

Thyroid Disease in Women

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Seven Questions:

- Should a serum TSH be a routine component of the periodic health exam in women?
- What is the appropriate biochemical endpoint for adequate thyroid hormone replacement in hypothyroid women? What TSH should be targeted? Are there risks associated with over-replacement?
- Are all l-thyroxine products therapeutically equivalent? Should combination T4/T3 preparations be used?
- What is the impact of pregnancy and hormone replacement therapy on thyroxine therapy in hypothyroid women?

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Seven Questions (cont.):

- What is the impact of breast-feeding on the management of maternal hypo and hyperthyroidism?
- Should women with subclinical hypothyroidism be treated with l-thyroxine?
- Should euthyroid women with benign thyroid nodules be placed on thyroid hormone suppression therapy?

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Case 1 – Screening for thyroid disease:

A 46 year old woman comes to your office for her yearly check-up. She has no complaints and physical examination is normal. You discuss appropriate health maintenance issues and are about to send her off to the lab, when she asks if you are going to check her thyroid status. She recently spoke with several of her friends who told her that their doctors said that all women should be "screened" for possible thyroid disease. What do you do now?

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Question 1:

Should a serum TSH be a routine component of the periodic health examination in women?

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Is a serum TSH the best screening test?

Yes!! With the exception of the rare patient with secondary hypothyroidism, a serum TSH is the best screening test for both hyperthyroidism and hypothyroidism.

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Characteristics of a Good Screening Test:

- Disease has significant impact on health
- Disease has a high prevalence in target population
- Treatment in asymptomatic period results in better outcome
- Tests are sensitive and specific
- Tests are acceptable to patients and inexpensive
- Treatment is acceptable, available, and effective

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Prevalence of Hypothyroidism:

- Prevalence will vary with age, gender, diagnostic criteria, etc.
- Significantly more prevalent in women
- Prevalence of subclinical hypothyroidism in elderly women is particularly high--7-17%
- Prevalence of overt hypothyroidism approaches 1% in women, 0.2% in men

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Consensus Statements:

- US Preventive Services Task Force: Does not advocate screening except in newborns
- ATA (JAMA, 2000): Adults should be screened for thyroid dysfunction with a serum TSH beginning at age 35 and every 5 years thereafter
- Expert Panel (JAMA, Jan 04): There is insufficient evidence to support population-based screening. Aggressive case-finding is appropriate in pregnant women, women >60, and others at high risk for thyroid dysfunction.

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Joint Statement of AACE, ATA and Endocrine Society:

Lack of definitive evidence for a benefit does not equate to evidence for lack of benefit. Potential benefits of early detection and treatment of subclinical thyroid dysfunction outweigh the potential side effects that could result from early detection and therapy.... Therefore, we favor screening for subclinical thyroid dysfunction in adults, including pregnant women and those contemplating pregnancy.

Thyroid, January, 2005

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Are there subsets of women who should be screened?:

- Newborns
- Women over the age of 60
- Women with other autoimmune disorders, positive thyroid ab's, or strong FH of thyroid disease
- Women with hypercholesterolemia
- Women with psychiatric disorders
- Women taking lithium, amiodarone, or interferon-alpha

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Are there subsets of women who should be screened?:

- Women with Type 1 diabetes or other autoimmune endocrinopathies
- Women with sleep apnea (?)
- Women with prior history of thyroid disease
- Women planning pregnancy or soon after conception
- Women who have had previous head and neck irradiation

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Case 2 – What is the goal TSH in a hypothyroid patient?

A 46 year old woman presents to your office for follow-up of her longstanding hypothyroidism. She is taking l-thyroxine 125 ug/d, and reports that she is feeling “pretty well”, except for some fatigue and a 5 lb weight gain over the last year. Physical examination is normal. Thyroid studies are as follows:

| | |
|---------|----------------------|
| Free T4 | 1.2 ng/ml (0.8-1.8) |
| TSH | 4.9 uU/ml (0.35-5.5) |

Should you make any changes in her dose of thyroid hormone replacement?

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Question 2:

What biochemical endpoint should be chosen for adequate thyroid hormone replacement? What level of TSH should be targeted? Are there risks associated with “therapeutic” over-replacement?

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Primary hypothyroidism:

The serum TSH concentration is the single best test for assessing the adequacy of thyroid hormone therapy.

Secondary hypothyroidism:

The serum TSH is no longer of any diagnostic value. In these patients the free T4 (or FTI) is the best indicator of the adequacy of thyroid hormone therapy.

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What level of TSH should be targeted?:

- Simple answer: TSH within the normal range for the assay utilized—usually 0.35 – 5.5 uU/mL
- BUT....there is now accumulating body of evidence that the upper limit of normal for most assays is too high and appropriate upper limit should be 2.5 uU/mL.
- This is based on studies that rigorously exclude subjects with even the mildest degrees of thyroid failure

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TSH reference range should be determined from the 95% confidence limits of log-transformed values of at least 120 rigorously screened volunteers who have:

- a. No detectable thyroid antibodies
- b. No personal or family history of thyroid disease
- c. No visible or palpable goiter
- d. No medications (except estrogen)

National Academy of Clinical Biochemistry, 2003

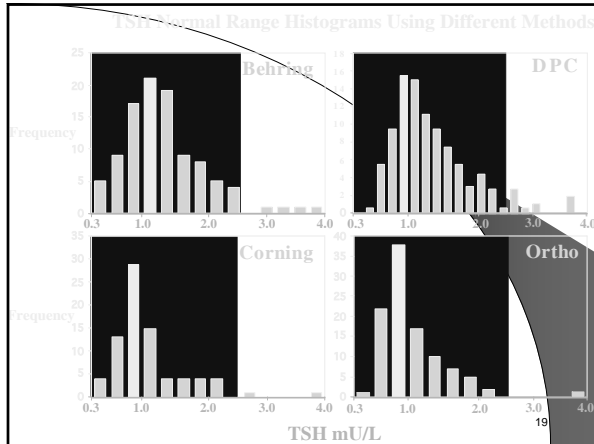
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Application of these criteria to several commercial TSH assays results in:

- a. Mean serum TSH in normals of 1.0 uU/mL
- b. Upper limit of normal of 2.5 uU/mL

Demers & Spencer, 2003

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Conclusion:

“In the future, it is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 uU/mL, because >95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 uU/mL”.

Demers & Spencer, 2003

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NHANES III (3rd National Health and Nutrition Examination Survey) examined TSH values in a “disease-free” subset (n=13344) of an ethnically diverse population >12 years old, excluding pregnant women, patients with positive thyroid antibodies, on no interfering meds, and established a reference range of 0.45 – 4.12 uU/mL (mean = 1.4).

JCEM, 2002

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My opinion:

- The upper limit of normal for the serum TSH concentration is probably between 2.5 and 4.0 uU/mL
- A reasonable target TSH for most patients with primary hypothyroidism is in the 1.0 – 2.5 uU/mL range

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Are there risks associated with “therapeutic” over-replacement?

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Subclinical hyperthyroidism:

A 36 year old woman is being treated for hypothyroidism secondary to Hashimoto’s disease. She is taking 125 ug of l-thyroxine per day, and based on her history and PE is euthyroid. Laboratory studies are as follows:

| | |
|-----|------------|
| T4 | 9.6 ug/dL |
| TU | 32% |
| FTI | 9.9 |
| TSH | 0.03 uU/mL |

You recommend decreasing her dose of T4, but she tells you that every time this has been done by other physicians, she feels extremely fatigued, gains weight, etc., and she insists that you prescribe the same dose of T4. What is the diagnosis and what should you do at this point?

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Risks of Over-Replacement (i.e. Subclinical Hyperthyroidism):

- Osteoporosis
- Heart disease
- Symptomatic hyperthyroidism

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Osteoporosis:

- While some of the published data is contradictory, there is evidence that subclinical hyperthyroidism has adverse effects on bone density, especially cortical bone
- Bone loss appears to be minimal in men and pre-menopausal women, but PMP women appear to be at greatest risk
- Recent study (Bauer et al, 2001) showed an increased fracture risk in women over the age of 65 with suppressed TSH levels

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Vertebral Fracture Risk:

| | <u>Adjusted Odds Ratio</u> |
|----------------------------|----------------------------|
| Normal TSH (0.5-5.5) | 1.0 (reference) |
| Borderline low (>0.1-<0.5) | 2.8 (1.0-8.5) |
| Low (≤ 0.1) | 4.5 (1.3-15.6) |

Bauer et al, 2001

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Heart Disease:

- Increased pulse rate
- Increase left ventricular mass
- Increased risk of atrial fibrillation
- Increased mortality, especially cardiovascular mortality

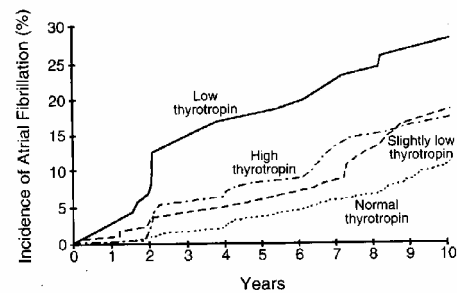
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Risk of Atrial Fibrillation:

Sawin et al, NEJM, 1994

Suppressed TSH levels (<0.1 uU/mL) in otherwise healthy individuals over 60, were associated with a threefold increased risk of atrial fibrillation over 10 year follow-up.

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Sawin et al, NEJM, 1994

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Summary for Question 2:

- Endpoint for thyroid hormone replacement in primary hypothyroidism is serum TSH in 1.0-2.5 uU/mL range
- In patients with “secondary” hypothyroidism, the goal should be a free T4 in the mid to high end of the normal range
- Potential adverse effects of over-replacement are primarily skeletal and cardiac, but there may be an increased mortality rate as well!

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Case 3:

A 52 year old woman returns for follow-up of her longstanding hypothyroidism. She is doing well but has several questions about her thyroid hormone replacement therapy. She has read on the internet that a combination of T4/T3 is superior to T4 alone and wonders whether that would be a good idea for her. In addition, at the time of her last refill of her Levoxy, she was told by her pharmacist that she could save some money by switching to a generic T4 preparation and that the FDA had approved such a switch. What should you tell her? Thyroid studies done one week prior to her visit showed a TSH of 1.2 uU/mL.

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Question 3:

Are all l-thyroxine preparations therapeutically equivalent? Should combination T4/T3 preparations be used?

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Are all levothyroxine preparations therapeutically equivalent?

Appropriate studies comparing all available brand-name and generic preparations have not been performed, so a definitive answer is not available!

All l-thyroxine products must meet the US Pharmacopeia standard of containing 90-110% of stated potency as measured by HPLC.

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Cost Differences:

| <u>Brand</u> | <u>Cost of 100 0.1 mg tabs</u> |
|--------------|--------------------------------|
| Levoxy | \$39.50 – 42.65 |
| Levothroid | 31.75 – 35.20 |
| Synthroid | 46.05 – 60.75 |
| Generic | 16.95 – 21.50 |

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In June, 2004, the FDA approved a policy that commercial l-thyroxine products and generic preparations are interchangeable and can be substituted unless prohibited by prescribing MD (shown by indicating “dispense as written”).

The Endocrine Society, American Thyroid Association, and AACE strongly disagree with this decision, because “l-T4 is a drug with a narrow toxic to therapeutic ratio with significant clinical consequences of excessive or inadequate treatment.”

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My Opinion:

Use a brand name preparation and consistently prescribe that brand for a given patient. Any change in brand requires a follow-up TSH in 8-10 weeks.

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Should combination T4/T3 preparations be used?

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The New England Journal of Medicine

EFFECTS OF THYROXINE AS COMPARED WITH THYROXINE PLUS TRIIODOTHYRONINE IN PATIENTS WITH HYPOTHYROIDISM

ROBERTAS BUNEVIČIUS, M.D., PH.D., GINTAUTAS KAŽANAVIČIUS, M.D., PH.D., RIMAS ŽALINKEVIČIUS, M.D., AND ARTHUR J. PRANGE, JR., M.D.

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Bunevicius et al., 1999:

- Compared effects of T4 alone with T4/T3 combination in 33 patients with hypothyroidism in 5-week prospective RCT. Replaced 50 ug of usual T4 dose with 12.5 ug T3
- Among 17 tests of cognitive performance and mood, 6 were better after treatment with T4/T3
- Among 15 visual analogue tests of mood and physical status, 10 were significantly better with T4/T3
- TSH levels were similar in the 2 treatment groups, but indirect tests of thyroid hormone action (SHBG, pulse rate) were significantly higher in T4/T3 group

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Three Recent Negative Studies:

- Clyde et al. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism. JAMA 2003; 290:2952.
- Walsh et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared with thyroxine alone: a randomized control trial in patients with primary hypothyroidism. JCEM 2003; 88:4543.
- Sawka et al. Does a combination regimen of T4 and T3 improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. JCEM 2003; 88:4551.

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Conclusions from available studies:

There is insufficient evidence at this time to support the routine addition of T3 to T4 replacement in hypothyroid patients. Results of the Bunevicius study have not been confirmed in subsequent RCT's.

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Case 4:

A 28 year old woman with longstanding hypothyroidism on l-thyroxine therapy comes to you to discuss her plans for starting a family some time in the next 6 months. She asks if there will be any problems related to her current treatment with l-thyroxine. What is the appropriate answer to her question?

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Question 4:

What is the potential impact of pregnancy on thyroxine treatment in hypothyroid women?

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A. What are the adverse effects of maternal hypothyroidism?

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Morbidity Associated with Hypothyroidism During Pregnancy:

- Infertility and subfertility
- Spontaneous miscarriages
- Gestational hypertension and preeclampsia
- Premature delivery
- Increased frequency of neonatal ICU admissions
- Increased fetal mortality
- Impaired neuropsychological development

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MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD

JAMES E. HADDOW, M.D., GLENN E. PALOMAKI, B.S., WALTER C. ALLAN, M.D., JOSEPHINE R. WILLIAMS, GEORGE J. KNIGHT, Ph.D., JUNE GAGNON, M.A., CHERYL E. O'HEIR, M.Ed., Ed.S., MARVIN L. MITCHELL, M.D., ROSALIE J. HERMOS, M.P.H., SUSAN E. WAISBREN, Ph.D., JAMES D. FAX, M.D., AND ROBERT Z. KLEIN, M.D.

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Haddow et al. - Summary

- Serum samples from 25,216 pregnant women were obtained
- 62 women with elevated TSH (mean 13.2 uU/mL) were compared with 124 matched normal controls
- 14 of 62 hypothyroid women were treated during pregnancy
- No significant differences between children in terms of birth weight, Apgar scores, gestational age at delivery, etc. All were euthyroid at birth
- 7-9 year old offspring of hypothyroid and control mothers underwent extensive neuropsych testing

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| | Children of Treated Women with Hypothyroidism (N=14) | Children of Untreated Women with Hypothyroidism (N=48) | Control Children (N=124) |
|------------------------------------|--|--|--------------------------|
| Full Scale IQ Score | 111 | 100* | 107 |
| % with IQ \leq 85 | 0 | 19* | 5 |
| Freedom from distractibility score | 103 | 97* | 102 |
| Verbal IQ score | 111 | 101* | 107 |
| Performance IQ score | 109 | 99* | 105 |

*P-value \leq 0.01 for comparison of untreated vs. control children

Unresolved Issue:

Should all women be screened for hypothyroidism prior to or shortly after conception?

B. Does pregnancy affect thyroid hormone replacement dosage in hypothyroid women?

Thyroxine replacement during pregnancy:

- The daily dose of thyroxine to maintain the euthyroid state in pregnancy will increase in 50-70% of women
- Average dose increase ranges from 20-50%
- Increased T4 requirements may be apparent as early as 5-6 weeks of gestation

TABLE 1. PREGNANT WOMEN REQUIRING LEVOTHYROXINE DOSAGE INCREMENTS IN PREGNANCY

| Author | | Pregnancies | | |
|-----------|--------|--------------|---------------------|-------|
| | | Total number | Elevated TSH number | (%) |
| Pekonen | (1984) | 37 | 8 | (27) |
| Mandel | (1990) | 12 | 9 | (75) |
| Tamaki | (1990) | 6 | 3 | (50) |
| Kaplan | (1992) | 42 | 27 | (64) |
| Girling | (1992) | 33 | 7 | (21) |
| McDougal | (1995) | 20 | 20 | (100) |
| Caixas | (1999) | 41 | 19 | (46) |
| Abalovich | (2002) | 95 | 66 | (70) |
| Chopra | (2003) | 13 | 6 | (46) |
| Overall | | 299 | 165 | (55) |

TSH, thyrotropin.

Mean Serum FT₄ and TSH before and during pregnancy (n=25):

| | Before | During |
|-------------------------------|--------|--------|
| T ₄ dose (ug/day) | 112 | 112 |
| Serum FT ₄ (ng/dL) | 1.60 | 0.84 |
| Serum TSH (uU/mL) | 1.44 | 14.1 |

Kaplan, 1992

Recommendations:

- Adjust T4 rx to serum TSH < 2.0 prior to pregnancy
- Check TSH early in pregnancy—by week 5
- Monitor TSH every 6-8 weeks during 1st half of pregnancy; less often in 2nd half of pregnancy
- T4 dose adjustments should be based on trimester-specific TSH normal ranges
- Separate T4 ingestion by at least 4 hours from iron supplements, calcium supplements, and soy milk

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C. What is the impact of estrogen therapy on thyroid hormone requirements in hypothyroid women?

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Conclusions from Arafah study:

Serum TSH concentration should routinely be checked in hypothyroid women on thyroxine replacement 12 weeks after the initiation of estrogen replacement therapy.

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Question 5:

What is the impact of breast-feeding on the management of maternal hypothyroidism and hyperthyroidism?

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Maternal Hypothyroidism (treated):

Are there adverse effects associated with maternal thyroid hormone therapy on either mother or infant during breast-feeding? No!

Does breast-feeding necessitate a change in maternal thyroid hormone dose? No!

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Is breastfeeding contraindicated in a mother taking antithyroid drugs for hyperthyroidism?

While there is good evidence that these drugs are present in breast milk, there is virtually no evidence of any adverse effects on the infant in terms of physical or intellectual development.

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Recommendations re: ATD's and Breast-Feeding:

- Doses of methimazole up to 20 mg/day and PTU up to 450 mg/day appear to be safe
- Mothers should take the ATD just after breast-feeding
- Infant's thyroid function does not need to be monitored
- The possibility of an adverse drug reaction in the infant should be considered

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Case 6 – Subclinical hypothyroidism:

A 36 year old woman presents with a question regarding recent thyroid studies. She saw her ob-gyn 2 weeks ago for routine gyn care, and "screening" labwork showed a TSH of 7.6 uU/ml (0.35-5.5). A subsequent free T4 was in the mid-normal range. She is generally feeling well, but does report occasional fatigue, and a 3-4 lb weight gain in the last 6 months. Examination is unremarkable and she appears clinically euthyroid. She understands that a high TSH indicates hypothyroidism and wants to know if she should be started on a thyroid supplement. What's the diagnosis and should she be treated?

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Question 6:

Should women with subclinical hypothyroidism be treated with l-thyroxine?

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What is subclinical hypothyroidism?:

- Elevated serum TSH concentration and normal serum thyroid hormone levels in an apparently asymptomatic patient
- Prevalence is 5-10% in general population, with women over 60 having a prevalence as high as 15-20%
- Most commonly due to autoimmune thyroid disease

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What are the adverse effects of subclinical hypothyroidism?:

- Neuropsychiatric symptoms
- Abnormal lipids
- Increased risk of atherosclerotic disease

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Neuropsychiatric symptoms:

- Often vague and nonspecific
- Fatigue
- Depression
- Memory loss
- Decreased energy

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Symptoms in Patients with Subclinical Hypothyroidism and Euthyroid Controls:

| | Patients (n=33) | Euthyroid Controls (n=20) |
|--------------------------|--------------------|---------------------------------|
| Muscle cramps | 10 | 3 |
| Dry skin | 18 | 6 |
| Cold intolerance | 13 | 1 |
| Constipation | 5 | 3 |
| Poor energy | 14 | 5 |
| Easy fatiguability | 14 | 4 |
| Total symptoms | 74 | 22 |
| Mean sx's/patient | 2.2 | 1.1 |

Cooper et al, 1984

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Lipid Abnormalities:

- **Elevated total and LDL-cholesterol**
- Decreased HDL levels
- Elevated lipoprotein (a)
- Elevated oxidized LDL levels

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Colorado Thyroid Disease Prevalence Study:

Mean Cholesterol Levels

| | Total* | LDL* |
|----------------------------|--------|------|
| Overt Hypothyroidism | 251 | 170 |
| Subclinical Hypothyroidism | 224 | 146 |
| Euthyroid | 216 | 140 |

*P<0.01 by trend analysis

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Hak et al. Ann Intern Med, Feb, 2000:
Population-based, cross-sectional study of
1149 women, mean age - 69

Adjusted Odds Ratio

| | |
|----------------------------|-----|
| Aortic atherosclerosis | |
| Subclinical hypothyroidism | 1.9 |
| Subclinical hypo + ATA's | 2.2 |
| Myocardial infarction | |
| Subclinical hypothyroidism | 2.3 |
| Subclinical hypo + ATA's | 3.5 |

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Subclinical Hypothyroidism:

So, while many patients appear to be asymptomatic, there may be significant clinical sequelae of subclinical hypothyroidism, but data in the literature is not entirely consistent!

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What is the likelihood of progression to overt hypothyroidism?:

The risk is high, particularly in

1. Older patients (>60)
2. Patients with positive thyroid antibodies
3. Patients with TSH>10
4. Patients with prior history of radioactive iodine treatment or thyroid surgery

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What are the benefits of treatment?:

- Preventing progression to overt hypothyroidism
- Correction of mild lipid abnormalities with potential for decreasing CAD risk
- Relief of subtle signs and symptoms
- Data supporting these “potential” benefits is contradictory

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Treatment of Subclinical Hypothyroidism:

- No studies have demonstrated an adverse effect from correction of subclinical hypothyroidism
- Patients with serum TSH > 10 uU/mL appear to derive the greatest benefits from treatment
- Adverse effects of therapy are only related to overtreatment

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It seems reasonable to recommend therapy for the following patients:

- TSH > 10 uU/ml
- Positive thyroid autoantibodies
- Lipid abnormalities
- Vague symptoms that might be attributable to hypothyroidism
- History of radioactive iodine treatment
- Psychiatric patients, especially those with depression
- Pregnant women

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BUT....

Expert Panel (JAMA, 2004) says:

“Data supporting association of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few. The consequences of subclinical hypothyroidism (TSH 4.5 – 10) are minimal and we recommend against routine treatment of patients with TSH levels in this range.”

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But, again....

Consensus Statement of AACE, ATA, and Endocrine Society (Thyroid, 2005):

“Many patients with persistent serum TSH elevations of any degree will benefit from therapy, and the physician’s judgment, in conjunction with patient input, should be paramount in this decision making process.”

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All women with subclinical hypothyroidism not receiving treatment must be closely monitored for the development of overt hypothyroidism.

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