Subclinical Thyroid Disorders

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Screening. Should midlife women be screened for thyroid disorders? Among 3,000 multiethnic women aged 42 to 52 years participating in the Study of Women Across the Nation, thyroid-stimulating hormone (TSH) levels were abnormal in almost 10% (two thirds were above normal, one third was below).1 In NHANES III, the percentage of women with evidence of thyroid antibodies, a harbinger of thyroid dysfunction, increased from 15.8% in those aged 40 to 49 years to 26.5% in those over age 80 years. While the American Thyroid Association (ATA) recommends screening all adults beginning at age 35 years and every 5 years thereafter, the US Preventive Services Task Force concluded that the evidence was insufficient to recommend for or against routine screening,2 a position consistent with the American Academy of Family Physicians.3 The American Association of Clinical Endocrinologists (AACE) recommends that older women—age not specified—should be screened. The American College of Physicians recommends that women aged 50 years and older with an incidental finding suggestive of symptomatic thyroid disease should be evaluated.2 Other than the ATA recommendations, intervals for screening are not specified.

Subclinical hypothyroidism. A healthy, asymptomatic woman without history or signs of thyroid disease who has an elevated TSH level and normal thyroid hormone concentrations may qualify for a diagnosis of subclinical hypothyroidism.3 Prevalence of subclinical hypothyroidism is 4% to 8.5%, increasing to 15% in elderly populations. The increased incidence of TSH elevation in older persons with normal thyroid hormone levels might represent a normal manifestation of the aging hypothalamic-pituitary-thyroid axis.4 Based upon NHANES III data, there have been age-, gender-, and ethnicity-specific stratified norms proposed. Before making the diagnosis of subclinical hypothyroidism, repeat the TSH evaluation after 3 to 6 months to confirm the increased level. The presence of antithyroperoxidase antibodies (TPOAb) predicts progression to overt hypothyroidism.2 Up to 60% of suspected cases will regress to euthyroidism over 5 years, whereas 5% to 25% (perhaps more in persons with positive TPOAb) will become frankly hypothyroid over a 5-year period.3

Some observational studies link subclinical hypothyroidism with an increased risk of coronary heart disease (CHD), heart failure, and mortality.3 Potential risks may depend on the age of the
patient as well as the relative degree of thyroid failure. In a recent analysis, even persons whose TSH level was on the high side of the normal range had subtle increases in blood pressure and lipid levels.\(^5\) Cardiovascular events and mortality appear to be increased more often in persons aged less than 65 to 70 years with subclinical hypothyroidism.\(^2\) In a nested case-cohort design within the Women’s Health Initiative observational study, subclinical hypothyroidism was not associated with an increased risk of myocardial infarction.\(^7\) In a reanalysis of 11 prospective cohort studies, subclinical hypothyroidism was associated with a twofold increase in CHD events and CHD mortality but only if the TSH level was greater than 10 mIU/L.\(^2\)

Treating a midlife woman with subclinical hypothyroidism is controversial. In the absence of clinical trial evidence of benefit, current recommendations for treatment are largely based on observational studies and expert opinion.\(^2\) In one database, treatment of subclinical hypothyroidism in patients with TSH levels of 5 mIU/L to 10 mIU/L for a median follow-up of 7.6 years was associated with fewer CHD events in younger patients (aged 40-70 y), but not in older ones (>70 y).\(^8\)

In AACE/ATA guidelines, treatment should be considered in patients whose TSH level falls between the upper limit of normal and 10 mIU/L and who have symptoms of hypothyroidism (dry skin, cold sensitivity, fatigue, muscle cramps, voice changes, constipation), positive TPOAb, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors.\(^2\) Treatment is also recommended for patients with TSH levels above 10 mIU/L.\(^2\) Those younger than 65 years might derive greater benefit with less risk than older persons.

Subclinical hypothyroidism does not necessarily require full replacement doses; treatment with 25 µg to 75 µg of thyroxine daily usually suffices\(^2\) and might reduce the likelihood of induced subclinical hyperthyroidism with attendant complications.\(^5\) Therapy should be initiated at 25 µg to 50 µg per day in patients over age 50 to 60 years without CHD and lower doses in those with CHD.\(^2\) Titrate by increasing the dose 12.5 µg to 25 µg at 6 to 8 week intervals. The target TSH should eventually fall within the normal range; monitor every 6 to 12 months.

If your patient starts oral estrogen therapy, measure TSH within 6 to 8 weeks and anticipate that the thyroxine dose may need to increase. Oral (but not transdermal) estrogens increase thyroid-binding globulin, which in turn reduces free thyroxine. Conversely, when oral estrogen therapy is discontinued, TSH should be rechecked in 6 to 8 weeks as the dose may need to be reduced. Raloxifene may interfere with thyroxine absorption and should be administered separately.\(^2\)

**Subclinical hyperthyroidism.** If the TSH level falls below the normal range in the presence of normal thyroid hormone levels (check T3 if free T4 is normal), your patient might meet criteria for the diagnosis of subclinical hyperthyroidism, a condition associated with osteoporosis, fracture, atrial fibrillation, heart failure, and possibly increased CHD events and CHD mortality, especially in older patients.\(^3\) In one study of women aged over 65 years, TSH suppression (≤ 0.1 mIU/L) by either excess endogenous or exogenous thyroid hormone was associated with a threefold increase in hip and a fourfold increase in vertebral fractures. Subclinical hyperthyroidism occurs in less than 2% of the population, with the mild form being more common.\(^3\) Suppressed TSH can also reflect severe nonthyroid illness, as well as changes in the hypothalamic-pituitary set point in some persons of advanced age and African-American race.\(^3\) It is reasonable to monitor an asymptomatic, healthy woman over 3 to 6 months to document persistence of these findings. If the TSH level remains below normal, especially if less than 0.1
mIU/L, with normal thyroid hormone concentrations, the specific thyroid disorder should be
diagnosed. Radionuclide thyroid scanning with $^{123}\text{I}$ or $^{99m}\text{Tc}$ assesses thyroid functional
autonomy consistent with toxic multinodular goiter or Graves disease.

The 2011 ATA/AACE guidelines recommend treatments similar to those for overt
hyperthyroidism if the TSH level is persistently less than 0.1 mIU/L in persons aged 65 years
and older, in postmenopausal women not taking estrogen or bisphosphonates and therefore at
risk of accelerated bone loss, and in persons aged less than 65 years with heart disease,
osteoporosis, or persistent hyperthyroid symptoms. Treatment can also be considered if TSH
values fall between 0.1 mIU/L and 0.4 mIU/L in persons aged over 65 years, and those aged less
than 65 years with heart disease, who are postmenopausal, or who have hyperthyroid symptoms.
Permanent hypothyroidism can result from radioactive iodine therapy.

**Summary**

- **Because current recommendations do not consistently support routine screening of**
  women for thyroid disorders, a high index of suspicion for testing seems prudent.
- **Patience in making the diagnosis is essential as laboratory evidence of subclinical**
  thyroid disorders often reverts to normal over time.
- **Current recommendations for treating subclinical thyroid disorders are largely**
  based on observational studies and expert opinion.
- **When treating subclinical hypothyroidism, avoid overtreating to prevent sequelae of**
  thyroid excess such as atrial fibrillation and osteoporosis.
- **Research is likely to provide more concrete guidelines in the future.**

**References**

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**Disclosures**

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This *Practice Pearl*, developed by the author(s), provides practical information on current controversial topics of clinical interest. It is not an official position of The North American Menopause Society (NAMS). Clinicians must always take into consideration the individual patient along with any new data published since the publication of this statement on October 9, 2014.