Topic proposal

I understand that this proposal will be retained by the SIGN Programme Lead and be made available on the SIGN website for time period that the proposal is being considered. **Only proposals with a completed Declaration of Interests for the principal proposer will be considered**	
1.	**What is the problem/need for a guideline/clinical scenario?**
	Inadequate diagnosis and treatment of a significant proportion of patients on therapy for thyroid dysfunction.
2.	**Burden of the condition**
	1.7 fold increase in risk for hyperthyroidism. Little increase in patients on treatment for hypothyroidism but see below
	About 5% of women and 0.5% of men (at the minimum)
3.	**Variations**
	In most diagnostic situations only a measure of Thyroid Stimulating Hormone (TSH) is deemed sufficient to adequately diagnose thyroid dysfunction and thyroxine therapy. Free thyroxine (FT4) may also be measured on occasion, but free triiodothyronine (FT3) is almost never used as a diagnostic aid. Suppressed TSH levels in blood are deemed to promote osteoporosis and atrial fibrillation especially in older subjects. Such levels are therefore deprecated in spite of the evidence of very low extra adverse events.
	The failure to adequately diagnose patients on therapy affects up to 10-15% of such patients. Triodothyronine (T3) therapy combined with thyroxine (T4) is only very rarely sanctioned, in spite of the evidence of patient presentation that indicates its value in treatment. Accordingly a significant number of subjects (probably up to 25000 in Scotland) do not receive adequate treatment
4.	**Areas of uncertainty to be covered**
	Key question 1 Relationship of extra cost of carrying out TSH, FT4 and FT3 tests on all patients under thyroxine therapy versus the costs both actual and social of delayed diagnosis, incorrect medication, repeated doctor's visits, and inability to work.
	Key question 2 Speed of acceptance of new emerging paradigms in thyroid diagnosis and treatment
	Key question 3
5.	**Areas that will not be covered**
	Retraining of doctors
6.	**Aspects of the proposed clinical topic that are key areas of concern for patients, carers and/or the organisations that represent them**
	Inordinate delays in accurate diagnosis and treatment for a significant number of patients with thyroid dysfunction, incorrect diagnoses , futile costly irrelevant attempts to diagnose otherwise than thyroid dysfunction with the prescription of useless medication. Refusal or great reluctance to prescribe T3 either alone or in conjunction with T4. Absolute refusal to

	prescribe the natural product Natural Desiccated Thyroid (NDT) owing to lack of registration and permission for use (even though this product has been shown to be efficacious).
7.	**Population**
	250000-300000
	5 million
8.	**Healthcare setting**
	Diagnosis by endocrinologists and routine treatment by general practitioners. Confirmatory or ongoing tests performed by clinical chemistry laboratories in hospitals.
	Not included
9.	**Potential**
	1) Include all three (TSH, FT4, FT3) tests in diagnosis, treating and maintaining patients with thyroid dysfunction. 2) Use more intelligent diagnostic protocols in interpreting such test results.
	Better treatment and quality of life for 10-15% of patients with thyroid dysfunction
	Estimated £500000 extra cost for additional tests (based on an estimate of £6 million for UK as a whole from BTH).
10.	**What evidence based guidance is currently available?**
	None
	Out-of-date (list)
	Current (list)
11.	**Relevance to current Scottish Government policies**
	Aim of more efficient and timely diagnosis and treatment, leading to significant savings overall.
12.	**Who is this guidance for?**
	Doctors and endocrinologists
13.	**Implementation**
	Links with existing audit programmes
	Existing educational initiatives
	1) Rationalise measurement methods to promote consistency of results by 2) ensuring all laboratories use methods that closely agree in measurements 3) Education of all parties as to optimize diagnostic and treatment strategies 4) monitor the resulting cost increases from extra testing modalities.
14.	**Primary contact for topic proposal**

15.	Group(s) or institution(s) supporting the proposal

Declaration of Interests

Please complete all sections and if you have nothing to declare please put 'N/A

Having read the SIGN Policy on Declaration of Competing Interests I declare the following competing interests for the previous year, and the following year. I understand that this declaration will be retained by the SIGN Programme Lead and be made available on the SIGN website for time period that the proposal is being considered.

Signature:	
Name:	
Relationship to SIGN:	Topic proposal primary contact
Date:	
Date received at SIGN:	

Personal Interests

Remuneration from employment

	Name of Employer and Post held	Nature of Business	Self or partner/ relative	Specific?
Details of employment held which may be significant to, or relevant to, or bear upon the work of SIGN				

Remuneration from self employment

	Name of Business	Nature of Business	Self or partner/ relative	Specific?
Details of self employment held which may be significant to, or relevant to, or bear upon the work of SIGN				

Remuneration as holder of paid office

	Nature of Office held	Organisation	Self or partner/ relative	Specific?
Details of office held which may be significant to, or relevant to, or bear upon the work of SIGN				

Remuneration as a director of an undertaking

	Name of Undertaking	Nature of Business	Self or partner/ relative	Specific?
Details of directorship held which may be significant to, or relevant to, or bear upon the work of SIGN				

Remuneration as a partner in a firm

	Name of Partnership	Nature of Business	Self or partner/ relative	Specific?
Details of Partnership held which may be significant to, or relevant to, or bear upon the work of SIGN				

Shares and securities

	Description of organisation	Description of nature of holding (value need not be disclosed)	Self or partner/ relative	Specific?
Details of interests in shares and securities in commercial healthcare companies, organisations and undertakings				

Remuneration from consultancy or other fee paid work commissioned by, or gifts from, commercial healthcare companies, organisations and undertakings

	Nature of work	For whom undertaken and frequency	Self or partner/ relative	Specific?
Details of consultancy or other fee paid work which may be significant of to, or relevant to, or bear upon the work of SIGN				

Details of gifts which may be significant to, or relevant to, or bear upon the work of SIGN				

Non-financial interests

	Description of interest	Self or partner/ relative	Specific?
Details of non-financial interests which may be significant to, or relevant to, or bear upon the work of SIGN			

Non-personal interests

	Name of company, organisation or undertaking	Nature of interest
Details of non-personal support from commercial healthcare companies, organisations or undertakings		

Signature _____ *Date:* _____

Thank you for completing this form.

Please return to
Roberta James
SIGN Programme Lead
SIGN Executive, Healthcare Improvement Scotland,
Gyle Square | 1 South Gyle Crescent | Edinburgh | EH12 9EB

t: **0131 623 4735**
e:**roberta.james@nhs.net**

Data Protection

Your details will be stored on a database for the purposes of managing this guideline topic proposal. We may retain your details so that we can contact you about future Healthcare Improvement Scotland activities. We will not pass these details on to any third parties. Please indicate if you do not want your details to be stored after the proposal is published.

Initial screen

Purpose: initial screening by SIGN Senior Management Team to exclude proposals that are neither clinical, nor multi-professional, nor appropriate for the SIGN process.

1.	**Is this an appropriate clinical topic for a SIGN guideline?** Is it a clinical topic, what is the breadth of the topic and is there a need for the guideline as identified in the proposal?	
	Probably, scoping required	
2.	**Is there a suitable alternative product which would address this topic?** Would another Healthcare Improvement Scotland product better address the topic?	
	Not clear	
3.	**Has this topic been considered before and rejected?** What were the reasons for rejection and are they still applicable	
	Two proposals have been received. One from Scottish Government and one from an individual.	
4.	**Outcome**	
	Go forward to the next stage of topic selection Further development of the proposal required	**YES**
	Reject	

Scope of recent evidence

Summary:

One **Guideline** from the USA published in 2012 was identified, which makes recommendations for clinical management of hypothyroidism in ambulatory adult patients. Topics addressed include the etiology, epidemiology, clinical and laboratory evaluation, management, and consequences of hypothyroidism. Screening, treatment of subclinical hypothyroidism, pregnancy, and areas for future research are also covered. It concludes that a serum thyrotropin is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations. The standard treatment is replacement with L-thyroxine. The decision to treat subclinical hypothyroidism when the serum thyrotropin is less than 10 mIU/L should be tailored to the individual patient.

One Scottish **Health technology assessment** from 2014 was identified looking at the effectiveness of diagnostic tests and thyroid hormone replacement therapies.

Two **Cochrane reviews** were identified from 2007 and 2013 looking at clinical and subclinical hypothyroidism including pre-pregnancy and during pregnancy. Interventions included levothyroxine.

A further **8** systematic reviews identified.

See Annex 1 for further details

Suitability screen

Purpose: screening by the Guideline Programme Advisory Board to select applications suitable for inclusion in the SIGN topic selection process.

1.	**Is there an owner for the project?** (preferably an individual)
	Yes
2.	**Is this a clinical priority area for NHSScotland?**
	The topic is the subject of Public Petition 1463 on Thyroid and Adrenal Disorders
3.	**Is there a gap between current and optimal practice? OR Is there wide variation in current practice?** (is this an area of clinical uncertainty)
	It appears that no all patients are being promptly diagnosed or receiving optimal treatment.
4.	**Is there a suitable guideline already available that could be adapted?** (not necessarily by SIGN)
	Only one relevant guideline was identified in the scoping search
5.	**Is there adequate literature to make an evidence-based decision about appropriate practice?** (is effective intervention proven and would it reduce mortality or morbidity)
	Very little evidence was identified. That which was identified would not change significantly existing guidelines, which hold for the majority of people. Insufficient evidence was identified to support the proposed questions.
6.	**Would the proposed practice change result in sufficient change in outcomes** (health status, provider and consumer satisfaction and cost) **to justify the effort?**
	It is difficult to quantify whether the change would justify effort, as there is little evidence on which to base change in practice.
	How big is the gap?
	Not sure
	How much effort will it take to close the gap?
	Not sure
7.	**Is there a perceived need for the guideline, as indicated by a network of relevant stakeholders?**
	The topic is the subject of Public Petition 1463 on Thyroid and Adrenal Disorders
8.	**Is there a reasonable likelihood that NHSScotland could implement the change?**
	n/a
9.	**Does the proposer have any conflicts of interest? If so how will these be managed?**
	Not stated
10.	**Outcome**
	Go forward to the next stage of topic selection

	Reject Developing a guideline based on the available evidence base would not address the proposers questions. SIGN is also not able to recommend unlicensed medicines. GPAG was of the opinion that the issue was more to do with raising awareness of those for whom standard treatment regimes did not work. The Group noted there was scarce current evidence and the number of patients affected was very small. It was suggested that the Royal College of General Practitioners could get involved in how best to go forward.	**YES**

Annex 1 Scope of recent evidence

Topic: Hypothyroidism – diagnosis and treatment

Resources searched:

GIN
National Guidelines Clearinghouse
NICE
Cochrane Library
CRD databases (includes DARE, HTA, NHS EED)

Dates searched:
GIN, NGC, NICE – 18/3/15
Cochrane, DARE, HTA, NEED 18-19/3/15
CENTRAL – 19/3/15

Guidelines

Garber et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012 Nov-Dec;18(6):988-1028. Available from http://aace.metapress.com/content/611883025v735392/fulltext.pdf

Abstract
OBJECTIVE:
Hypothyroidism has multiple etiologies and manifestations. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions. This paper describes evidence-based clinical guidelines for the clinical management of hypothyroidism in ambulatory patients.
METHODS:
The development of these guidelines was commissioned by the American Association of Clinical Endocrinologists (AACE) in association with American Thyroid Association (ATA). AACE and the ATA assembled a task force of expert clinicians who authored this article. The authors examined relevant literature and took an evidence-based medicine approach that incorporated their knowledge and experience to develop a series of specific recommendations and the rationale for these recommendations. The strength of the recommendations and the quality of evidence supporting each was rated according to the approach outlined in the American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Guidelines-2010 update.
RESULTS:
Topics addressed include the etiology, epidemiology, clinical and laboratory evaluation, management, and consequences of hypothyroidism. Screening, treatment of subclinical hypothyroidism, pregnancy, and areas for future research are also covered.
CONCLUSIONS:
Fifty-two evidence-based recommendations and subrecommendations were developed to aid in the care of patients with hypothyroidism and to share what the authors believe is current, rational, and optimal medical practice for the diagnosis and care of hypothyroidism. A serum thyrotropin is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations. The standard treatment is replacement with L-thyroxine. The decision to treat subclinical hypothyroidism when the serum thyrotropin is less than 10 mIU/L should be tailored to the individual patient.

Relevant Recommendations:-
How should patients with hypothyroidism be treated and monitored?
• **RECOMMENDATION 22.1** Patients with hypothyroidism should be treated with L-thyroxine monotherapy. **Grade A, BEL 1**
See: *L-thyroxine treatment of hypothyroidism*
• **RECOMMENDATION 22.2** The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. **Grade B, BEL 1**
See: *L-thyroxine treatment of hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*; *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Desiccated thyroid*; **Areas for Future Research—** *L-thyroxine /L-triiodothyronine combination therapy*

Recommendation 22.2 was downgraded to Grade B because of still unresolved issues raised by studies that report that some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine.
• **RECOMMENDATION 22.3.** L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy. **Grade B, BEL 3**
See: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy
Recommendation 22.3 was upgraded to B because of potential for harm.
• **RECOMMENDATION 22.4** There is no evidence to support using desiccated thyroid hormone in preference to L-thyroxine monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism. **Grade D, BEL 4**
See: *L-thyroxine treatment of hypothyroidism*; *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Desiccated thyroid*
Recommendation 22.4 was a unanimous expert opinion.
RECOMMENDATION 22.5 3,5,3´-triiodothyroacetic acid (TRIAC; tiratricol) should not be used to treat primary and central hypothyroidism due to suggestions of harm in the literature. **Grade C, BEL 3**
See: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *3,5,3´-Triiodothyroacetic acid*
RECOMMENDATION 34 Patients taking dietary supplements and nutraceuticals for hypothyroidism should be advised that commercially available thyroid-enhancing products are not a remedy for hypothyroidism and should be counseled about the potential side effects of various preparations particularly those containing iodine or sympathomimetic amines as well as those marked as “thyroid support” since they could be adulterated with L-thyroxine or L-triiodothyronine. **Grade D, BEL 4**
See: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Thyroid enhancing preparations*; *Thyromimetic preparations*
Recommendation 34 was a unanimous expert opinion.

Health Technology Assessments

Thompson L. ***Technologies scoping report 22: In the context of hypothyroidism, what is the evidence for the effectiveness of diagnostic tests and thyroid hormone replacement therapies?***. Glasgow: NHS Quality Improvement Scotland (NHS QIS), 2014.
http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_scoping_reports/technologies_scoping_report_22.aspx
Author’s Conclusions
An American non-systematic literature review reported that serum T3 measurement has little specificity or sensitivity for diagnosing primary hypothyroidism, since enhanced T4 to T3 conversion maintains T3 concentrations until hypothyroidism becomes severe. No systematic reviews were identified assessing the clinical or cost effectiveness of routine adrenal function testing in the context of primary hypothyroidism. UK guidelines state that tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism. No studies were identified on the diagnostic validity or clinical utility of the adrenal stress index test/adrenal stress profile.A meta-analysis found no statistically significant differences between the clinical effectiveness of combined LT-4+L-T3 therapy and L-T4 monotherapy. In an analysis of patient preference based on five crossover trials, 48% of study participants preferred combined therapy, compared with 27% who preferred L-T4 monotherapy. Only one small trial comparing effectiveness of DTE with L-T4 was identified. There was no evidence of a difference between study periods on symptoms, general wellbeing and cognitive function. A meta-analysis of studies of L-T4 treatment in patients with subclinical hypothyroidism reported no benefit to symptom scores or quality of life. Some small improvements in cardiac function tests were identified although the clinical significance of these is unclear. There was significant heterogeneity across studies and the study authors concluded that treatment should be based on clinical judgment and patient preference.Only one small trial of L-T4 treatment in patients with thyroid function tests within the reference range was identified. Across a battery of tests, clinical benefit of treatment was identified only in a test which assesses memory for non-verbal visual stimuli.

Cochrane reviews

Reid SM. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy**. 2013**
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007752.pub3/pdf

Over the last decade there has been enhanced awareness of the appreciable morbidity of thyroid dysfunction, particularly thyroid deficiency. Since treating clinical and subclinical hypothyroidism may reduce adverse obstetric outcomes, it is crucial to identify which interventions are safe and effective.

Objectives

To identify interventions used in the management of hypothyroidism and subclinical hypothyroidism pre-pregnancy or during pregnancy and to ascertain the impact of these interventions on important maternal, fetal, neonatal and childhood outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 March 2013).

Selection criteria

Randomised controlled trials (RCTs) and quasi-randomised controlled trials that compared a pharmacological intervention for hypothyroidism and subclinical hypothyroidism pre-pregnancy or during pregnancy with another intervention or placebo.

Data collection and analysis

Two review authors assessed trial eligibility and quality and extracted the data.

Main results

We included four RCTs of moderate risk of bias involving 362 women. In one trial of 115 women, levothyroxine therapy to treat pregnant euthyroid (normal thyroid function) women with thyroid peroxidase antibodies was not shown to reduce pre-eclampsia significantly (risk ratio (RR) 0.61; 95% confidence interval (CI) 0.11 to 3.48) but did significantly reduce preterm birth by 72% (RR 0.28; 95% CI 0.10 to 0.80). Two trials of 30 and 48 hypothyroid women respectively compared levothyroxine doses, but both trials reported only biochemical outcomes. A trial of 169 women compared the trace element selenomethionine (selenium) with placebo and no significant differences were seen for either pre-eclampsia (RR 1.44; 95% CI 0.25 to 8.38) or preterm birth (RR 0.96; 95% CI 0.20 to 4.61). None of the four trials reported on childhood neurodevelopmental delay.

There was a non-significant trend towards fewer miscarriages with levothyroxine, and selenium showed some favourable impact on postpartum thyroid function and a decreased incidence of moderate to advanced postpartum thyroiditis.

Authors' conclusions

This review found no difference between levothyroxine therapy and a control for treating pregnant euthyroid women with thyroid peroxidase antibodies for the outcome of pre-eclampsia, however a reduction in preterm birth and a trend towards reduced miscarriage with levothyroxine was shown. This review also showed no difference for pre-eclampsia or preterm birth when selenium was compared with placebo, however a promising reduction in postpartum thyroiditis was shown. Childhood neurodevelopmental delay was not assessed by any trial included in the review.

Given that this review is based on four trials of moderate risk of bias, with only two trials contributing data (n = 284), there is insufficient evidence to recommend the use of one intervention for clinical or subclinical hypothyroidism pre-pregnancy or during pregnancy over another, for improving maternal, fetal, neonatal and childhood outcomes.

Villar HCCE. **Thyroid hormone replacement for subclinical hypothyroidism**. 2007.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003419.pub2/pdf

Subclinical hypothyroidism is defined as an elevated serum thyroid-stimulating hormone (TSH) level with normal free thyroid hormones values. The prevalence of subclinical hypothyroidism is 4% to 8% in the general population, and up to 15% to 18% in women who are over 60 years of age. There is considerable controversy regarding the morbidity, the clinical significance of subclinical hypothyroidism and if these patients should be treated.

Objectives

To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE and LILACS. Ongoing trials databases, reference lists and abstracts of congresses were scrutinized as well.

Selection criteria

All studies had to be randomised controlled trials comparing thyroid hormone replacement with placebo or no treatment in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for missing or additional information.

Main results

Twelve trials of six to 14 months duration involving 350 people were included. Eleven trials investigated levothyroxine replacement with placebo, one study compared levothyroxine replacement with no treatment. We did not identify any trial that assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation, as indicated by a significant prolongation of the isovolumic relaxation time as well as diastolic dysfunction. Only four studies reported adverse events with no statistically significant differences between groups.
Authors' conclusions
In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

Other Systematic reviews

Grozinsky-Glasberg S. **Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials. *Clinical Endocrinology and Metabolism*.2006;91(7):2592-2599**
Context: In some patients symptoms of hypothyroidism persist despite therapy with T4.
Objective: The objective of the study was to compare the effectiveness of T4-T3 combination *vs.* T4 monotherapy for the treatment of clinical hypothyroidism in adults.
Data Sources: PubMed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.
Study Selection: All randomized trials that compared the effectiveness of T4-T3 combination *vs.* T4 monotherapy for the treatment of clinical hypothyroidism in adults were included.
Data Extraction: The data were extracted by two independent reviewers.
Data Synthesis: We included 11 studies, in which 1216 patients were randomized. No difference was found in the effectiveness of combination *vs.* monotherapy in any of the following symptoms: bodily pain [standardized mean difference (SMD) 0.00, 95% confidence interval (CI) _0.34, 0.35], depression (SMD 0.07, 95% CI _0.20, 0.34), anxiety (SMD 0.00, 95% CI _0.12, 0.11), fatigue (SMD _0.12, 95% CI _0.33, 0.09), quality of life (SMD 0.03, 95% CI_0.09, 0.15), body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and highdensity lipoprotein. Adverse events did not differ between regimens.
Conclusions: T4 monotherapy should remain the treatment of choice for clinical hypothyroidism.

Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. ***Human Reproduction Update***.2013;**19**(3):251-258
BACKGROUND Previous meta-analyses of observational data indicate that pregnant women with subclinical hypothyroidism have an increased risk of adverse pregnancy outcome. Potential benefits of levothyroxine (LT4) supplementation remain unclear, and no systematic review or meta-analysis of trial findings is available in a setting of assisted reproduction technologies (ART). METHODS Relevant trials published until August 2012 were identified by searching MEDLINE, EMBASE, Web of Knowledge, the Cochrane Controlled Trials Register databases and bibliographies of retrieved publications without language restrictions. RESULTS From 630 articles retrieved, we included three trials with data on 220 patients. One of these three trials stated 'live delivery' as outcome. LT4 treatment resulted in a significantly higher delivery rate, with a pooled relative risk (RR) of 2.76 (95% confidence limits 1.20-6.44; P = 0.018; I(2) = 70%), a pooled absolute risk difference (ARD) of 36.3% (3.5-69.0%: P = 0.030) and a summary number needed to treat (NNT) of 3 (1-28) in favour of LT4 supplementation. LT4 treatment significantly lowered miscarriage rate with a pooled RR of 0.45 (0.24-0.82; P = 0.010; I(2) = 26%), a pooled ARD of -31.3% (-48.2 to -14.5%: P < 0.001) and a summary NNT of 3 (2-7) in favour of LT4 supplementation. LT4 treatment had no effect on clinical pregnancy (RR 1.75; 0.90-3.38; P = 0.098;

I(2) = 82%). In an ART setting, no data are available on the effects of LT4 supplementation on premature delivery, arterial hypertension, placental abruption or pre-eclampsia. CONCLUSIONS Our meta-analyses provide evidence that LT4 supplementation should be recommended to improve clinical pregnancy outcome in women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing ART. Further research is needed to determine pregnancy outcome after close monitoring of thyroid function to maintain thyroid-stimulating hormone and free T4 levels within the trimester-specific reference ranges for pregnancy.

van Harten AC, Leue C, Verhey FR. Should depressive symptoms in patients with subclinical hypothyroidism be treated with thyroid hormone?. ***Tijdschrift voor Psychiatrie***.2008;**50**(8):539-543
background Although there are theoretical grounds for using hormone therapy to treat depressive symptoms in patients with hypothyroidism, the clinical evidence for this is unclear.
objective To investigate the efficacy of treating depression with thyroid hormone in a population with subclinical hypothyroidism.
method Literature search in various databases for double-blind randomised placebocontrolled studies that provided clinical evidence for the effect of thyroid hormone on depressive symptoms in a population with subclinical hypothyroidism.
results Three randomized controlled trials (rcts) were included. None of these was concerned primarily with patients suffering from depressive disorder, but focused mainly on subjects with subclinical hypothyroidism, with the score on the depressive scale as secondary outcome. In all the studies selected subclinical hypothyroidism was treated with levothyroxine which had no beneficial effect on depression.
conclusion Since there is a lack of evidence of beneficial effects in a population with subclinical hypothyroidism and a lack of research into the effects in a depressive population, no definite answer can yet be given to the question posed in the title.

Helfand M, Redfern C C. Clinical guideline - part 2. Screening for thyroid disease: an update. ***Annals of Internal Medicine***.1998;**129**(2):144-158
Purpose: To review information on the benefits of screening with a sensitive thyroid-stimulating hormone (TSH) test for thyroid dysfunction in asymptomatic patients seeking primary care for other reasons. This paper focuses on whether screening should be aimed at detection of subclinical thyroid dysfunction and whether persons with mildly abnormal TSH levels can benefit.
Data Sources: A MEDLINE search for studies of screening for thyroid dysfunction and of treatment for complications of subclinical thyroid dysfunction.
Study Selection: Studies of screening with thyroid function tests in the general adult population or in patients seen in the general office setting were selected (*n* = 33). All controlled studies of treatment in patients with subclinical hypothyroidism or subclinical hyperthyroidism were also included (*n* = 23).
Data Extraction: The prevalence of overt and subclinical thyroid dysfunction, the evidence for the efficacy of treatment, and the incidence of complications in defined age and sex groups were extracted from each study.
Data Synthesis: Screening can detect symptomatic but unsuspected overt thyroid dysfunction. The yield is highest for women older than 50 years of age: In this group, 1 in 71 women screened could benefit from relief of symptoms. Evidence of the efficacy of treatment for subclinical thyroid dysfunction is inconclusive.
Conclusions: Even though treatment for subclinical thyroid dysfunction is controversial, office-based screening to detect overt thyroid dysfunction may be indicated in women older than 50 years of age. Large randomized trials are needed to determine the likelihood that treatment will improve quality of life in otherwise healthy patients who have mildly elevated TSH levels.

Ma C, Xie J, Huang X, Wang G, Wang Y, Wang X, Zuo S. Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. ***Nuclear Medicine Communications***.2009;**30**(8):586-593
Standard therapy for patients with hypothyroidism is replacement with synthetic thyroxine (T4). However, thyroxine plus triiodothyronine (T3) replacement therapy resulted in marked improvements in several items of the Profile of Mood States and in a few indices of psychometric function and quality of life. The adequacy of thyroxine alone versus thyroxine plus triiodothyronine to treat hypothyroidism has yielded conflicting results. Therefore, we conducted a systematic review of all included published, randomized controlled trials to evaluate the effects of thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. We electronically searched Medline, Embase, the Cochrane Library, and China National Infrastructure. We also manually searched the Chinese Journal of Isotopes, Radiologia pratica, and the Chinese Journal of Endocrinology and Metabolism. A total of 10 randomized, double-blind trials (six crossovers, four parallel trials) were identified. Pooled analyses were

suggestive of a statistically significant increase of free and total triiodothyronine, significant decrease of serum-free and total thyroxine in patients treated with thyroxine plus triiodothyronine, weighted mean difference (WMD) 0.03, -31.25, 2.19, 3.00; 95% confidence interval (CI) -0.14 to 0.20, -47.04 to -15.47, 0.46-3.92, 1.64-4.36, respectively. Thyroxin alone indicated significant benefits for psychological or physical well-being in terms of the General Health Questionnaire-28 (WMD: -2.90; 95% CI: -3.18 to -2.63), general health (WMD: -0.38; 95% CI: -0.71 to -0.05), physical component summary (WMD: 0.7; 95% CI: 0.53-0.87), and mental component summary (WMD: 0.58; 95% CI: 0.25-0.75); physical functioning (WMD: 1.60; 95% CI: 1.29-1.90), role-physical test (WMD: 3.60; 95% CI: 2.66-4.54), bodily pain (WMD: 2.50; 95% CI: 2.11-2.88), role-emotional (WMD: 2.08; 95% CI: 1.17-2.99), mental health (WMD: 1.30; 95% CI: 0.97-1.64) in items of the Short Form-36 Health Survey; general well-being in items of the Thyroid Symptom Questionnaire (WMD: -1.90; 95% CI: -2.48 to -1.32); better performance in the Letter Number Sequencing-working memory test in items of cognitive performance scores (WMD: 1.10; 95% CI: 0.08-2.13), significant treatment effect for blurred vision, aches, and pain (WMD: -4.66, -0.80; 95% CI: -5.339 to -4.00, -1.34 to -0.26, respectively). However, T4 plus T3 replacement improved cognitive performance (WMD: -0.49; 95% CI: -0.90 to -0.08). No significant statistical differences were found in biochemical variables, mood states clinical variables, adverse effects, and drop-out. In subgroup analysis, two included studies examined the relationship between mental improvement and causes of hypothyroidism, autoimmune, and nonautoimmune hypothyroidism, respectively. T4 alone suggested significantly higher total T4 (autoimmune and nonautoimmune thyroid, WMD: 4.5, 3.7; 95% CI: 2.24-6.76, 1.66-5.74, respectively), and significantly decreased thyroid-stimulating hormone (WMD: -0.05; 95% CI: -0.09 to -0.01). Statistically significant improvement occurred in pairs correctly recalled in the Digit Symbol Test for T4 plus T3 replacement (WMD: -1.60; 95% CI: -2.97 to -0.23) for nonautoimmune thyroid. In conclusion, on the basis of data from recent studies, we conclude that combined T4 and T3 treatment does not improve well-being, cognitive function, or quality of life compared with T4 alone. T4 alone may be beneficial in improving psychological or physical well-being. According to the current evidence, T4 alone replacement may remain the drug of choice for hypothyroid patients

Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. ***Journal of Clinical Endocrinology and Metabolism***.2012;**97**(7):2243-2255

CONTEXT:

The reported risk of hypothyroidism after hemithyroidectomy shows considerable heterogeneity in literature.

OBJECTIVE:

The aim of this systematic review and meta-analysis was to determine the overall risk of hypothyroidism, both clinical and subclinical, after hemithyroidectomy. Furthermore, we aimed to identify risk factors for postoperative hypothyroidism.

DATA SOURCES:

A systematic literature search was performed using several databases, including PubMed.

STUDY SELECTION:

Original articles in which an incidence or prevalence of hypothyroidism after primary hemithyroidectomy could be extracted were included.

DATA EXTRACTION:

Study identification and data extraction were performed independently by two reviewers. In case of disagreement, a third reviewer was consulted.

DATA SYNTHESIS:

A total of 32 studies were included in this meta-analysis. Meta-analysis was performed using logistic regression with random effect at study level. The overall risk of hypothyroidism after hemithyroidectomy was 22% (95% confidence interval, 19-27). A clear distinction between clinical (supranormal TSH levels and subnormal thyroid hormone levels) and subclinical (supranormal TSH levels and thyroid hormone levels within the normal range) hypothyroidism was provided in four studies. These studies reported on an estimated risk of 12% for subclinical hypothyroidism and 4% for clinical hypothyroidism. Positive anti-thyroid peroxidase status is a relevant preoperative indicator of hypothyroidism after surgery. Effect estimates did not differ substantially between studies with lower risk of bias and studies with higher risk of bias.

CONCLUSIONS:

This meta-analysis showed that approximately one in five patients will develop hypothyroidism after hemithyroidectomy, with clinical hypothyroidism in one of 25 operated patients

Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force. ***Annals of Internal Medicine***.2014

Background: In 2004, the U.S. Preventive Services Task Force found insufficient evidence to recommend thyroid screening.

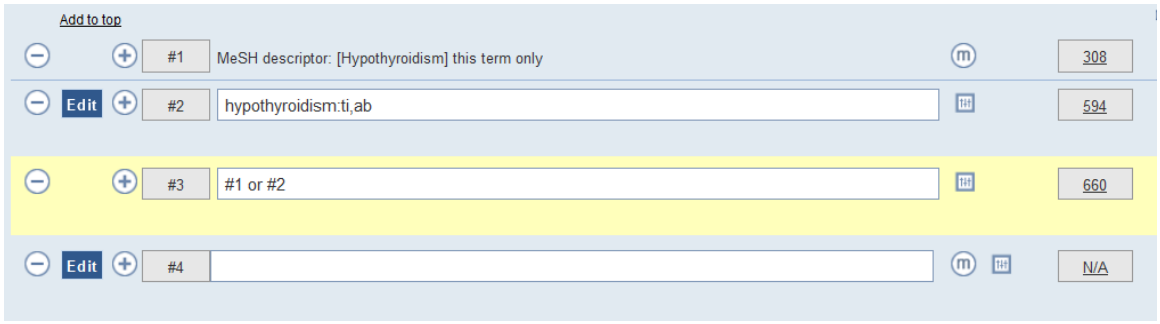
Purpose: To update the 2004 U.S. Preventive Services Task Force review on the benefits and harms of screening and treatment of subclinical and undiagnosed overt hypothyroidism and hyperthyroidism in adults without goiter or thyroid nodules.
Data Sources: MEDLINE and Cochrane databases through July 2014.
Study Selection: Randomized, controlled trials and observational studies of screening and treatment.
Data Extraction: One investigator abstracted data, and a second investigator confirmed; 2 investigators independently assessed study quality.
Data Synthesis: No study directly assessed benefits and harms of screening versus no screening. For subclinical hypothyroidism (based on thyroid-stimulating hormone levels of 4.1 to 11.0 mIU/L), 1 fair-quality cohort study found that treatment of subclinical hypothyroidism was associated with decreased risk for coronary heart disease events versus no treatment. No study found that treatment was associated with improved quality of life, cognitive function, blood pressure, or body mass index versus no treatment. Effects of treatment versus no treatment showed potential beneficial effects on lipid levels, but effects were inconsistent, not statistically significant in most studies, and of uncertain clinical significance (difference, −0.7 to 0 mmol/L [−28 to 0 mg/dL] for total cholesterol levels and −0.6 to 0.1 mmol/L [−22 to 2 mg/dL] for low-density lipoprotein cholesterol levels). Treatment harms were poorly studied and sparsely reported. Two poor-quality studies evaluated treatment of subclinical hyperthyroidism but examined intermediate outcomes. No study evaluated treatment versus no treatment of screen-detected, undiagnosed overt thyroid dysfunction.
Limitation: English-language articles only, no treatment study performed in the United States, and small trials with short duration that used different dosage protocols.
Conclusion: More research is needed to determine the clinical benefits associated with thyroid screening

Vissenberg R, van den boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, Goddijn M. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. ***Human Reproduction Update***.2012;**18**(4):360-373
BACKGROUND Thyroid disorders are associated with pregnancy complications. Universal screening is currently not recommended because of a lack of evidence on the effectiveness of treatment. Women with hyperthyroidism and hypothyroidism evidently require treatment but this is less clear for women with subclinical hypothyroidism and thyroid autoimmunity. Therefore, we conducted a systematic review to provide a comprehensive overview on the available treatment interventions.
METHODS Relevant studies were identified by searching Medline, EMBASE and Cochrane Controlled Trials Register, published until December 2011.
RESULTS From a total of 7334 primary selected titles, 22 articles were included for the systematic review and 11 were appropriate for meta-analyses. Eight studies reported on hyperthyroidism. Propylthiouracil (PTU) and methimazole reduce the risk for preterm delivery [risk ratio (RR): 0.23, confidence interval (CI): 0.1–0.52], pre-eclampsia (RR: 0.23, CI: 0.06–0.89) and low birthweight (RR: 0.38, CI: 0.22–0.66). The nine studies that reported on clinical hypothyroidism showed that levothyroxine is effective in reducing the risk for miscarriage (RR: 0.19, CI: 0.08–0.39) and preterm delivery (RR: 0.41, CI: 0.24–0.68). For treatment of subclinical hypothyroidism, current evidence is insufficient. The five studies available on thyroid autoimmunity showed a not significant reduction in miscarriage (RR: 0.58, CI: 0.32–1.06), but significant reduction in preterm birth by treatment with levothyoxine (RR: 0.31, CI: 0.11–0.90).
CONCLUSION For hyperthyroidism, methimazole and PTU are effective in preventing pregnancy complications. For clinical hypothyroidism, treatment with levothyroxine is recommended. For subclinical hypothyroidism and thyroid autoimmunity, evidence is insufficient to recommend treatment with levothyroxine. The overall lack of evidence precludes a recommendation for universal screening and is only justified in a research setting.

CENTRAL – RCTs
No new relevant RCTs found since SHTG Scoping Report

Search Strategy

Cochrane


Add to top
#1
MeSH descriptor: [Hypothyroidism] this term only
308
Edit
#2
hypothyroidism:ti,ab
594
#3
#1 or #2
660
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N/A