.[28] The recent ATA guidelines for the diagnosis and management of thyroid disease during pregnancy recommend TRAb testing in early pregnancy for women on ATD therapy for GD during pregnancy, those treated with RAI or thyroidectomy for GD in the past and in those with a history of delivering an infant with hyperthyroidism. If TRAb is elevated in early pregnancy, repeat testing is recommended at 18–22 weeks. Those with elevated TRAb >5 IU/l or three times the upper limit of normal need close monitoring for foetal thyrotoxicosis. Further TRAb testing is required later in pregnancy (30–34 weeks) for women with elevated TRAb at 18–22 weeks to assess the need for neonatal and postnatal monitoring. If TRAb becomes undetectable during pregnancy in a woman on ATD, it may be feasible to reduce or withdraw ATD.[29] The Endocrine Society guidelines recommend TRAb testing at 22 weeks of gestation to determine the risk of foetal and neonatal thyrotoxicosis.[27]

Does TRAb measurement affect the management of Graves' ophthalmopathy?

TSH receptor antibodies influences the pathogenesis of GO by increasing hyaluronic acid synthesis and also enhancing

adipogenesis in the orbital fibroblasts and preadipocytes via PI3 kinase activation.[30,31] TRAb titres parallel the course of GO. In a prospective study of 159 patients with GO, those with a severe course of GO had significantly higher levels of TRAb at diagnosis and on follow-up. A TRAb value of >8·8 IU/l after 5–8 months of onset of GO was associated had 18-fold increased risk of a severe course of GO.[32] A meta-analysis of eight randomized controlled trials and retrospective controlled trials evaluated 850 patients treated with RAI for GD comparing steroid therapy *vs* placebo or no treatment to prevent progression of GO. Patients in the included studies either had no GO or mild-to-moderate GO before RAI therapy. Prednisone (0·4–0·5 mg/kg tapered over 3 months) was the best validated regimen for use in patients with mild-to-moderate GO who had high risk of progression, while low-dose prednisone (0·2–0·3 mg/kg tapered over four to 5 weeks) was found to be useful in patients with mild GO and in patients without preexisting GO who had risk factors (smoking and/or elevated TRAb).[33]

In conclusion, TRAb is the key modulator of Graves' hyperthyroidism. TRAb measurement with the second- and third-generation assays that have high sensitivity and specificity has simplified the diagnostic algorithm of GD. TRAb measurements at presentation and after 12 and/or 18 months of ATD therapy predict the risk of relapse, and hence could potentially guide treatment choices. Elevated TRAb favours definitive treatment. Women of childbearing age at greater risk of relapse of GD should be offered definitive treatment to avoid the risks associated with ATDs in pregnancy. A comprehensive prediction model incorporating TRAb, clinical and genetic parameters improves the prediction of relapse, but needs further validation in long-term studies. TRAb level should be checked in pregnant women with GD on ATDs or those previously treated with RAI or thyroidectomy. TRAb ≥5 IU/l in the latter part of pregnancy is associated with increased risk of foetal and neonatal thyrotoxicosis and hence needs close monitoring. TRAb levels parallel the course of GO and determine the need for steroid prophylaxis in those treated with RAI.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

1 Barbesino, G. & Tomer, Y. (2013) Clinical utility of TSH receptor antibodies. *Journal of Clinical Endocrinology and Metabolism*, **98**, 2247–2255.

2 Prabhakar, B.S., Bahn, R.S. & Smith, T.J. (2003) Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. *Endocrine Reviews*, **24**, 802–835.

3 Smith, B.R. & Hall, R. (1974) Thyroid-stimulating immunoglobulins in Graves' disease. *Lancet*, **2**, 427–431.

4 Zöphel, K., Roggenbuck, D. & Schott, M. (2010) Clinical review about TRAb assay's history. *Autoimmunity Reviews*, **9**, 695–700.

5 Sanders, J., Jeffreys, J., Depraetere, H. *et al.* (2002) Thyroid-stimulating monoclonal antibodies. *Thyroid*, **12**, 1043–1050.

6 Schott, M., Hermsen, D., Broecker-Preuss, M. *et al.* (2009) Clinical value of the first automated TSH receptor autoantibody assay for the diagnosis of Graves' disease (GD): an international multicentre trial. *Clinical Endocrinology - Oxford*, **71**, 566–573.

7 Tozzoli, R., Bagnasco, M., Giavarina, D. *et al.* (2012) TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. *Autoimmunity Reviews*, **12**, 107–113.

8 Jang, S.Y., Shin, D.Y., Lee, E.J. *et al.* (2013) Relevance of TSH-receptor antibody levels in predicting disease course in Graves' orbitopathy: comparison of the third-generation TBII assay and Mc4-TSI bioassay. *Eye (Lond)*, **27**, 964–971.

9 Massart, C., Gibassier, J. & d'Herbomez, M.. (2009) Clinical value of M22-based assays for TSH-receptor antibody (TRAb) in the follow-up of antithyroid drug treated Graves' disease: comparison with the second generation human TRAb assay. *Clinica Chimica Acta*, **407**, 62–66.

10 Laurberg, P., Wallin, G., Tallstedt, L. *et al.* (2008) TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *European Journal of Endocrinology*, **158**, 69–75.

11 Abraham, P., Avenell, A., McGeoch, S.C. *et al.* (2010) Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database Systematic Review*, **1**, CD003420 doi: 10.1002/14651858.CD003420.pub4.

12 Sundaresh, V., Brito, J.P., Wang, Z. *et al.* (2013) Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. *Journal of Clinical Endocrinology and Metabolism*, **98**, 3671–3677.

13 Feldt-Rasmussen, U., Schleusener, H. & Carayon, P. (1994) Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. *Journal of Clinical Endocrinology and Metabolism*, **78**, 98–102.

14 Tun, N.N., Beckett, G., Zammitt, N.N. *et al.* (2016) Thyrotropin receptor antibody levels at diagnosis and after thionamide course predict Graves' disease relapse. *Thyroid*, **26**, 1004–1009.

15 Eckstein, A.K., Lax, H., Lösch, C. *et al.* (2007) Patients with severe Graves' ophthalmopathy have a higher risk of relapsing hyperthyroidism and are unlikely to remain in remission. *Clinical Endocrinology - Oxford*, **67**, 607–612.

16 Okamoto, Y., Tanigawa, S., Ishikawa, K. *et al.* (2006) TSH receptor antibody measurements and prediction of remission in Graves' disease patients treated with minimum maintenance doses of antithyroid drugs. *Endocrine Journal*, **53**, 467–472.

17 Carella, C., Mazziotti, G., Sorvillo, F. *et al.* (2006) Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period. *Thyroid*, **16**, 295–302.

18 Quadbeck, B., Hoermann, R., Roggenbuck, U. *et al.* ; Basedow Study Group (2005) Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves' disease. *Thyroid*, **15**, 1047–1054.

19 Vos, X.G., Endert, E., Zwinderman, A.H. *et al.* (2016) Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **101**, 1381–1389.

20 Ross, D.S., Burch, H.B., Cooper, D.S. *et al.* (2016) 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*, **26**, 1343–1421.
21 Andersen, S.L., Olsen, J. & Laurberg, P. (2016) Antithyroid drug side effects in the population and in pregnancy. *Journal of Clinical Endocrinology and Metabolism*, **101**, 1606–1614.
22 Patel, N.N., Abraham, P., Buscombe, J. *et al.* (2006) The cost effectiveness of treatment modalities for thyrotoxicosis in a U.K. Center. *Thyroid*, **16**, 593–598.
23 Sisson, J.C., Freitas, J., McDougall, I.R. *et al.* (2011) Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I: practice recommendations of the American Thyroid Association- The American Thyroid Association Taskforce on Radioiodine Safety. *Thyroid*, **21**, 335–346.
24 Royal College of Physicians. (2007) Radioiodine in the Management of Benign Thyroid Disease: clinical guidelines. Report of a Working Party. London: RCP, 2007.
25 Bartalena, L., Baldeschi, L., Boboridis, K. *et al.* (2016) European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' Orbitopathy. *European Thyroid Journal*, **5**, 9–26.
26 Donovan, P.J., McLeod, D.S., Little, R. *et al.* (2016) Cost–utility analysis comparing radioactive iodine, anti-thyroid drugs and total thyroidectomy for primary treatment of Graves' disease. *European Journal of Endocrinology*, **175**, 595–603.
27 De Groot, L., Abalovich, M., Alexander, E.K. *et al.* (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, **97**, 2543–2565.
28 Abeillon-du Payrat, J., Chikh, K., Bossard, N. *et al.* (2014)) Predictive value of maternal second-generation thyroid-binding inhibitory immunoglobulin assay for neonatal autoimmune hyperthyroidism. *European Journal of Endocrinology*, **171**, 451–460.
29 Alexander, E.K., Pearce, E.N., Brent, G.A. *et al.* (2017) 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*, **27**(3), 315–389.
30 Iyer, S. & Bahn, R. (2012) Immunopathogenesis of Graves' ophthalmopathy: the role of the TSH receptor. *Best Practice & Research. Clinical Endocrinology & Metabolism*, **26**, 281–289.
31 Kumar, S., Nadeem, S., Stan, M.N. *et al.* (2011) A stimulatory TSH receptor antibody enhances adipogenesis via phosphoinositide 3-kinase activation in orbital preadipocytes from patients with Graves' ophthalmopathy. *Journal of Molecular Endocrinology*, **46**, 155–163.
32 Eckstein, A.K., Plicht, M., Lax, H. *et al.* (2006) Thyrotropin receptor autoantibodies are independent risk factors for graves' ophthalmopathy and help to predict severity and outcome of the disease. *Clinical Endocrinology & Metabolism*, **91**, 3464–3470.
33 Shiber, S., Stiebel-Kalish, H., Shimon, I. *et al.* (2014) Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. *Thyroid*, **24**, 1515–1523.