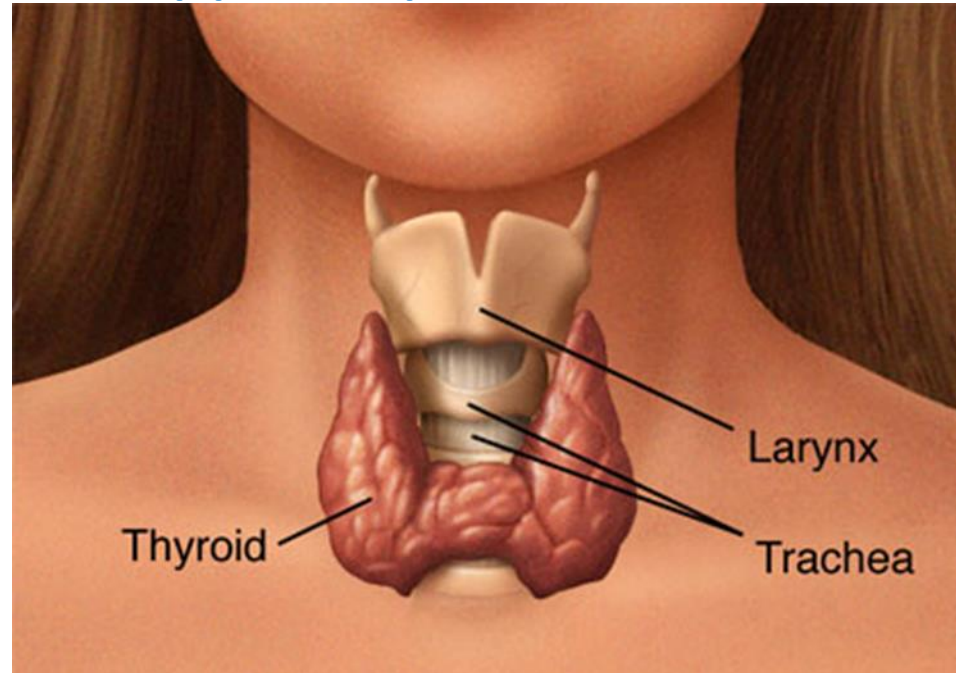


Case Scenario Approach to Thyroid Disorders (Hypothyroidism)



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Scenario-1

A 35 years old Lady came to your clinic with

➤ C/O – Malaise, fatigue, constipation and weight gain

➤ On Examination – puffy face, HR- 52/min

• Provisional diagnosis ??

Clinical Features

Symptoms

- Tiredness, fatigue
- Weight gain
- Cold intolerance
- Constipation
- Dry skin, hair loss
- Muscle pain, joint pain
- Depression
- Menorrhagia

Signs

- Coarse facial feature, periorbital puffiness
- Goiter
- Nonpitting oedema
- Bradycardia
- Pericardial effusion
- Delayed relaxation of ankle reflex
- Dry skin
- Erythema ab igne
- Vitiligo
- Jaundice, pallor



Faces of Clinical Hypothyroidism



Investigation??

- TSH is usually regarded as the most useful investigation of thyroid function
- However, interpretation of TSH values without considering thyroid hormone levels may be misleading in patients with pituitary disease
- Therefore, thyroid hormone level should be done.

RECOMMENDATION

- Apart from pregnancy, assessment of serum free T4 should be done instead of total T4 in the evaluation of hypothyroidism
- thyroid function can be assessed reliably from a single blood sample taken at any time of day and does not usually require any dynamic stimulation or suppression tests

Her Thyroid function test shows...

- Free T4 (9-19) 7.2 pmol/L
- TSH (0.35-4.94) 35.5mU/L

Diagnosis??

Normal range of TSH values?

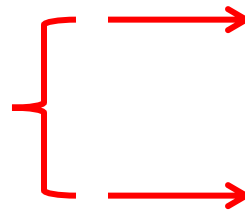
TSH levels may rise with age. If an age based upper limit of normal for a third generation TSH assay is not available in an **iodine sufficient area**, an upper limit of normal of 4.12 should be considered.

Grade A, BEL 1.

Dx – Primary hypothyroidism

Causes of hypothyroid ?

90%



20.10 Causes of hypothyroidism		
Causes	Anti-TPO antibodies ¹	Goitre ²
<u>Autoimmune</u>		
Hashimoto's thyroiditis	++	±
Spontaneous atrophic hypothyroidism	-	-
Graves' disease with TSH receptor-blocking antibodies	+	±
<u>Iatrogenic</u>		
Radioactive iodine ablation	+	±
Thyroidectomy	+	-
Drugs		
Carbimazole, methimazole, propylthiouracil	+	±
Amiodarone	+	±
Lithium	-	±
<u>Transient thyroiditis</u>		
Subacute (de Quervain's) thyroiditis	+	±
Post-partum thyroiditis	+	±
<u>Iodine deficiency</u> , e.g. in mountainous regions	-	++
<u>Congenital</u>		
Dyshormonogenesis	-	++
Thyroid aplasia	-	-
<u>Infiltrative</u>		
Amyloidosis, Riedel's thyroiditis, sarcoidosis etc.	+	++
<u>Secondary hypothyroidism</u>		
TSH deficiency	-	-



20.8 Prevalence of thyroid autoantibodies (%)

	Antibodies to:		
	Thyroid peroxidase ¹	Thyroglobulin	TSH receptor ²
Normal population	8–27	5–20	0
Graves' disease	50–80	50–70	80–95
Autoimmune hypothyroidism	90–100	80–90	10–20
Multinodular goitre	~30–40	~30–40	0
Transient thyroiditis	~30–40	~30–40	0

¹Thyroid peroxidase (TPO) antibodies are the principal component of what was previously measured as thyroid 'microsomal' antibodies.

²TSH receptor antibodies (TRAb) can be agonists (stimulatory, causing Graves' thyrotoxicosis) or antagonists ('blocking', causing hypothyroidism)

Anti-Thyroid Antibodies

❖ Markers of Chronic Thyroiditis

❖ Anti- Thyroglobulin Antibodies

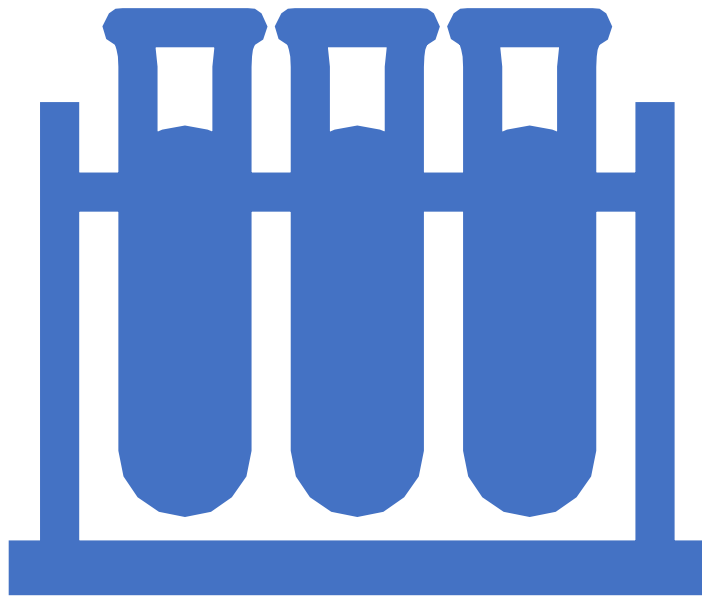
- Does not Correlate with hypothyroidism

❖ Anti-Thyroid Peroxidase Antibodies (formerly known as Anti-microsomal Antibodies)

- Correlate with the development of hypothyroidism

RECOMMENDATION

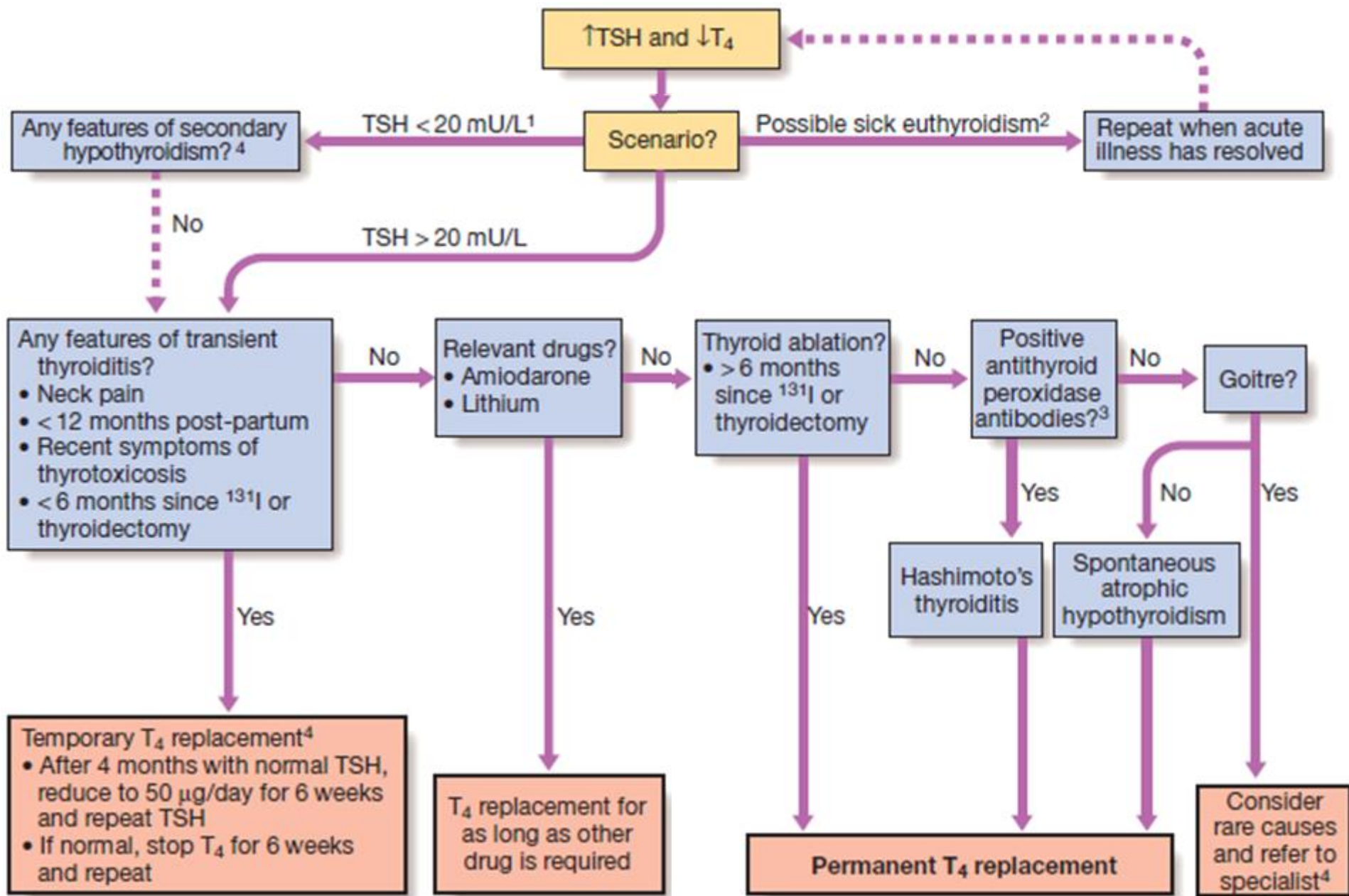
- TPOAb measurement should be considered in order to identify autoimmune thyroiditis when nodular thyroid disease is suspected to be due to autoimmune thyroid disease. **Grade D, BEL 4.**
- Measurement of TSHRAs using a sensitive assay should be considered in hypothyroid pregnant patients with a history of Graves' disease who were treated with radioactive iodine or thyroidectomy prior to pregnancy.



Other additional tests ?

Additional abnormal tests.

- Serum enzymes: raised creatine kinase, aspartate aminotransferase, lactate dehydrogenase (LDH)
- Hypercholesterolaemia
- Anaemia: normochromic normocytic or macrocytic
- Hyponatraemia



Treatment ??

- Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. **Grade B, BEL 1**

Any precaution before thyroid hormone replacement ?

- Treatment with glucocorticoids in patients with combined adrenal insufficiency and hypothyroidism should precede treatment with L-thyroxine. **Grade B, BEL 2**

Which drug ???

LevoThyroxine

- synthetic thyroid hormone (**T4**)

Adv: long half life (7days), once –daily, occasional missing → no harm

- Provide constant physiologic blood level of both T₄ and T₃ with a single daily dose
- Hence the Levothyroxine is the agent of choice

How to prescribe L-Thyroxin

- The mean T4 dose required to normalize serum TSH is:
1.6 microg/kg per day which giving rise to serum free T4 conc; at slightly elevated or upper reference range.
- Daily maintenance dose of T4 varies from 75 to 250 microg
- L Thyroxin is only partly absorbed after oral ingestion, food and minerals, drugs tablet composition influence absorption
- To take empty stomach

How to initiate Thyroxin

- commonly initiated with 50 µg daily
- raised by increments of 25 to 50 µg, according to TSH measurements at six- to eight-week intervals
- Elderly or debilitated, or who have heart disease, lower starting dosages and slower increases are advisable.
- older than 50-60 years with overt hypothyroidism, without evidence of coronary heart disease → an L-thyroxine dose of 50 µg daily
- Can be started at anticipated full replacement doses in individuals who are young and otherwise healthy

What time of the day is the best to take thyroxime ?

- L-thyroxine should be taken with water consistently 30-60 minutes before breakfast or at bedtime 4 hours after the last meal.
- It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption. **Grade B, BEL 2**

What time of the day is the best to take thyroxine ?

- L-thyroxine should be taken with water consistently 30-60 minutes before breakfast or at bedtime 4 hours after the last meal.
- It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption. **Grade B, BEL 2**

Situations in which an adjustment of the dose of levothyroxine may be necessary

Increased dose required

❖ Use of other medication

Increase T4 clearance: phenobarbital, phenytoin, carbamazepine, rifampicin, sertraline*, chloroquine*

Interfere with intestinal T4 absorption: colestyramine, sucralfate, aluminium hydroxide, ferrous sulphate, dietary fibre supplements, calcium carbonate

❖ Pregnancy or oestrogen therapy

Increases concentration of serum thyroxine-binding globulin

❖ After surgical or 131I ablation of Graves' disease

Reduces thyroidal secretion with time

❖ Malabsorption

Situations in which an adjustment of the dose of levothyroxine may be necessary

Decreased dose required

❖ Ageing

- Decreases T4 clearance

❖ Graves' disease developing in patient with long-standing primary hypothyroidism

- Switch from production of blocking to stimulating TSH receptor antibodies

T3 needed routinely?

- Addition of levotriiodothyronine is controversial.
 - ◆ Physiologic argument
 - ◆ Some studies support and some refute

RECOMMENDATION

- The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. **Grade B, BEL 1**

What is the target ?

- **Non-pregnant** → the target range should be the normal range of a third generation TSH assay.
- In iodine-sufficient areas an upper limit of normal of 4.12 mIU/L should be considered and a lower limit of normal 0.45 mIU/L should be considered. **Grade B, BEL 2**
- Central hypothyroidism → assessments of serum free T4 should guide therapy and targeted to exceed the midnormal range value for the assay being used. **Grade B, BEL 3**

How to monitor ?

- Serum TSH measurements done **at 4-8 weeks** after initiating treatment or after a change in dose.
- Once an adequate replacement dose → periodic TSH measurements should be done **after 6 months** and then at **12-month intervals**, or more frequently if the clinical situation dictates otherwise. **Grade B, BE**

RECOMMENDATION

- In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within 4-8 weeks of initiation of treatment with drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose. **Grade A, BEL 1**
- Assessment of serum free T4, in addition to TSH, should be considered when monitoring L-thyroxine therapy. **Grade B, BEL 1**

How to restart thyroxine replacement after incompliance ?

- Patients resuming L-thyroxine therapy after interruption (less than 6 weeks) and without an intercurrent cardiac event or marked weight loss may resume their previously employed full replacement doses. **Grade D, BEL 4**

When to refer to endocrinologist?

- (i) children and infants,
- (ii) patients in whom it is difficult to render and maintain a euthyroid state,
- (iii) pregnancy,
- (iv) women planning conception,
- (v) cardiac disease,
- (vi) presence of goiter, nodule, or other structural changes in the thyroid gland,
- (vii) presence of other endocrine disease such as adrenal and pituitary disorders,
- (viii) unusual constellation of thyroid function test results

Scenario - 2

- 40 year old lady, married, came with fatigue and cold intolerance for 6 months.
- TSH - 3.0 μ IU/ml
- Free T4 - 7.5 pmol/L (11.5-22.7)
- What is diagnosis??
- Dx – Secondary Hypothyroidism

How to replace

- To prevent the exacerbation of adrenal insufficiency
- Treatment with **glucocorticoids** should **precede** treatment with L-thyroxine (if Adrenal plus Thyroid deficiency)

How to monitor

In patients with central hypothyroidism:

- T4 levels are used to guide treatment
- Not TSH
- free T4 level should be kept in the upper third of the reference range

Scenario - 3

- A 69-year-old woman is found to have abnormal thyroid function tests **when screened** by her primary care physician, and she is referred for further evaluation.
- She has a history of dyslipidemia and type 2 diabetes.
- She has no personal or family history of thyroid disease and no history of neck irradiation.

- Her physical examination is generally normal.
- Results of thyroid function tests are as follows:
- free T4-1.3 ng/dl (0.8-1.8) **(Normal)**
- T3- 135 ng/dl (80-180) **(Normal)**
- TSH-8 mU/liter (0.4- 4.0) **(High)**

- **Should this patient need to screen ?**
- **How to interpret the result?**
- **Dx ? ----- DDx ?**
- **How to proceed ?**
- **Need action ? (Why ? When? How ?)**

Recommendations of Six Organizations Regarding Screening of Asymptomatic Adults for Thyroid Dysfunction

Organization	Screening recommendations
American Thyroid Association	<u>Women and men >35 years of age</u> should be screened every 5 years.
American Association of Clinical Endocrinologists	<u>Older patients, especially women</u> , should be screened.
American Academy of Family Physicians	<u>Patients ≥60 years of age</u> should be screened.
American College of Physicians	<u>Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease</u> should be evaluated.
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

Screening for Disorders of Thyroid Function

Population	Testing Frequency
Men	Every 5 years beginning at 35 years of age
Women	Every 5 years beginning at 35 years of age
Pregnant women	As soon as possible after conception; up to 3 months after giving birth
Patients >60 years of age	Once a year

The Endocrine Society Web site. Available at: <http://www.endo-society.org/pubrelations/pressReleases/archives/1999/hypothyroid.cfm>. Accessed April 17, 2003.

Loyola University New Orleans Web site. Available at: <http://www.loyno.edu/~msthomas/hypo.html>. Accessed April 17, 2003.

• Should this patient need to screen ? ✓

• How to interpret the result?

• Dx ? ----- DDx ?

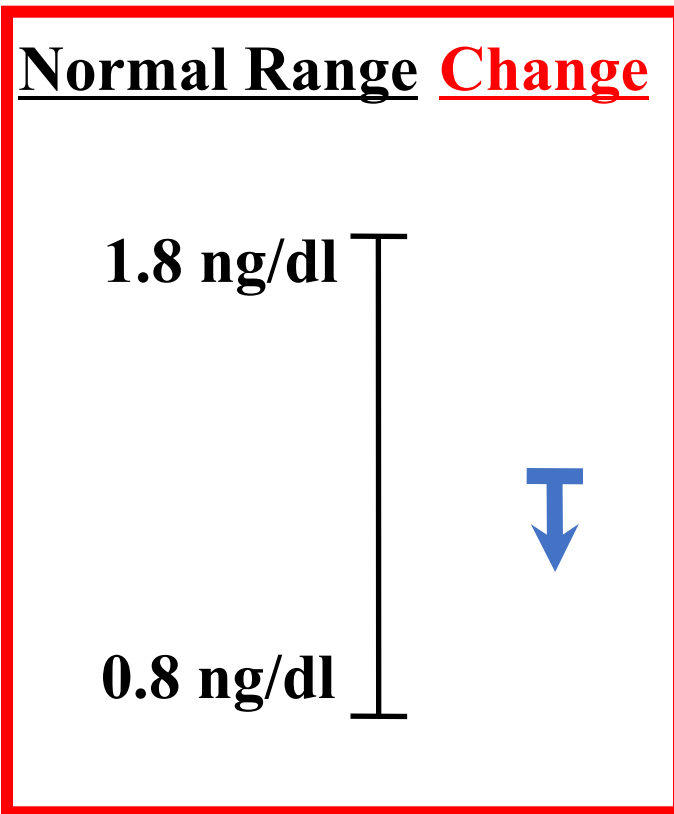
• How to proceed ?

• Need action ? (Why ? When? How ?)

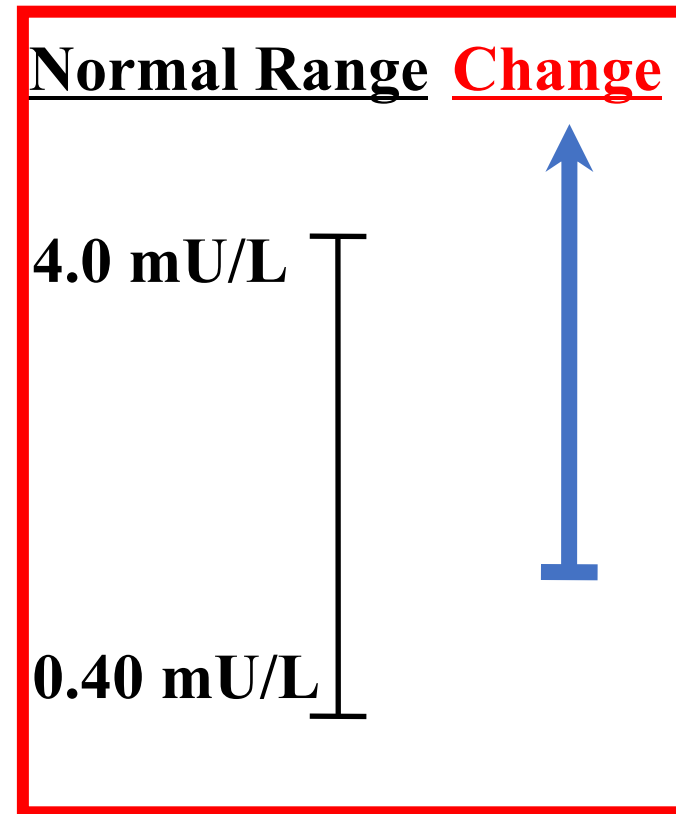
Subclinical Hypothyroidism

Small Decrease in Free T4 = Large Increase in TSH

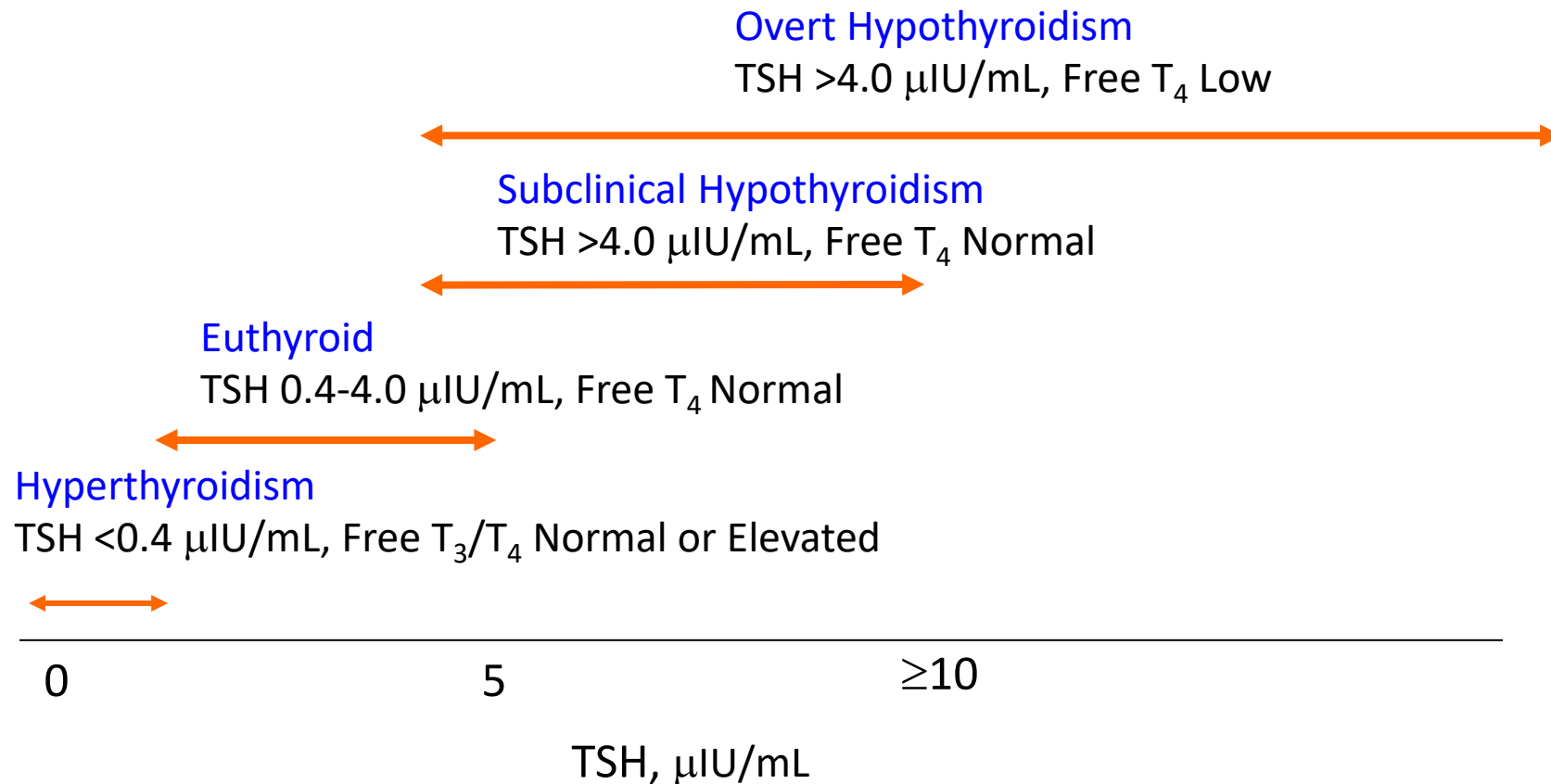
Free T4



TSH



Thyroid Disease Spectrum



Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. 2000.

Canaris GJ, et al. *Arch Intern Med*. 2000;160:526-534.

Vanderpump MP, et al. *Clin Endocrinol (Oxf)*. 1995;43:55-68.

Persistently high TSH ?

Remeasure TSH at 3 months later.

- 2nd time TSH – 8.6 mU/litre (0.4-4.0)
- 2nd time Free T4 – also Normal

Dx ?

Subclinical Hypothyroidism

Definition of Subclinical Hypothyroidism

- An **isolated elevated TSH level** in the setting of normal T₃ and T₄ levels
- Symptoms may be present or absent

Subclinical Hypothyroidism Prevalence

- Worldwide prevalence between 1% and 10%
- Highest rates are in women older than 60 years of age
- Over the age of 74, **16%** of men and **21%** of women have the disorder

DDx of High TSH

TSH an excellent test except some pitfalls

- Central disease
- Abnormal isoforms, TSH receptor polymorphisms
- Drugs (glucocorticoids, dopaminergic drugs [metoclopramide], ?metformin)
- Diurnal Variation
- Heterophilic antibodies--particularly low titer
- Requires steady state: pitfalls in an inpatient population and early phases of pregnancy
- Adrenal Insufficiency (may raise TSH)

Subclinical Hypothyroidism May Be Confused With Other Disorders

- Hyperlipidemia
- Depression
- Gynecological conditions
- Aging

Canaris GJ, et al. *Arch Intern Med*. 2000;160:526-534.

Aldin V, et al. *Am Fam Physician*. 1998;57:776-780.

Nemeroff CB. *J Clin Psychiatry*. 1989;50(suppl):13-20.

Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. 2000.

This patient ---

- Age - 75 years old
- Symptoms (-)
- Elevated TSH (8.6 mU/litre) (0.4-4.0) & Norm T3,T4
- **Dx: Subclinical Hypothyroidism**

- **Should this patient need to screen ?**
- **How to interpret the result?**
- **Dx ? ----- DDx ?**
- **How to proceed ?**
- **Need action ? (Why ? When? How ?)**

When Should **Antithyroid Antibodies** Be Measured?

- **R1. Thyroid peroxidase antibody (TPOAb) measurement should be considered when evaluating patients with subclinical hypothyroidism.**
(Grade B, BEL 1; Downgraded)
- **If positive, hypothyroidism rate of 4.3% versus 2.6% per year.**

20 Year % Probability of Developing Hypothyroidism

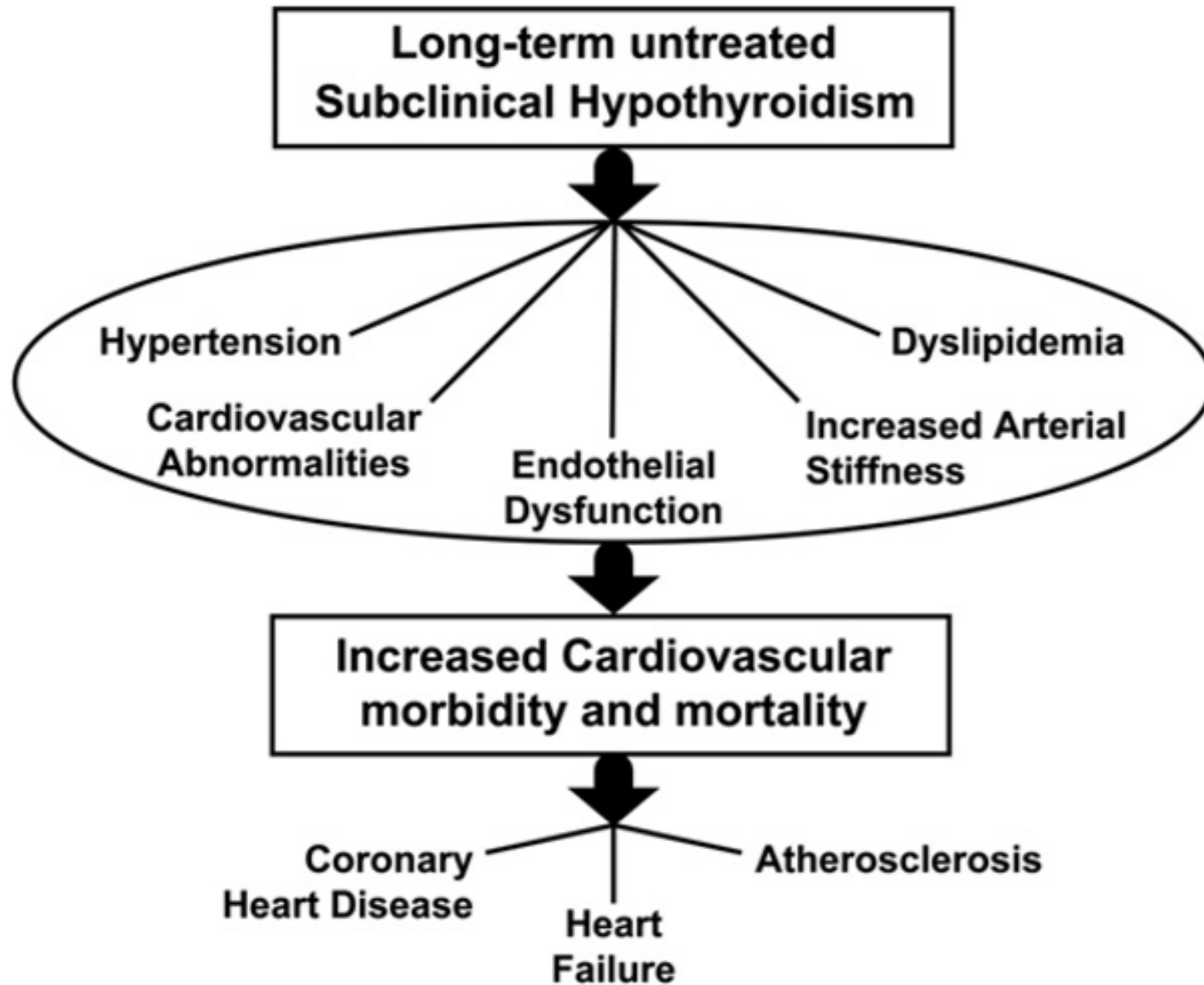
Age (yr)	TSH (mIU/liter)									
	1		2		3		4		5	
	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
20	1	6	1	6	3	13	4	21	7	29
30	1	8	2	8	3	17	6	26	8	35
40	2	10	2	11	4	21	7	32	11	42
50	2	13	3	13	5	25	9	38	14	48
60	3	17	3	17	7	31	12	44	17	55
70	4	21	4	21	9	37	15	51	21	62

TPOAb (+) patients with TSH of between 3-4 mIU/L have < 50% chance developing hypothyroidism over 20 years; if Negative, <20%!

This patient-----

- **Thyroid peroxidase antibody (TPOAb) – (+)**

- **Should this patient need to screen ?**
- **How to interpret the result?**
- **Dx ? ----- DDx ?**
- **How to proceed ?**
- **Need action ? (Why ? When? How ?)**



SUBCLINICAL HYPOTHYROIDISM METANALYSES CVD and Mortality

- Ten studies evaluating Subclinical Hypothyroidism
 - CHD RR 1.2
 - Higher quality studies: LOWER: RR (1.02-1.08)
 - Older than 65 : LOWER: RR (0.98-1.26)
 - Younger than 65 : HIGHER: RR (1.09.-2.09)
- Conclusion: **May increase risk of CVD, particularly in younger than 65**

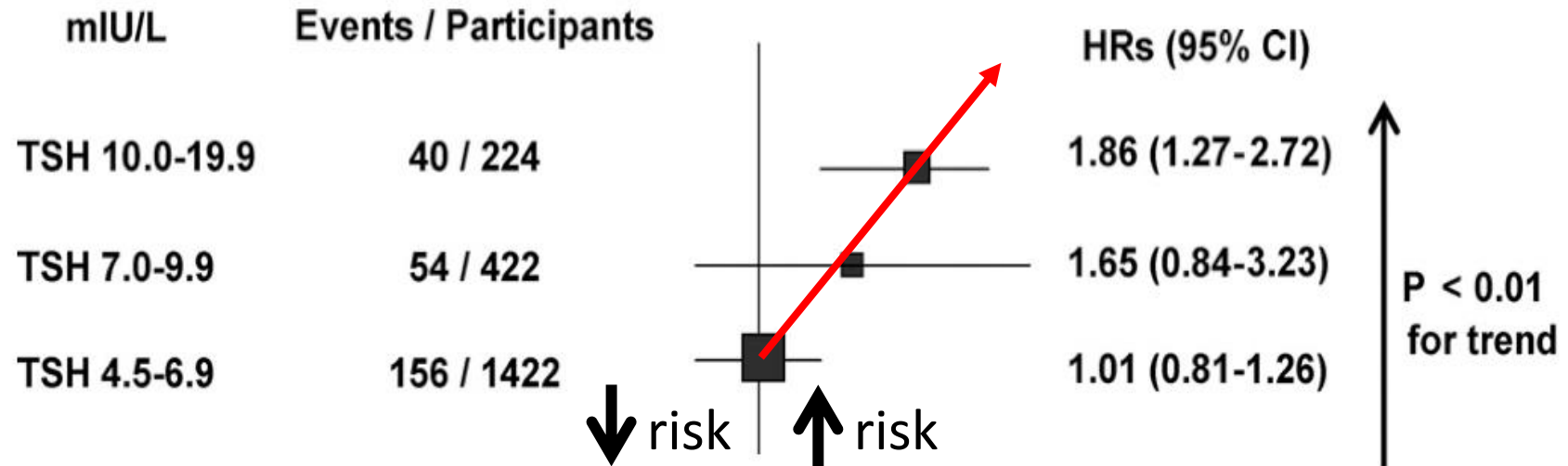
Ochs, AIM, 2008



Best to Date NON RCT--Observational: Benefit of Treatment?

- **UK General Practitioner** : In ~50% of individuals 40-70 yrs old treated with L-thyroxine, (TSH 4.5-10) hazard ratio cardiac events reduced (0.67, CI 0.49 – 0.92) .
- **Cleveland Clinic**: high risk ASCVD Clinic (TSH 6.1-10 and >10) who were under 65 yrs old and not treated with LT4 had higher all-cause mortality

Heart Failure Events by TSH



Until RCTs performed, data favors treating younger, higher TSH values (>10)

Subclinical Hypothyroidism and Cardiovascular Disease

- Cardiac manifestations
 - Left ventricular systolic and diastolic dysfunction
 - Increased systolic time interval
 - Myocardial infarction
- Coronary artery disease
 - Elevated total cholesterol levels, LDL-C levels, and triglyceride levels
 - Aortic atherosclerosis
 - Hyperhomocysteinemia

Biondi B, et al. *Ann Intern Med*. 2002;137:904-914.
Ayala AR, et al. *Cleve Clin J Med*. 2002;69:313-320.
Aldin V, et al. *Am Fam Physician*. 1998;57:776-780.

- **Should this patient need to screen ?**
- **How to interpret the result?**
- **Dx ? ----- DDx ?**
- **How to proceed ?**
- **Need action ? (Why ? When? How ?)**

Treatment of TSH > 10mIU/L

R15.

- **serum TSH levels exceed 10 mIU/L** are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.

Grade B.,BEL 1

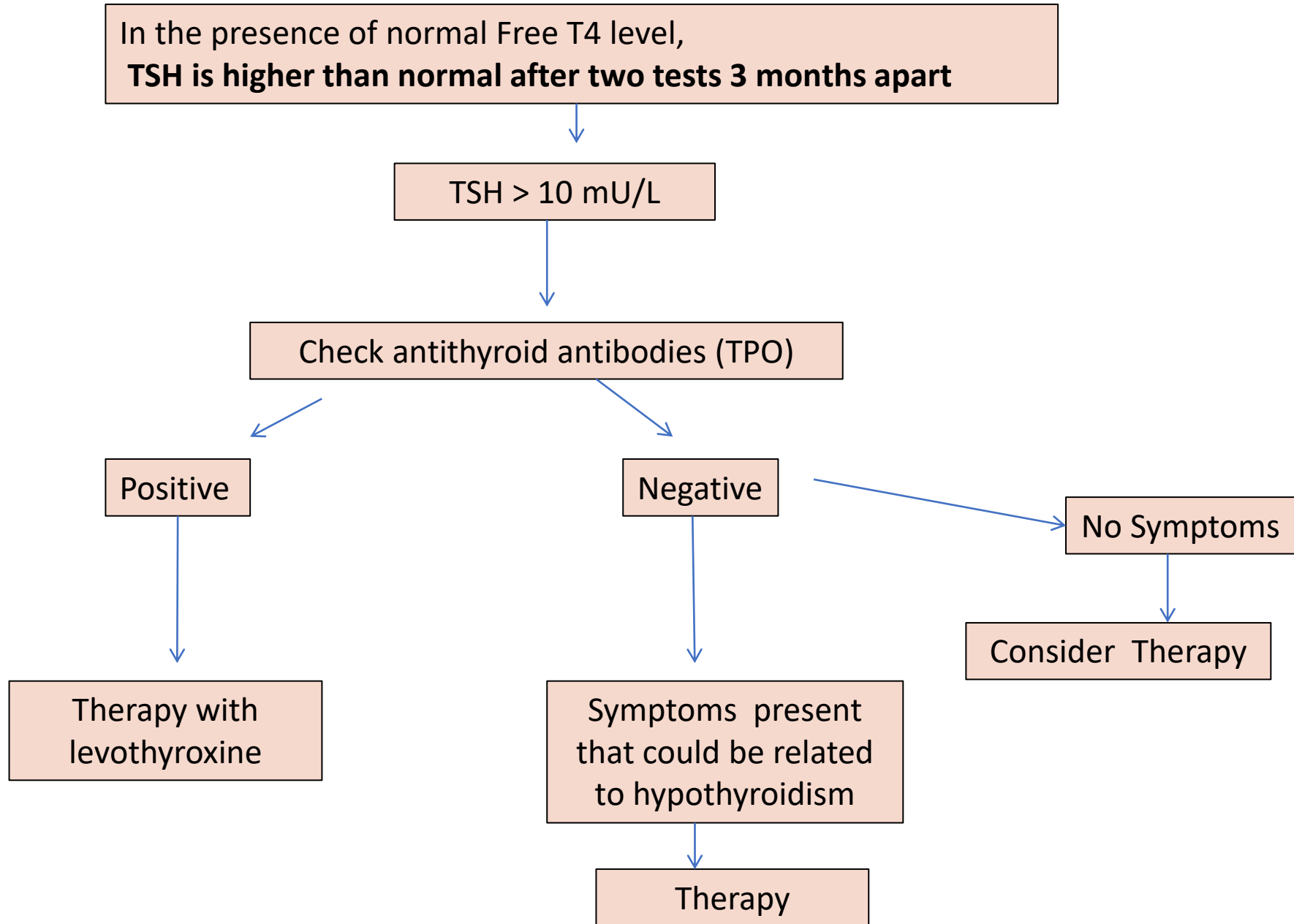
Treatment of TSH between 5 and 10?

Treatment should be considered particularly

- if they have **symptoms** suggestive of hypothyroidism,
- positive **TPO antibodies** or
- evidence of **atherosclerotic cardiovascular disease**,
- **heart failure** or have associated risk factors for these diseases.

Grade B, BEL 1; evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.

Vanderpump MP et al. 1995 Clin Endo 43:55-68 (EL2). Vanderpump MP & Tunbridge WM 2002 Thyroid 12:839-47 (EL4). Hollowell JG et al. 2002 JCEM 87:489-99 (EL1). Huber G et al. 2002 JCEM 87:3221-26 (EL2). McQuade C et al. 2011 Thyroid 21:837-43 (EL3). Ochs N et al. 2008 Ann IM 148:832-45 (EL1).



In the presence of normal T4 level,
TSH is higher than normal after two tests 3 months apart

TSH between 5-10 mU/L

Antibodies positive or
symptoms(+)

Consider Therapy

Antibodies negative or
Symptoms (-)

Observe and retest every 6
months

- **Should this patient need to screen ?**
- **How to interpret the result?**
- **Dx ? ----- DDx ?**
- **How to proceed ?**
- **Need action ? (Why ? When? How ?)**

This patient---

- 69 years old lady
 - Asymptomatic
 - TSH – between 5-10
 - TPO Ab (+)
-
- Consider Therapy

Initiating treatment in subclinical hypothyroidism

Recommendation 22.8:

In patients with **subclinical hypothyroidism**

- initial L-thyroxine **dosing is generally lower than** what is required in the treatment of overt hypothyroidism.
- A daily dose of **25 to 75 mcg** should be considered, depending on degree of TSH elevation.
- guided by clinical response and TSH values

Rationale for Treating Subclinical Hypothyroidism

Potential benefits from treatment

- Prevent progression to overt hypothyroidism
- Improve serum lipid profile, which may reduce the risk of death from cardiovascular causes
- Reduce symptoms, including psychiatric and cognitive abnormalities

Case scenario: 4

- A 35 years old lady, G2P0+1, 10th weeks gestation, TFT is checked due to bad obstetric history:

	Result	Reference
Free T4 (pmol/L)	16	(10-20)
TSH (mU/L)	2.8	(0.4-4.0)

This reference range is not trimester specific.

Normal TFT ?

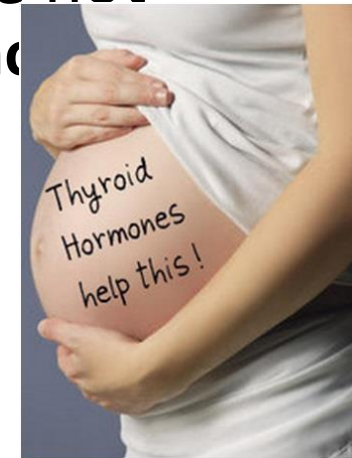
Pregnancy

- ***What should be considered the upper limit of the normal range of TSH values?***

In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory.

If trimester-specific reference ranges for TSH are not available in the laboratory, the following **upper normal reference ranges** are recommended:

- 1st trimester- 2.5 mIU/L**
- second trimester- 3.0 mIU/L**
- third trimester- 3.5 mIU/L**



Indications for targeted thyroid disease case finding in pregnancy

- Women with a history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy
- Women with a family history of thyroid disease
- Women with a goiter
- Women with thyroid antibodies (when known)
- Women with symptoms or clinical signs suggestive of thyroid underfunction

- Women with type I diabetes
- Women with other autoimmune disorders
- Women with infertility should have screening with TSH as part of their infertility work-up
- Women with prior therapeutic head or neck irradiation
- Women with a prior history of preterm delivery

ATA 2017

RECOMMENDATION 28

- Pregnant women with TSH concentrations **>2.5mU/L** should be evaluated for **TPOAb status**.

- Patient - TPO Ab (+)
- What should we do? Need treatment??

RECOMMENDATION 29

Subclinical hypothyroidism in pregnancy should be approached as follows:

LT4 therapy is recommended for

- TPOAb-positive women with a TSH greater than the pregnancy-specific reference range
(Strong recommendation, moderate-quality evidence)

- TPOAb-negative women with a TSH greater than 10.0 mU/L.
(Strong recommendation, low-quality evidence)

LT4 therapy is not recommended for

- TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range
or
- TSH <4.0 mU/L if unavailable

(Strong recommendation, high-quality evidence)

- G2P0+1
- 10th week gestation (1st trimester)
- Normal FreeT4
- TSH > 2.8 mU/L
(upper limit normal in 1st trimester- 2.5 mU/L)
- Subclinical hypothyroidism
- TPO Ab (+)

Treatment with Levothyroxine

Target TSH = Trimester specific range

ATA THYROID AND PREGNANCY GUIDELINES

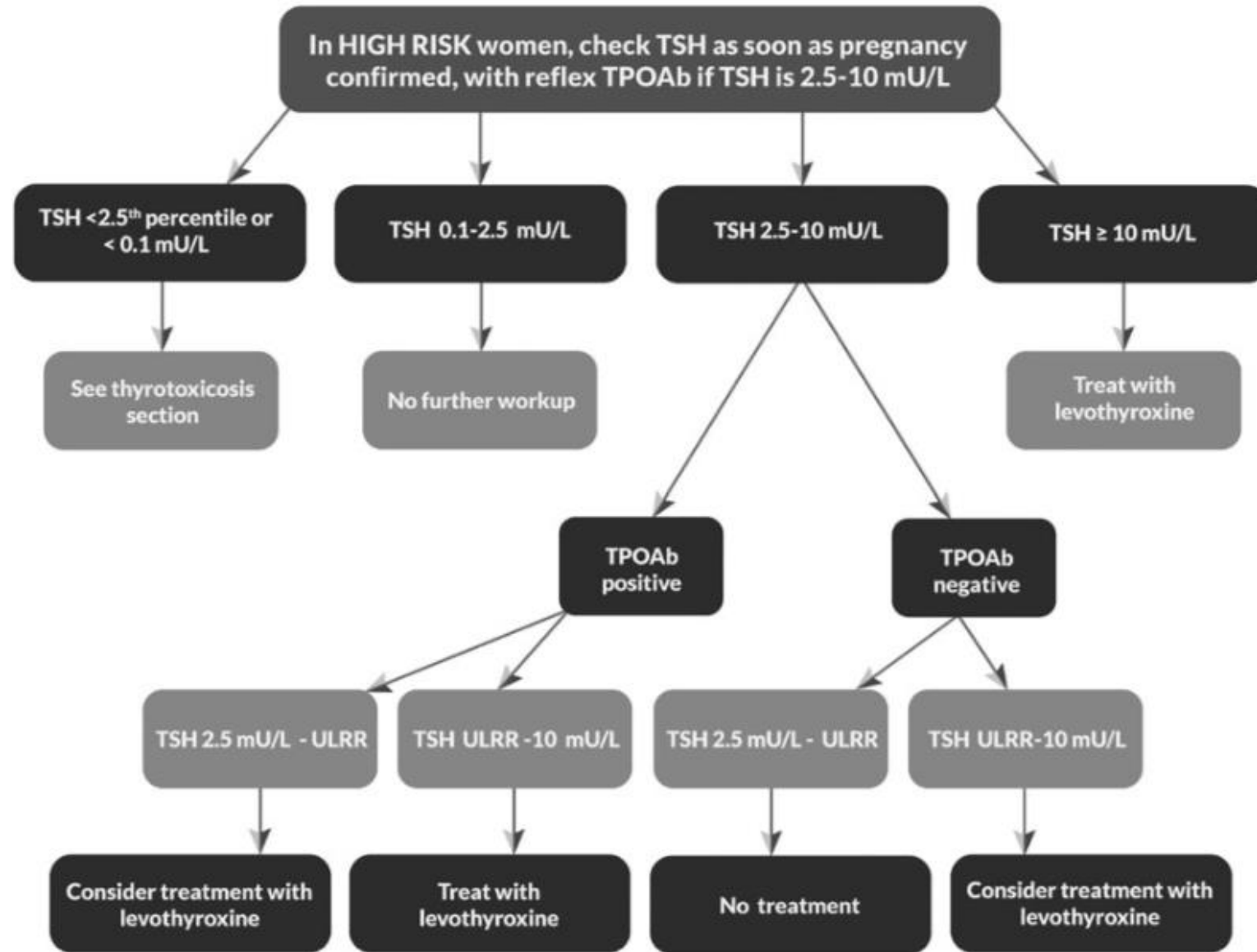


FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.

TSH values should be checked

- every 4–6 weeks during the first trimester
- once during the second and third trimesters

Target

- levothyroxine dose should be adjusted as necessary to reduce TSH to <2.5 mU/l or within the trimester-specific reference range.

Previous Hypothyroidism

- Following delivery the levothyroxine dose should be reduced to the preconception dose

Women diagnosed with SCH during pregnancy

- **TSH less than 5 mU/l and negative TPOAb could stop levothyroxine after delivery** and have thyroid function checked 6 weeks after delivery.
- should be re-evaluated 6 months and 1 year after delivery to ascertain the continuing requirement for levothyroxine

Take Home Messages

1. Serum total T3 or free T3 measurement should not be done to diagnose hypothyroidism.
2. Interpretation of TSH values without considering thyroid hormone levels may be misleading in patients with pituitary disease
3. There are limitations of TSH measurements during acute illness.
4. Treatment with glucocorticoids in patients with adrenal insufficiency should precede treatment with L-thyroxine.
5. During pregnancy, LT4 requirement is increased in previous overt hypothyroidism.
6. In patient with SCH during pregnancy, treatment depends on TSH level and TPO Ab status.

References

- Clinical practice guidelines for hypothyroidism in adults: AACE/ATA 2012
- 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum
- Bernadette Biondi and David S. Cooper (2008) The Clinical Significance of Subclinical Thyroid Dysfunction. *Endocrine Reviews*, 29(1):76–131
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THANK YOU

