Comparative Effectiveness Review
Number 24

Effective Health Care Program

Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism

Executive Summary

Background

Mildly elevated or decreased serum thyroid stimulating hormone (TSH, also called thyrotropin) levels are the most common abnormalities related to thyroid function. Subclinical thyroid dysfunction, defined as an abnormal TSH with normal levels of serum thyroid hormones (T3 and T4), affects 5 percent of women and 3 percent of men. Subclinical hypothyroidism is defined as a high TSH and normal T3/T4, and subclinical hyperthyroidism as having a low or undetectable TSH and normal T3/T4. Subclinical thyroid dysfunction has been shown to be a risk factor for the later development of overt thyroid disease. In addition, a high TSH level may be a risk factor for coronary events, elevated cholesterol levels, and increased rates of congestive heart failure, while a low TSH level is a risk factor for atrial fibrillation and osteoporosis. Therefore, it has been proposed that screening for and treating subclinical thyroid dysfunction might lead to a decrease in the morbidity associated with overt thyroid disease, heart disease, and possibly osteoporosis. To date, evidence-based reviews have recommended against routine screening and treatment of subclinical thyroid dysfunction, primarily based on the lack of evidence that treating subclinical thyroid dysfunction improves patient-centered outcomes. However, some experts, while acknowledging that evidence to support treatment is lacking, suggest that screening could decrease morbidity and mortality, and perceive the potential for harm as both minor and preventable. They argue it would be best to screen for and treat subclinical thyroid dysfunction until there are sufficient data to address this question definitively.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm.**

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Effective Health Care

Topic Development

This topic was nominated by the public as part of the Effective Health Care (EHC) Program of the Agency for Healthcare Research and Quality (AHRQ). The U.S. Preventive Services Task Force (USPSTF) also expressed interest in updating its 2004 recommendations.

After receiving an initial set of Key Questions and an analytic framework for the process of screening and treating subclinical hypothyroidism and subclinical hyperthyroidism from AHRQ, we revised the Key Questions and analytic framework with the input of external technical experts, members of the USPSTF, and additional input from AHRQ (Figure A). After this input, AHRQ personnel approved the scope and Key Questions for the report.

A 2004 review of screening for thyroid disease for the USPSTF established that subclinical thyroid dysfunction is quite prevalent, may be responsible for morbidity, and can be detected with a serum TSH assay, a readily available, reliable, and acceptable test.[1] However, in 2004, it remained unclear whether treating subclinical thyroid dysfunction would reduce morbidity. Consequently, this current review focuses on whether new evidence demonstrates that treatment improves clinically important outcomes in adults with screen-detected thyroid disease.

Key Questions

We reviewed published studies to answer the following Key Questions:

Key Question 1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?

Key Question 2. What are the harms of screening? Specifically, how frequently and how severely do patients screened for subclinical thyroid dysfunction experience adverse psychological impacts or other harms of workup from screening?

Key Question 3. Does treatment of patients with subclinical hypothyroidism or subclinical hyperthyroidism detected by screening affect outcomes? We were primarily interested in the comparative effectiveness of a strategy of routine treatment versus active surveillance to prevent the possible complications of untreated subclinical thyroid dysfunction.

Key Question 4. What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism? Specifically, what are the consequences of overtreatment, including effects on bone mineral density and incidence of atrial fibrillation, and how frequently do they occur?

Methods

Data Sources

A research librarian searched MEDLINE, the Cochrane Register of Systematic Reviews, and the Database of Abstracts of Reviews of Effects to identify systematic reviews of screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism, with no limits on dates. A number of systematic reviews have addressed this topic. Three reviews—Helfand (2004),[1] the USPSTF review; Surks et al. (2004);[2] and Villar et al. (2007),[3] a Cochrane review—adequately reflected the state of the evidence through 2006. Three reviews had largely concordant findings.

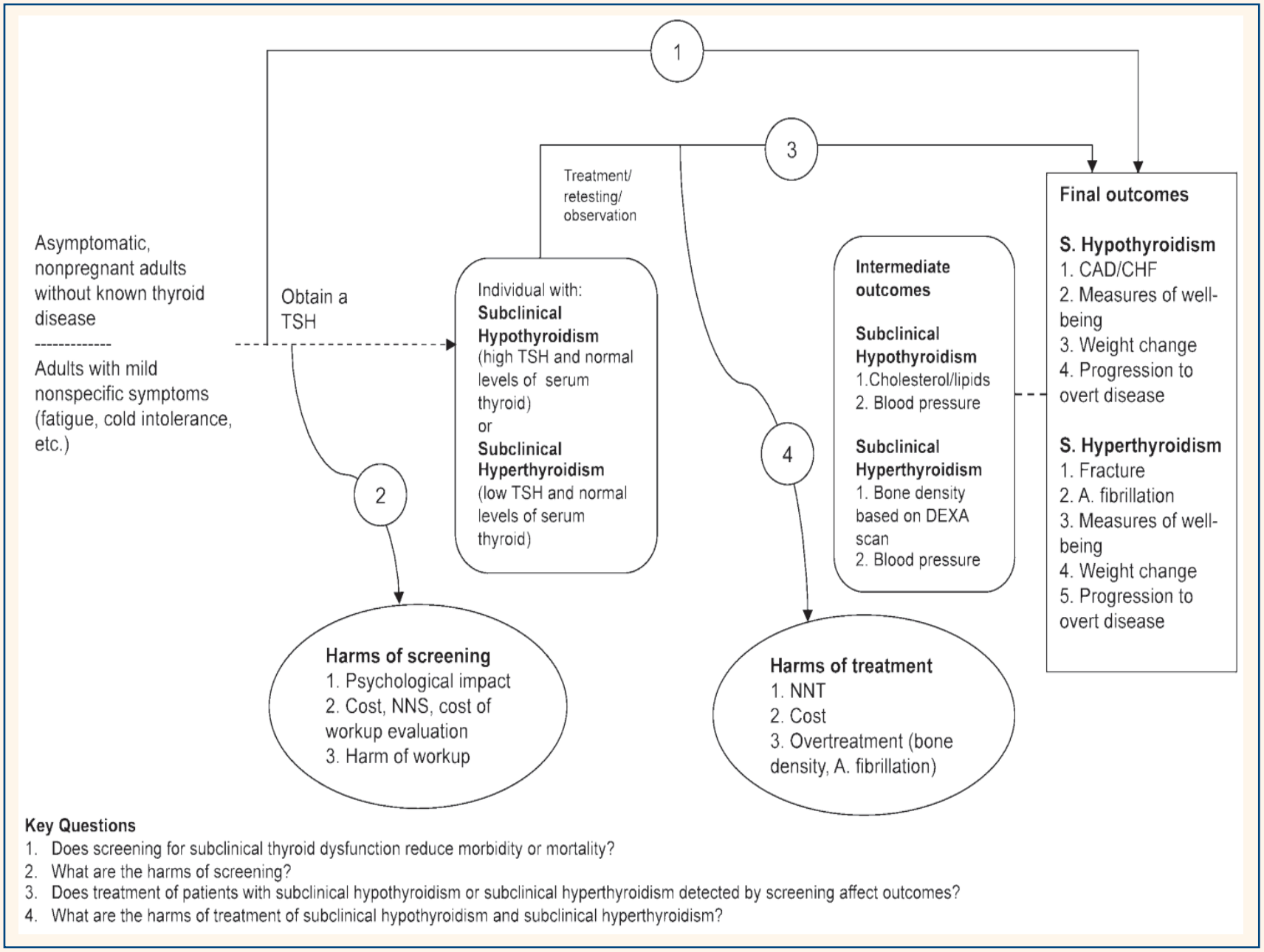

Figure A. Analytic framework

Note: A. fibrillation = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; DEXA = dual-energy x-ray absorptiometry; NNS = number needed to screen; NNT = number needed to treat; S = subclinical; TSH = thyroid stimulating hormone.

We also searched MEDLINE, AGELINE (AARP.org), EMBASE (embase.com), and the Cochrane Central Register of Controlled Trials to identify studies regarding screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism published from 2002 to May 2010. Additional materials were sought by searching for regulatory information, clinical trial registries, conference proceedings, and other sources of gray literature. Additional studies were identified from citations in relevant articles, discussions with experts, and requests to pharmaceutical companies.

We also performed a supplementary search of the foreign language literature. For this search we included CINAHL and the World Health Organization Global Health Library.

Study Selection

We defined the target population as community-living nonpregnant adults, without a history of thyroid disease or symptoms of overt hypothyroidism or hyperthyroidism, who are representative of adults who might be seen in primary care settings. Intermediate outcomes of interest for subclinical hypothyroidism were lipid levels and blood pressure; intermediate outcomes of interest for subclinical hyperthyroidism were bone mineral density and blood pressure. Final outcomes of interest for subclinical hypothyroidism were weight change; measures of well-being, including but not limited to cognition and memory; cardiovascular morbidity; and progression to overt disease. Final outcomes of interest for subclinical hyperthyroidism were weight change; measures of well-being, including but not limited to cognition and memory; cardiovascular morbidity; progression to overt disease; fractures; and atrial fibrillation.

The quality of each systematic review was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. The quality of each study was assessed using criteria established by the USPSTF, and poor quality studies were excluded from review except for subclinical hyperthyroidism, for which no good or fair quality studies were found. Information regarding the population, setting, treatments, and outcomes was all abstracted.

Data Synthesis

We assessed overall strength for each body of evidence addressing a particular outcome of each key question using the guidance from the Strength of Evidence chapter of the AHRQ EHC Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Available at http://effectivehealthcare.ahrq.gov. To assign an overall strength of evidence (high, moderate, low, or insufficient), we considered the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Findings

Findings are summarized in Tables A and B.

Key Question 1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?

We identified no randomized controlled trials (RCTs) or observational studies comparing the outcomes of screening versus not screening for subclinical hypothyroidism or subclinical hyperthyroidism in the general population.

Key Question 2. What are the harms of screening? Specifically, how frequently and how severely do patients screened for subclinical thyroid dysfunction experience adverse psychological impacts or other harms of workup from screening?

Information about the harms of screening remains sparse. We identified no RCTs or controlled observational studies that evaluated harms associated with screening for subclinical thyroid dysfunction. Two natural history studies suggest that a significant number of individuals with subclinical thyroid dysfunction will have normal thyroid function if followed up at about 3 years.

Key Question 3. Does treatment of patients with subclinical hypothyroidism or subclinical hyperthyroidism detected by screening affect outcomes?

Taken together, the 3 reviews listed earlier evaluated 14 controlled trials of treatment for subclinical hypothyroidism. The most recent of the 3 studies, a good-quality Cochrane review,[3] found that, while in the short term lipid profiles and left ventricular function may improve after treatment with levothyroxine,

treatment did not improve health-related quality of life or symptoms, and the trials were not suitable to assess survival or cardiovascular mortality and morbidity. The other two previous reviews had similar results.

Six trials of treatment for subclinical hypothyroidism were published from 2002 to 2010; none of these were included in the 2004 USPSTF review,[1] and four were not included in the 2007 Cochrane review.[3] None of the trials evaluated long-term cardiovascular outcomes, and none had more than 1 year of followup, the minimum time needed to compare immediate treatment versus a strategy of active surveillance with annual testing. The largest trial included 120 patients. The trials used different TSH cutoffs to diagnose subclinical thyroid dysfunction and different dosages of medication, and they assessed effects over different time periods. None of the included studies were conducted on U.S. populations; most patients included in the studies were recruited from specialty clinics rather than from primary care settings.

Four trials evaluated the effect of treatment on lipids; they had inconsistent findings. In two of the four studies, there were modest reductions in total cholesterol and low-density lipoprotein, but in two others, there was no improvement for any lipoproteins. Two other studies measured well-being; two looked at blood pressure; and four examined changes in weight or body mass index (BMI). Studies evaluating these measures consistently found no evidence of benefit.

Two controlled trials assessed the efficacy of treatment of subclinical hyperthyroidism; both of these were of poor quality. Both assessed changes in blood pressure. One also evaluated change in BMI. The other evaluated patient-reported fatigue, nervousness, sweating, change in appetite, and tremors; lipids; and bone mineral density. Evidence of efficacy was inconsistent.

Key Question 4. What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism? Specifically, what are the consequences of overtreatment, including effects on bone mineral density and incidence of atrial fibrillation, and how frequently do they occur?

None of the studies of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism systematically evaluated harms. An assessment of harms was likely not a part of any of the studies' protocol, nor does it appear that study participants were provided with a list of potential harms and asked to identify those that they experienced. Some patients initially diagnosed with subclinical hypothyroidism may revert to normal levels of TSH without treatment, suggesting unnecessary treatment as a possible harm from therapy with levothyroxine.

Table A. Summary of evidence for subclinical hypothyroidism

Key Question	Study type: Number of studies Number of subjects	Risks of bias	Consistency	Directness	Precision	Comments	Magnitude of effect (Strength of evidence)
KQ 1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies directly compared screening with an alternative strategy for detecting thyroid dysfunction	NA	NA	NA	NA		No evidence (Insufficient)
KQ 2. What are the harms of screening for subclinical thyroid dysfunction?	Two studies had indirect evidence about overdiagnosis	NA	No major	Indirect; inconsistency applicability to primary care	NA low to moderate	No RCTs were natural history studies demonstrating indirect evidence of potential harm were included	Insufficient identified; two
KQ 3. Does treatment of patients with subclinical hypothyroidism detected by screening affect outcomes?							
Cardiovascular events, coronary artery disease, and heart failure	No studies	NA	NA	NA	NA		No evidence (Insufficient)
Overall quality of life	RCT: 2 169	Medium	Consistent	Indirect; moderate applicability to primary care setting	Imprecise: small studies of 100 and 69 subjects		No effect (Low)
Changes in mood/cognition	RCT: 2 169	Medium	Consistent	Indirect; moderate applicability to primary care setting	Imprecise: small studies of 100 and 69 subjects		No effect (Low)
Weight/BMI changes	RCT: 4 305	Medium	Consistent	Indirect	Imprecise; the largest study had 100 subjects; the smallest had 23		No effect (Low)

Table A. Summary of evidence for subclinical hypothyroidism (continued)

Key Question	Study type: Number of studies Number of subjects	Risks of bias	Consistency	Directness	Precision	Comments	Magnitude of effect (Strength of evidence)
KQ 3. Does treatment of patients with subclinical hypothyroidism detected by screening affect outcomes? (continued)							
Blood pressure changes	RCT: 2 195	Medium	Consistent	Indirect; low applicability to asymptomatic patients in primary care settings	Imprecise		No effect (Low)
Changes in lipid levels	RCT: 4 379	Medium	Inconsistent	Indirect; low applicability to asymptomatic patients in U.S. primary care settings	Imprecise		Small effect for LDL and total cholesterol (Low)
KQ 4. What are the harms of treatment of subclinical hypothyroidism?	None of the trials in this update address the harms of levothyroxine treatment	NA	NA	NA	NA		Insufficient

Note: BMI = body mass index; LDL = low-density lipoprotein; NA = not applicable; RCT = randomized controlled trial.

Table B. Summary of evidence for subclinical hyperthyroidism							
Key Question	**Study type: Number of studies Number of subjects**	**Risks of bias**	**Consistency**	**Directness**	**Precision**	**Comments**	**Magnitude of effect (Strength of evidence)**
KQ 1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies	NA	NA	NA	NA		No evidence (Insufficient)
KQ 2. What are the harms of screening for subclinical thyroid dysfunction?	No studies	NA	NA	NA	NA		No evidence (Insufficient)
KQ 3. Does treatment of patients with subclinical hyperthyroidism detected by screening affect outcomes?							
Cardiovascular events, including angina, atrial fibrillation, and other clinically significant arrhythmias	No studies	NA	NA	NA	NA		No evidence (Insufficient)
Fractures	No studies	NA	NA	NA	NA		No evidence (Insufficient)
Overall quality of life	No studies	NA	NA	NA	NA		No evidence (Insufficient)
Changes in mood/cognition	No studies	NA	NA	NA	NA		No evidence (Insufficient)

Table B. Summary of evidence for subclinical hyperthyroidism (continued)							
Key Question	**Study type: Number of studies Number of subjects**	**Risks of bias**	**Consistency**	**Directness**	**Precision**	**Comments**	**Magnitude of effect (Strength of evidence)**
KQ 3. Does treatment of patients with subclinical hyperthyroidism detected by screening affect outcomes? (continued)							
Weight/BMI changes	Controlled trial: 1 14	High	NA	Direct	Imprecise		About 1% greater decrease in BMI in treated compared with placebo group; absolute change in BMI in treated group of 0.5 kg/m^2 (Insufficient)
Blood pressure changes	RCT:1 20 Controlled trial: 1 14	High	Inconsistent	Indirect; treated subjects in 1 study included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise		2.58 mmHG reduction in daytime systolic blood pressure from 1 study; no change in 2nd study (Insufficient)

Table B. Summary of evidence for subclinical hyperthyroidism (continued)							
Key Question	**Study type: Number of studies Number of subjects**	**Risks of bias**	**Consistency**	**Directness**	**Precision**	**Comments**	**Magnitude of effect (Strength of evidence)**
KQ 3. Does treatment of patients with subclinical hyperthyroidism detected by screening affect outcomes? (continued)							
Changes in bone density (as measured by DEXA scan)	RCT: 1 20	High	NA	Indirect; treated subjects included 2 patients with Graves disease and 8 with autonomous	Imprecise		No effect (Insufficient)
Changes in lipid levels	RCT: 1 20	High	NA	Indirect; treated subjects included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise		No effect (Insufficient)
KQ 4. What are the harms of treatment of subclinical hyperthyroidism?	No studies	NA	NA	NA	NA		Insufficient

Note: DEXA = dual-energy x-ray absorptiometry; NA = not applicable; RCT = randomized controlled trial.

Discussion

The findings of this review are consistent with those of a previous Cochrane review (2007),[3] and an older systematic review conducted for the USPSTF and the Institute of Medicine (2004)[1] and for the Surks review (2004).[2] We found that the benefits and harms of screening for subclinical thyroid dysfunction remain inadequately studied. We found no RCTs assessing the benefits or harms of screening for thyroid dysfunction in the general population. The evidence was insufficient to assess or quantify the effect of screening on cardiovascular events and cardiac risk factors.

With regard to treatment for subclinical hypothyroidism, no RCTs have directly compared well-defined strategies for routine or selective treatment with a strategy of watchful waiting (active surveillance). No trials have tested the theory that early treatment of subclinical hypothyroidism can prevent coronary events or other heart disease. The applicability of these trials to decisionmaking in primary care settings in the United States was poor.

We considered the evidence insufficient to estimate an effect size or to draw conclusions with regard to benefits of treatment for lipids. For all other outcomes, we assessed the reviewed studies as indicating that there is no benefit of treatment over watchful waiting for either subclinical hypothyroidism or subclinical hyperthyroidism, and we rated the quality of that evidence as low for subclinical hypothyroidism and insufficient for subclinical hyperthyroidism. Evidence was insufficient to assess the long-term harms of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism.

Currently, it is unclear whether screening and early treatment for thyroid disease is better than not screening or watchful waiting when a TSH is mildly abnormal. For patients who have been screened and have a mildly elevated TSH level, the balance of benefits and harms of treatment vs. active surveillance is unclear. Recent studies indicate that, in elderly individuals, a mildly high TSH may be a predictor of longevity and possibly of better functional status. A well-designed RCT or cohort study comparing the outcomes of well-defined alternative strategies—routine or selective treatment vs. active surveillance—is needed to determine which strategy has better outcomes.

References

1. Helfand M. Screening for Thyroid Disease. Systematic Evidence Review No. 23. (Prepared by the Oregon Health & Science University Evidence-based Practice Center under Contract No. 290-97-0018.) Rockville, MD: Agency for Healthcare Research and Quality. January 2004.

2. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA Jan 14;291(2):228-38.

3. Villar HC, Saconato H, Valente O, et al. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database of Systematic Reviews; 2007. Issue 3. Art. No.: CD003419. DOI: 10.1002/14651858.CD003419.pub2.

Full Report

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