

Evidence-Based Hypothyroidism

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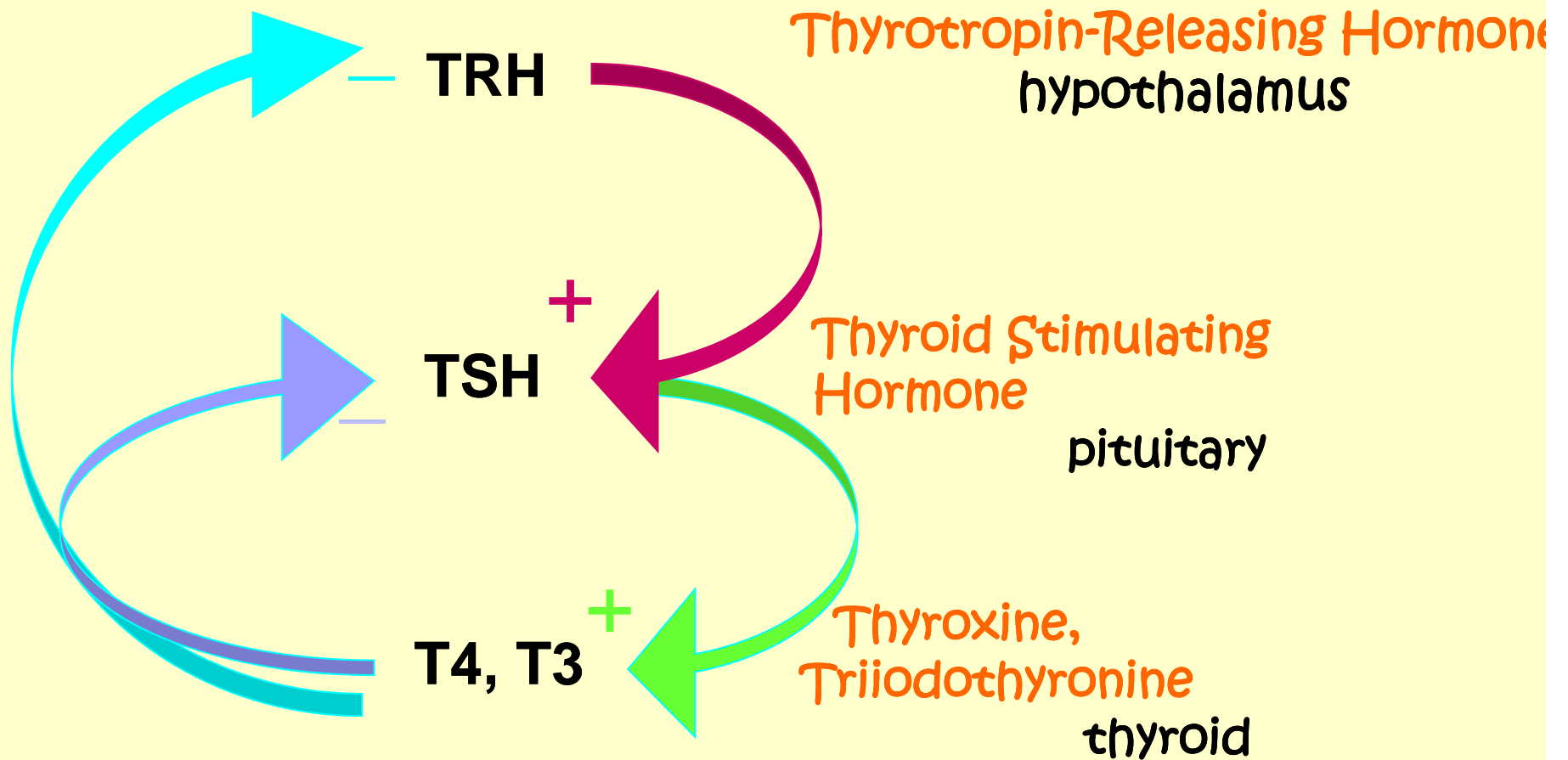
Outline

- Published guidelines from various expert sources
- Thyroid physiology review
- Diagnosis of Hypothyroidism
- Treatment of Hypothyroidism
 - Differences in thyroid hormone preparations
- Considerations in special populations
 - Hypothyroidism in Pregnancy (maternal and fetal)

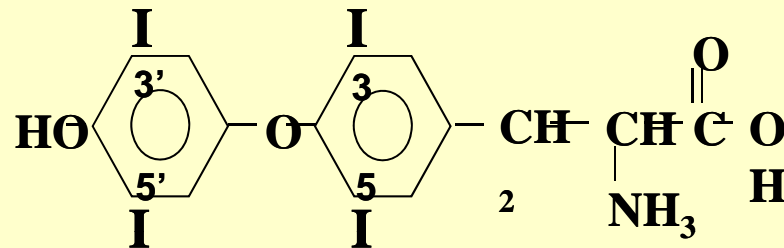
Published Guidelines

- American Association of Clinical Endocrinologists Guidelines
 - Endocrine Practice Vol 8 No. 6 November/December 2002
- *American Thyroid Association (ATA) Guidelines*
 - *JAMA*. 1995;273:808-812)
 - Archives of Internal Medicine 2000; 160:1573-1575
- Endocrine Society Guidelines
 - Pregnancy: JCEM August, 2007; Supplement S1-S47
- National academy of Clinical Biochemists.
- American Academy of Family Physicians
- USPSTF (US preventive services task force)
- American Academy of Neurology
- American Academy of Pediatrics

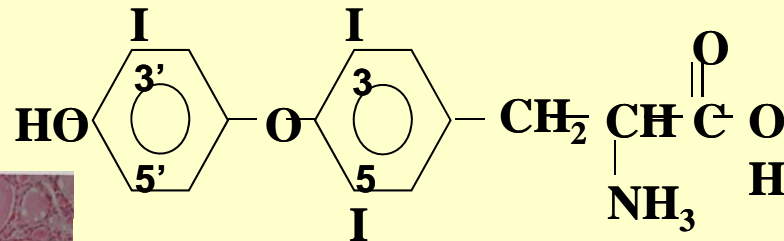
Thyroid Feedback Loops



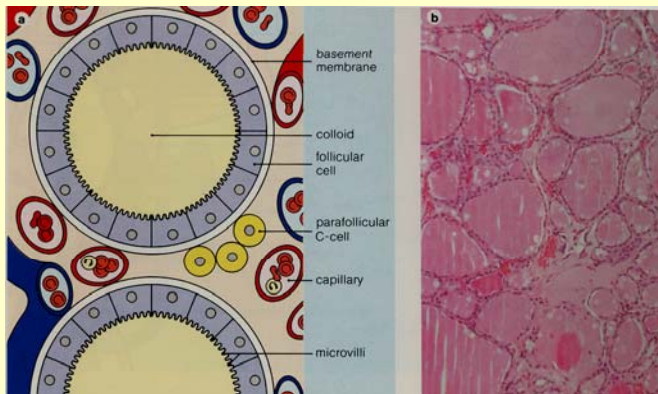
Hormone Products of the Thyroid

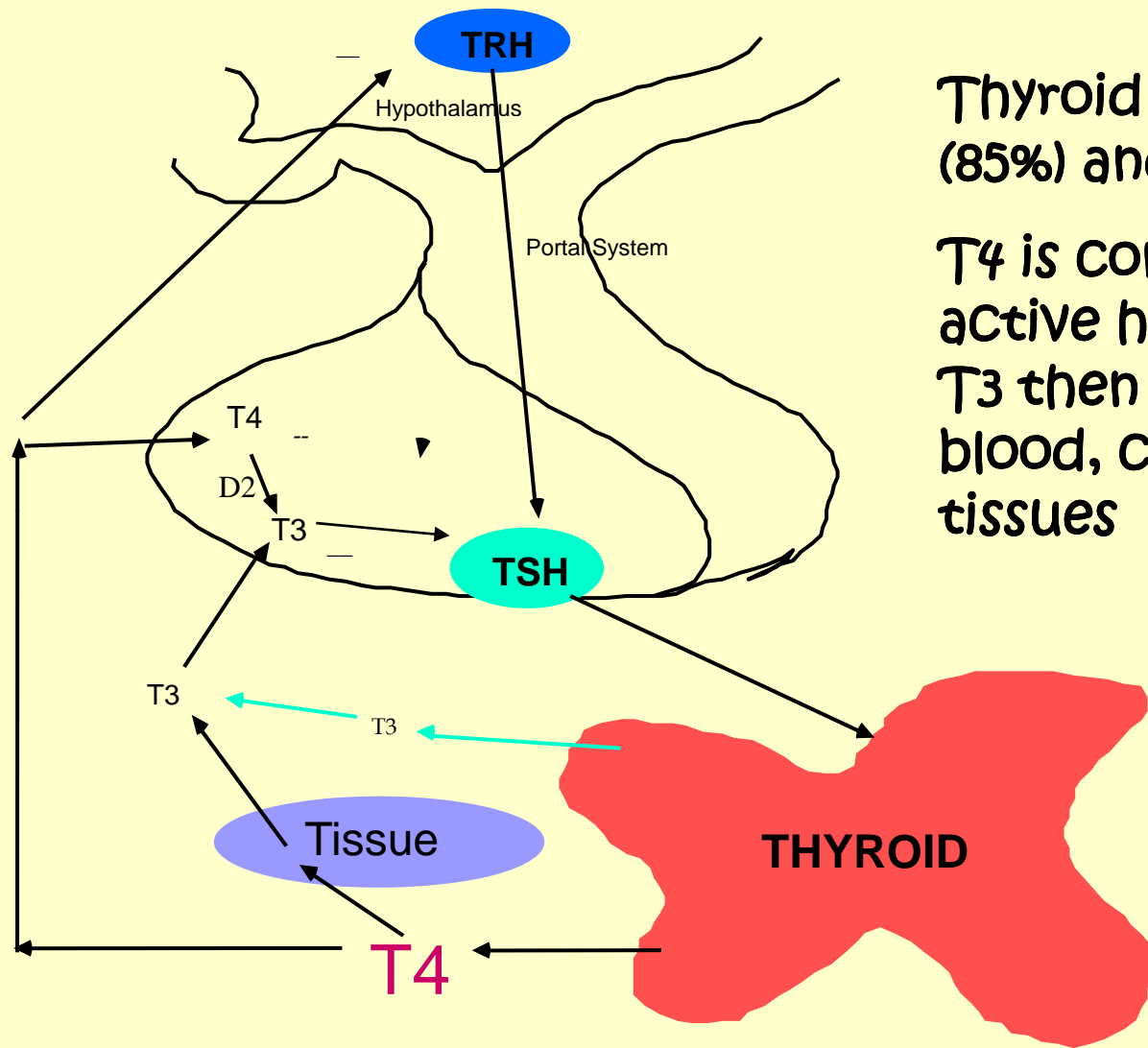


Thyroxine (T₄)



3,5,3'-Triiodothyronine (T₃)

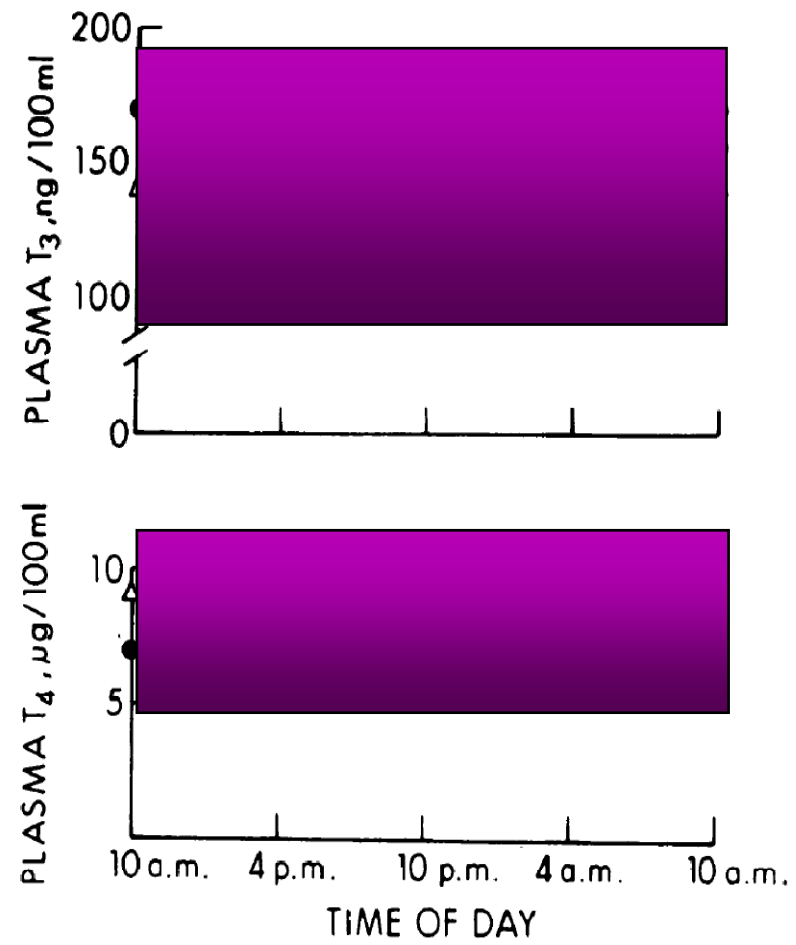




Thyroid gland secretes T4 (85%) and T3 (15%).

T4 is converted to T3, the active hormone in tissues. T3 then released into blood, carried to other tissues

T4 and T3 levels part of feedback loops to regulate the hypothalamus and pituitary



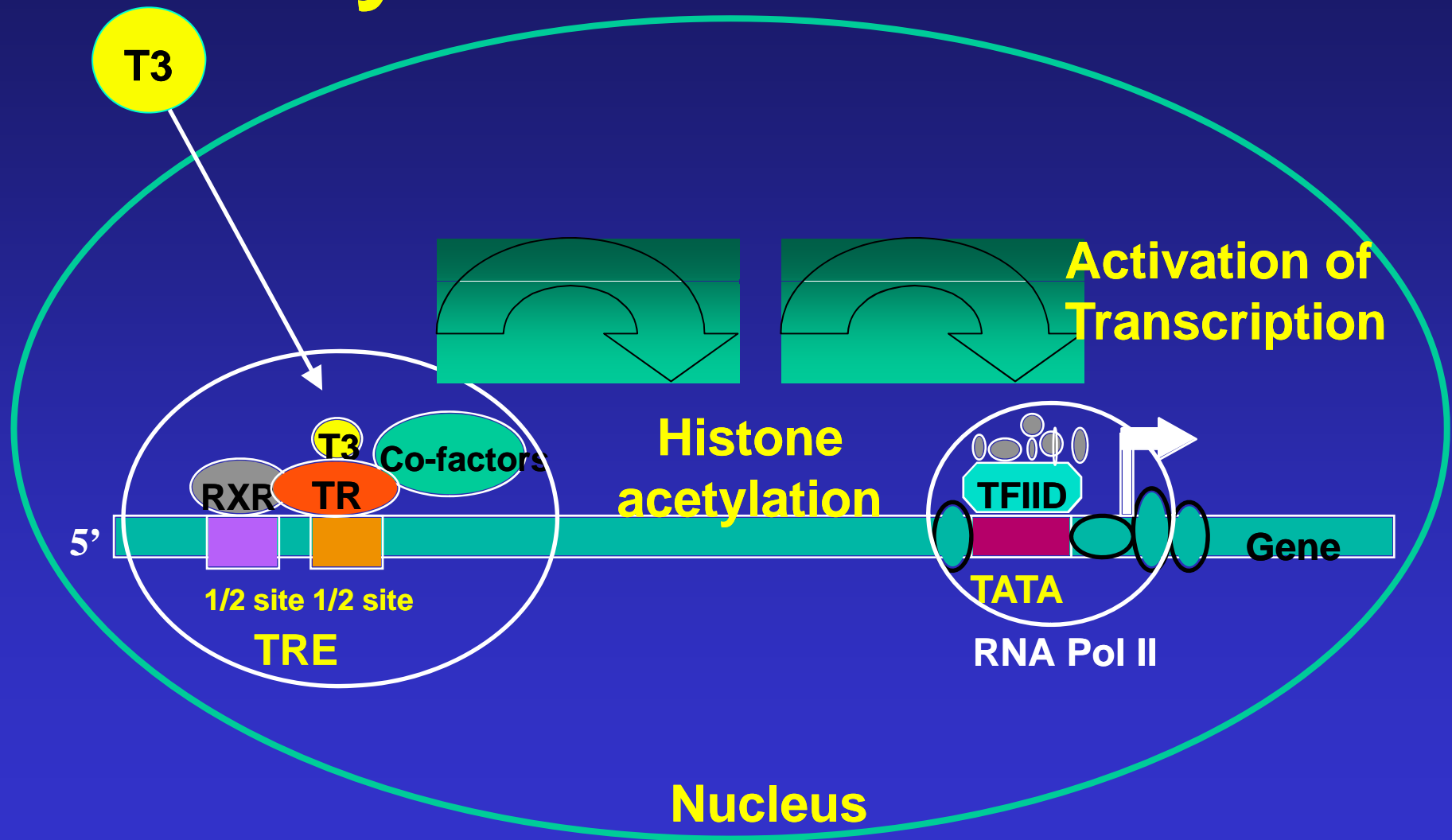
Euthyroid, Thyroid intact

Thyroid hormone transport

Binding Protein	T4	T3
Thyroxine binding globulin (TBG)	70%	70%
Transthyretin (TTR)	20%	0%
Albumin	~10%	~30%
Lipoproteins	~3%	~6%

	T4	T3
Mean total concentration (µg/dL)	8	0.14
Mean free concentration (ng/dl)	1.6	0.4
% Free Fraction	0.02%	0.3%
T 1/2 (days)	7	1
Volume of distribution	10 L	30 L
Potency	0.3	1

Thyroid Hormone Action



Functions of T3

- Increases oxygen consumption
- Increases metabolic rate
- Increases heat production
- Increases protein fat, and cholesterol synthesis and degradation
- Increases drug and anesthesia metabolism
- Increases tone of sympathetic nervous system
- Essential for normal brain development in infancy

Causes of Hypothyroidism

Primary

Iodine deficiency or excess

Autoimmune

Chronic lymphocytic thyroiditis or Hashimoto's thyroiditis

Silent thyroiditis / Post partum thyroiditis

Other Thyroiditis

Radioactive iodine or surgery

Anti-thyroid drugs

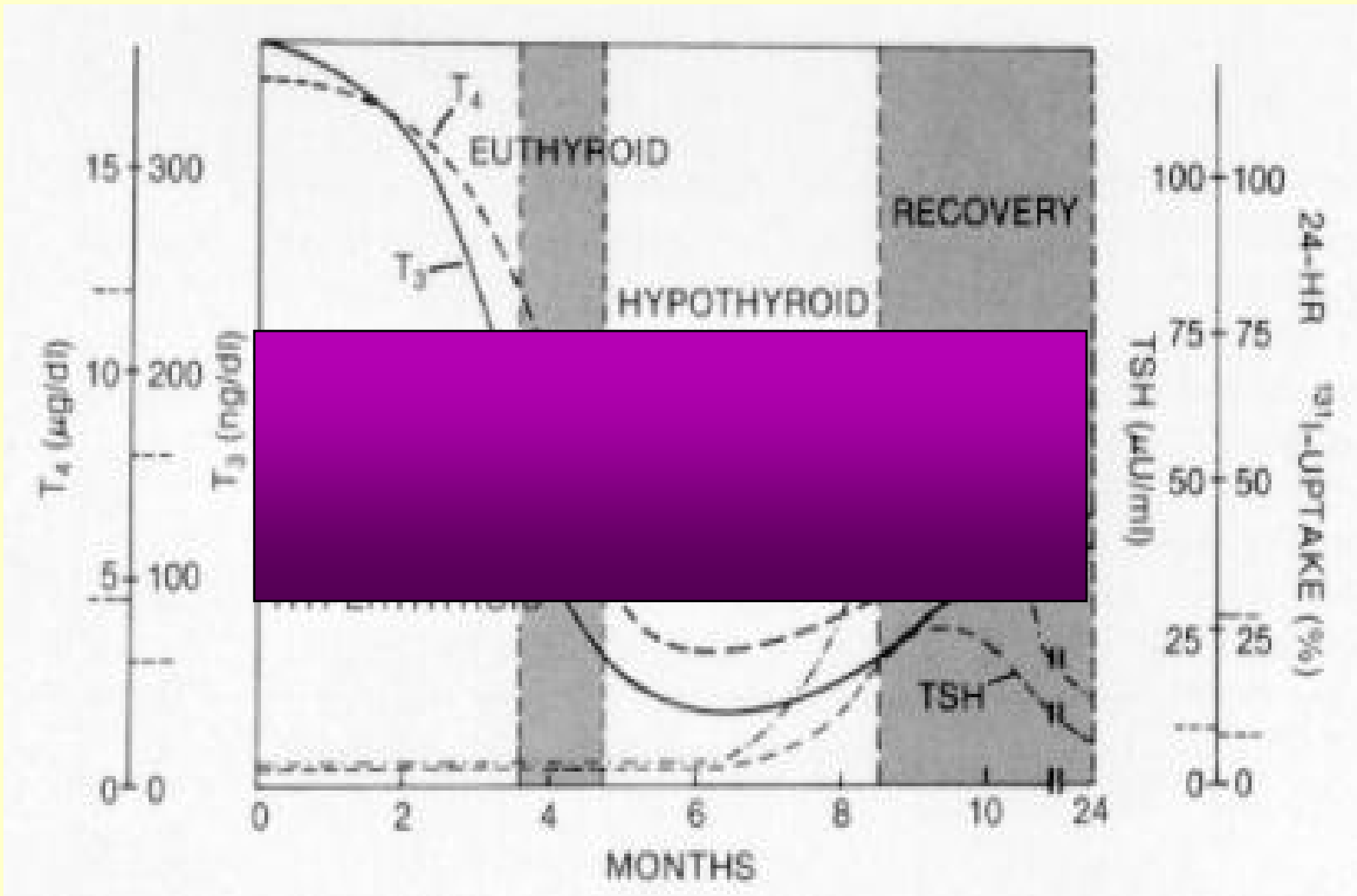
Congenital absence thyroid, dysmorphogenesis

other drugs drugs – iodine excess, amiodarone, interferon, lithium

Secondary

pituitary or hypothalamus damage

Thyroiditis





Signs & Symptoms of Hypothyroidism are Nonspecific

General fatigue, lethargy, low energy, sleepiness, weight gain, cold intolerance

Skin dry, coarse, hair changes, cool to the touch

HEENT goiter, periorbital swelling or edema, hoarse voice

Heart ↓ heart rate and contractility, diastolic dysfunction

Vascular vasoconstriction, hypertension

GI ↓ motility, constipation

Reproductive ↓ fertility, menorrhagia, miscarriage

Musculoskeletal arthralgia, cramping, weakness

Neuro-psych depression, mental impairment, slow reflex relaxation, slowed mentation

Growth delayed bone age, short stature

*ATA guideline history

DIAGNOSIS OF THYROID DISEASE

- “Physicians must consider and exclude thyroid dysfunction much more often than they will establish a diagnosis.
- If only patients presenting with clear suggestive symptoms and signs are evaluated, many affected individuals will remain undiagnosed.”

Should we screen for thyroid dysfunction?

- **Insufficient evidence to recommend for or against screening** (AAFP and USPSTF)

<http://www.ahrq.gov/clinic/uspstf/uspsthyr.htm>

http://www.guideline.gov/summary/summary.aspx?doc_id=11830&nbr=006077&string=thyroid

- **Yes, in selected populations**

- **Neonates** (AAFP, USPSTF, American Academy of Pediatrics, ATA)

http://www.guideline.gov/summary/summary.aspx?doc_id=11830&nbr=006077&string=thyroid

<http://www.ahrq.gov/clinic/uspstf08/conhypr/Conhyprs.pdf>

- **Initial evaluation of elderly dementia patients** (American Academy of Neurology, ATA)

http://www.guideline.gov/summary/summary.aspx?doc_id=2817&nbr=002043&string=thyroid

- **unexplained depression, cognitive dysfunction** (ATA)
- **women past 60 years** (ATA, 1995)
- **At age 35 and then every 5 years** thereafter (ATA, 2000)
- **prior history of any medically or surgically treated thyroid disease** should be screened yearly (ATA)
- **Patients with other autoimmune diseases** (ATA)
- **Hypercholesterolemia** (ATA)
- **Before pregnancy or during 1st trimester** for all women (ACE)

JAMA. 1995;273:808-812

Arch Intern Med 2000;160:1573-1575.

Ann Intern Med 2004 Jan 20;140(2):125-7.

Pediatrics. 2006 June 2006;117(6):2290-303

Endocrine Practice Vol 8 No. 6 November/December 2002

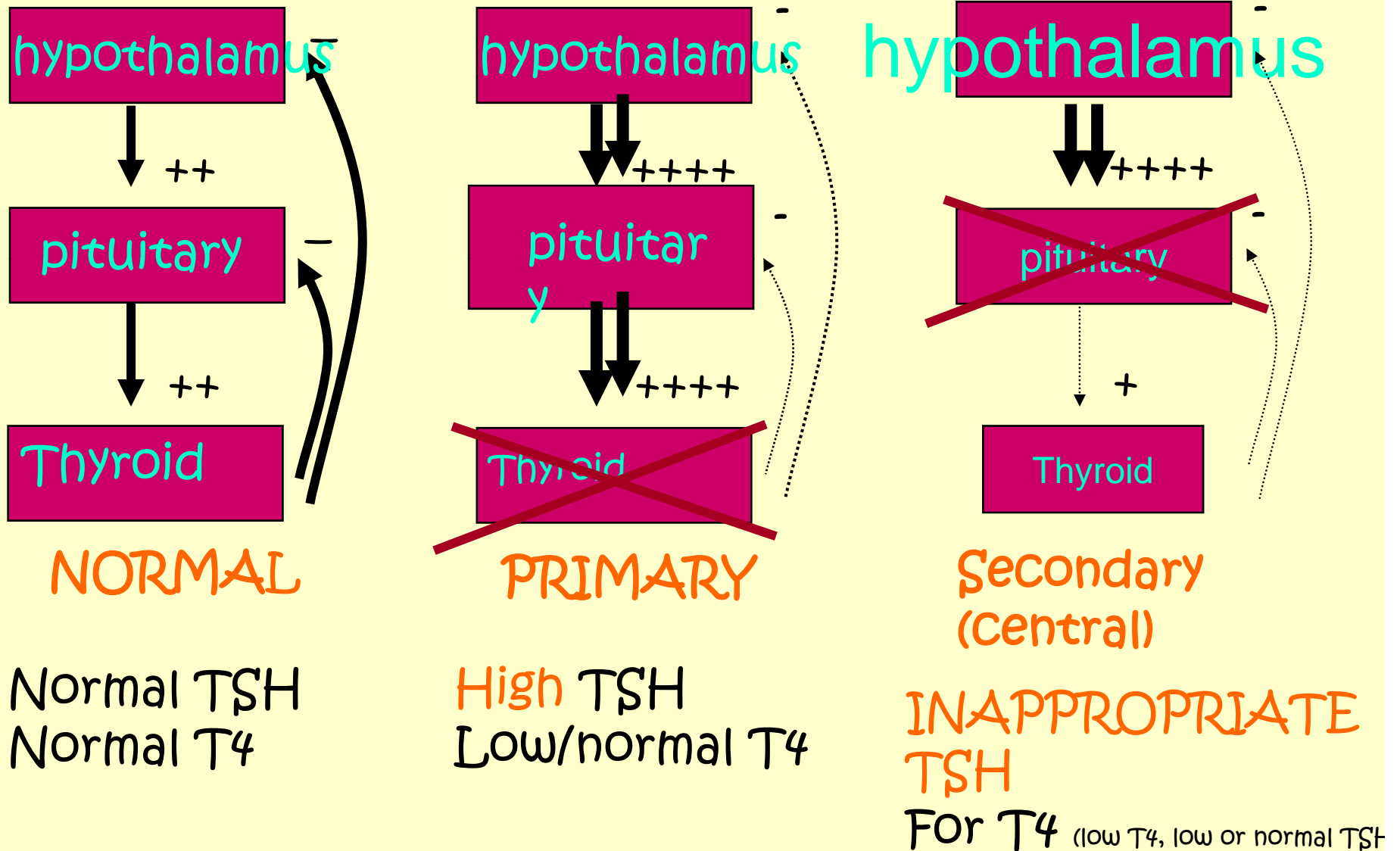
Associations with Hypothyroidism

- Previous thyroid dysfunction, previous PPTD
- Previous surgery or radiotherapy affecting the thyroid
- Personal or family history of autoimmune diseases
Diabetes mellitus, vitiligo, pernicious anemia, Addison's disease, leukotrichia, celiac sprue, SLE, alopecia areata, MS
- Down syndrome, Turner syndrome
- Abnormal labs (anemia, hyponatremia, increased CPK, LDH, hyperprolactinemia, hyperhomocysteinemia, hypercholesterolemia)
- Drugs :iodine containing (amiodarone, radiocontrast, kelp, expectorants containing KI) lithium, interferon, dopamine, sunitinib, sorafenib, thalidomide)

ATA Guideline

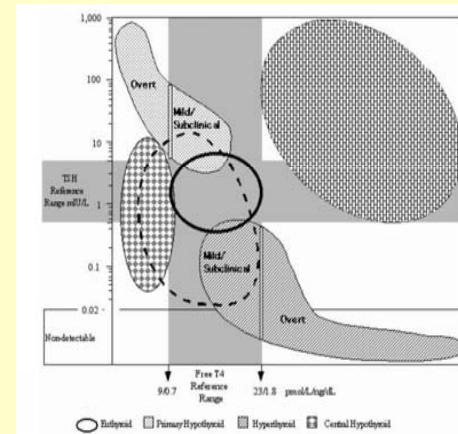
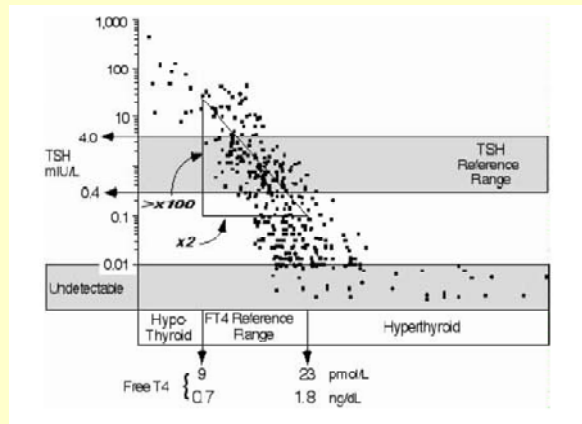
- To establish the diagnosis of hypothyroidism:
 - serum TSH measurement
 - free T4 estimate (or direct measurement)
- helpful to confirm antithyroid antibody titers, either antimicrosomal antibody (thyroid peroxidase antibody) or antithyroglobulin antibody

LAB DIAGNOSIS OF HYPOTHYROIDISM



ATA Guideline

- thyroid function tests obtained from ill hospitalized patients must be interpreted with caution, since serum T4 and/or TSH levels may suggest hypothyroidism



- **OVERT hypothyroidism**

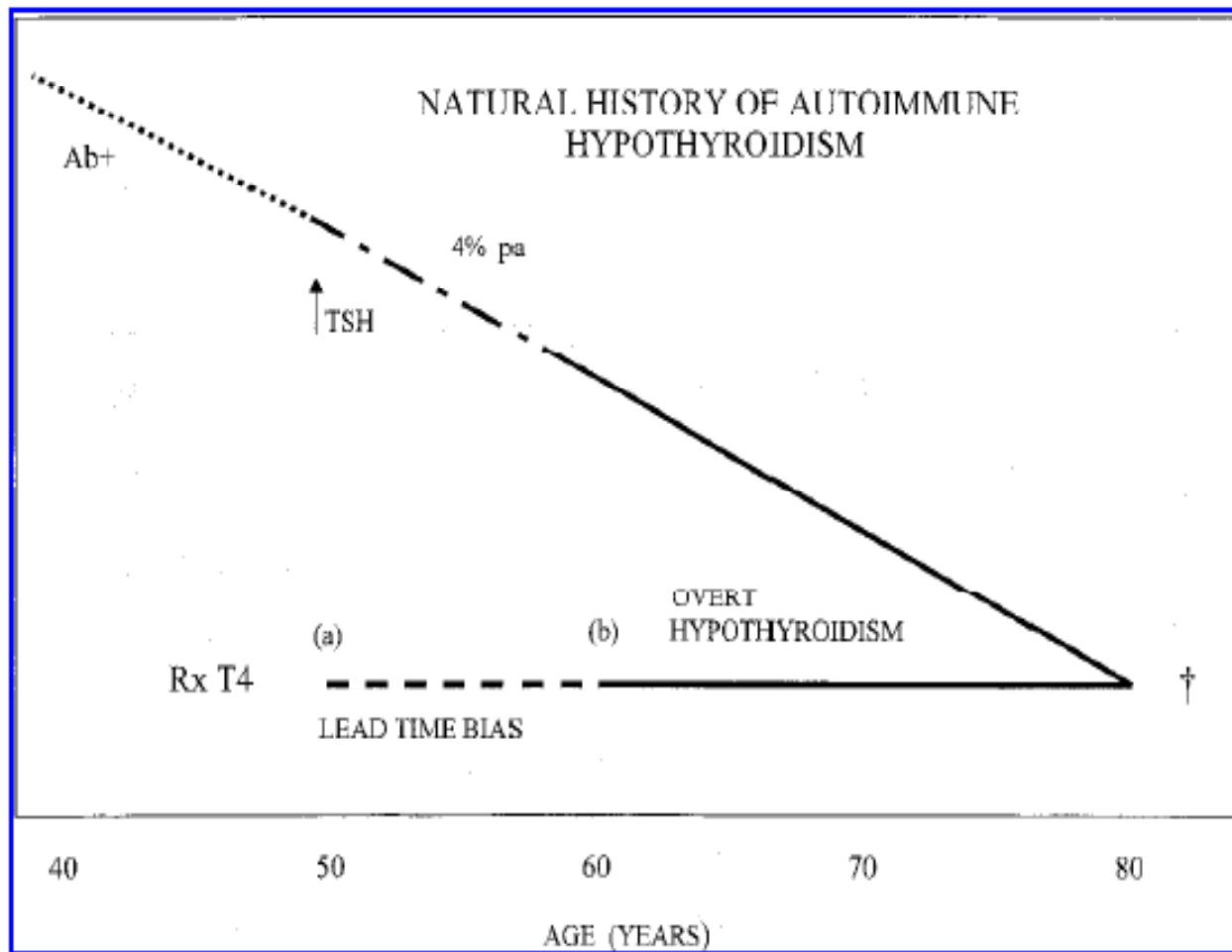
- TSH HIGH
- Free T4 LOW
- Prevalence 1-2%
- Women > Men
- Treatment is indicated

- **Subclinical Hypothyroidism**

- TSH HIGH (most often < 10)
- Free T4 normal
- Prevalence 9-12%
- Women > Men
- Treatment is controversial for TSH < 10

ATA Guideline

Therapy for **subclinical hypothyroidism** is **probably advisable**, especially if **antithyroid antibodies** are present, because **overt hypothyroidism** develops with **high frequency** in such patients. If decision to not treat they should be **evaluated yearly** for progression of biochemical and clinical thyroid dysfunction.



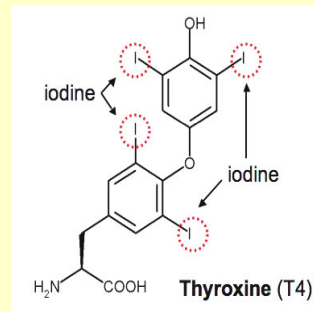
ATA Guidelines

Thyroid hormone therapy has been used for nonthyroidal problems, including obesity, infertility, menstrual irregularity, short stature, and chronic fatigue. There is no scientific proof that such conditions respond to thyroid hormone therapy and its use is not felt to be appropriate.

Some psychiatrists, however, report the benefit of adding thyroid hormone medication to tricyclic antidepressants in selected patients with depression, and clinical improvements have been noted.

ATA Guideline

- **Levothyroxine sodium is the treatment of choice** for the routine management of hypothyroidism.



ATA advocates the use of high quality **brand** levothyroxine

The patient should receive the same brand preparation throughout treatment

Brand vs Generic Levothyroxine

- Brands

- Synthroid (Abbott)
- Levo-T (Alara pharm)
- Levoxyl (King)
- Levothroid (Lloyd)
- Unithroid (Stevens J)

- Generic Manufacturers

- Mylan
- Sandoz
- Lannett
- Genpharm

Current FDA Bioequivalence Standards Cannot Distinguish a 12.5% Dose Difference



ATA guideline

- Certain drugs may interfere with absorption of levothyroxine. L-T₄ should be spaced at least 4 hours apart from these medications:
 - Cholestyramine
 - ferrous sulfate
 - Sucralfate, cimetidine
 - aluminum hydroxide antacids
 - Calcium
 - Sevelamer (Renagel)
 - Chromium picolinate

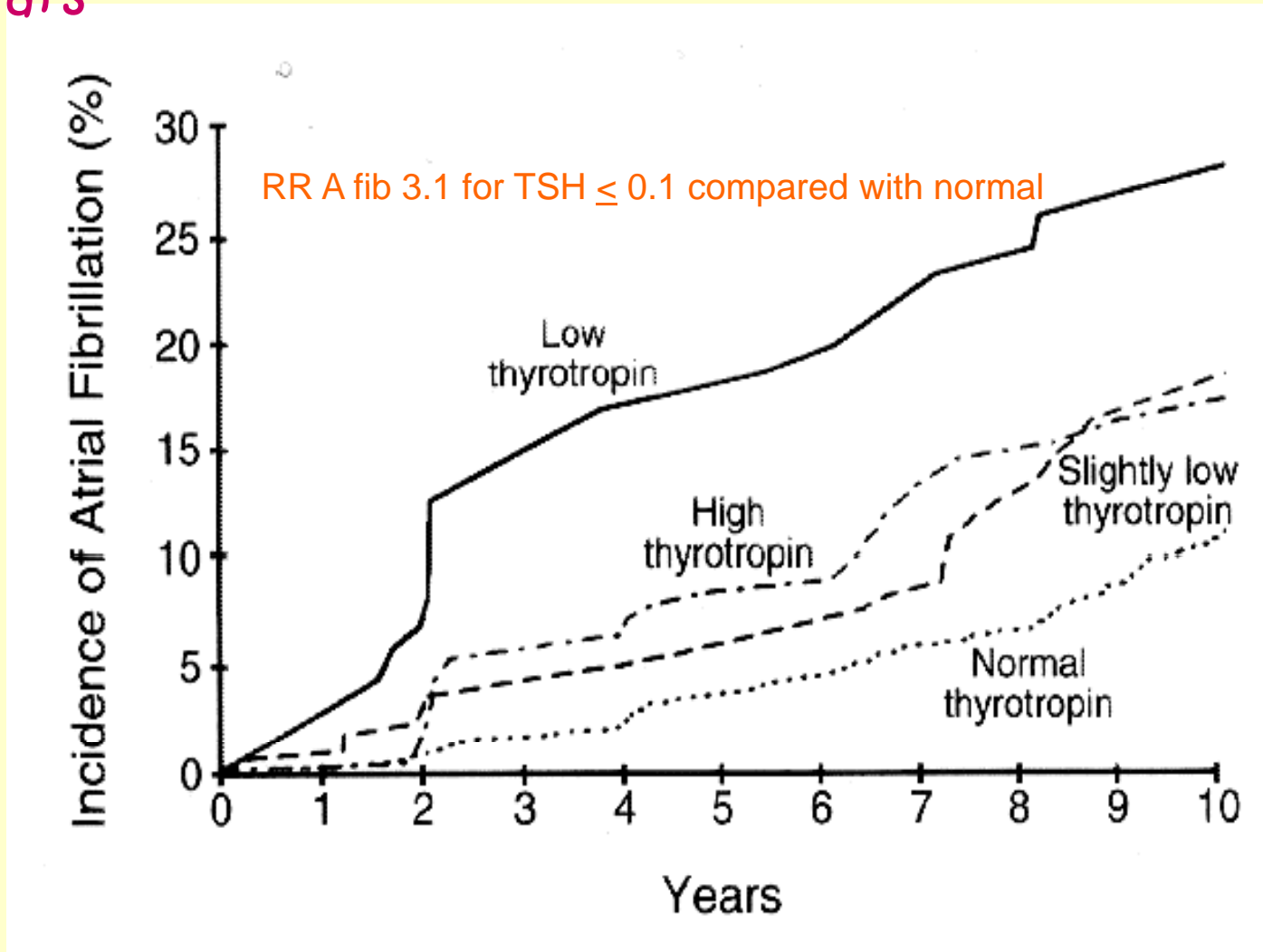
ATA Guideline

Therapy should be directed at using the dose of L-T4 to maintain normal TSH concentration

-~~AACE~~: TSH < 3

-~~NACB~~: TSH < 2

Framingham Cohort over age 60, studied for 10 years



Sawin, et al, NEJM 1994

ATA Guideline

- Adults with hypothyroidism require approximately 1.7 microg/kg of body weight per day for full replacement.
- Children may require higher doses (up to 4 microg/kg of body weight per day).
- Older patients may need less than 1 microg/kg per day

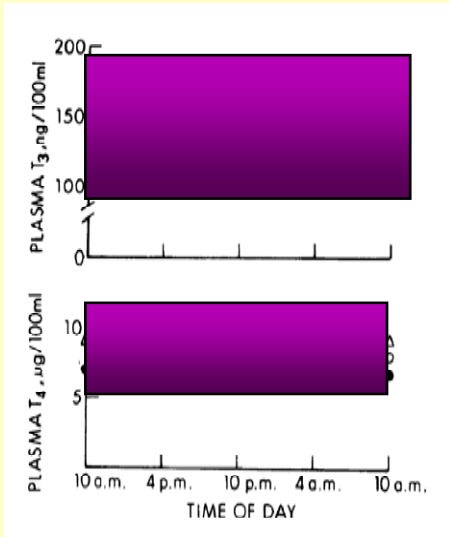
ATA Guideline

STARTING DOSE in LEVOTHYROXINE THERAPY

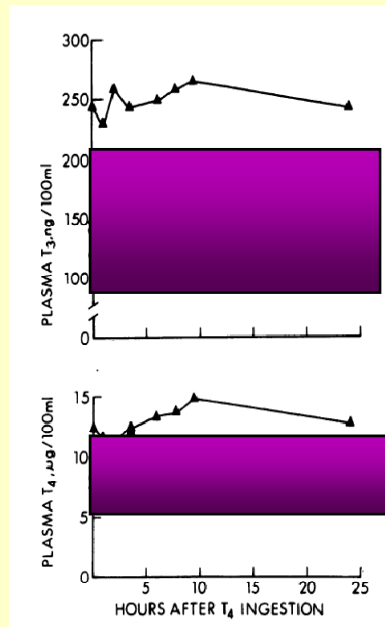
- Age < 50 years: full replacement.
- Age > 50 or cardiac disease: 0.025 to 0.05 mg of levothyroxine daily

ATA & AACE Guideline

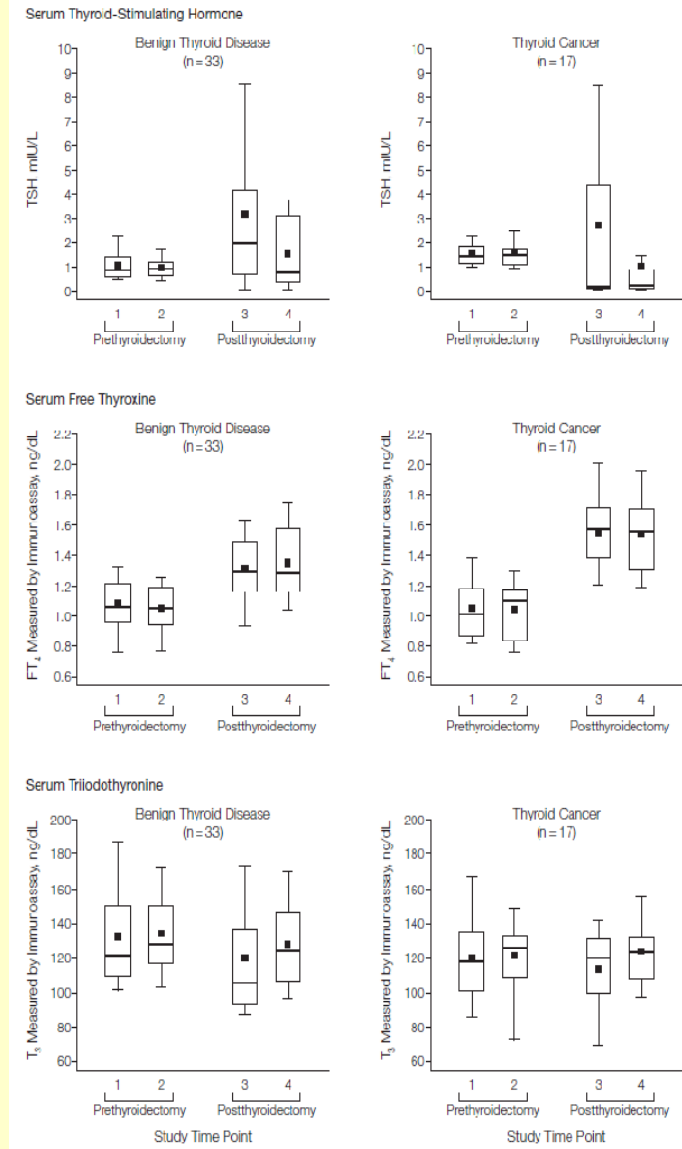
- Periodic monitoring is essential
 - Evaluate treatment response (TSH, Free T4)
 - Assess Compliance
 - ? Drug interactions
 - Physical exam relevant to the thyroid annually
 - Adjust Dose
- initially every 6-8 weeks
- Once stable every 6-12 months
- Change in dose: reassess in 2-3 months



Euthyroid, Thyroid intact



Hypothyroid, L-T₄ 200 mcg/day



TSH indicates thyroid-stimulating hormone; FT_4 , free thyroxine; T_3 , triiodothyronine. To convert FT_4 to pmol/L, multiply by 12.871; and T_3 to nmol/L, multiply by 0.0154. Ithyroidectomy and levothyroxine (L_T_4) initiation occurred between time points 2 and 3. L_T_4 adjustment was made between time points 3 and 4. The top, bottom, and middle lines of the boxes correspond to the 75th percentile, 25th percentile, and 50th percentile (median), respectively. The whiskers extend from the 10th percentile to the 90th percentile. The filled squares indicate the arithmetic mean.

Jonklaas et al, JAMA 2008; 299(7):769-777

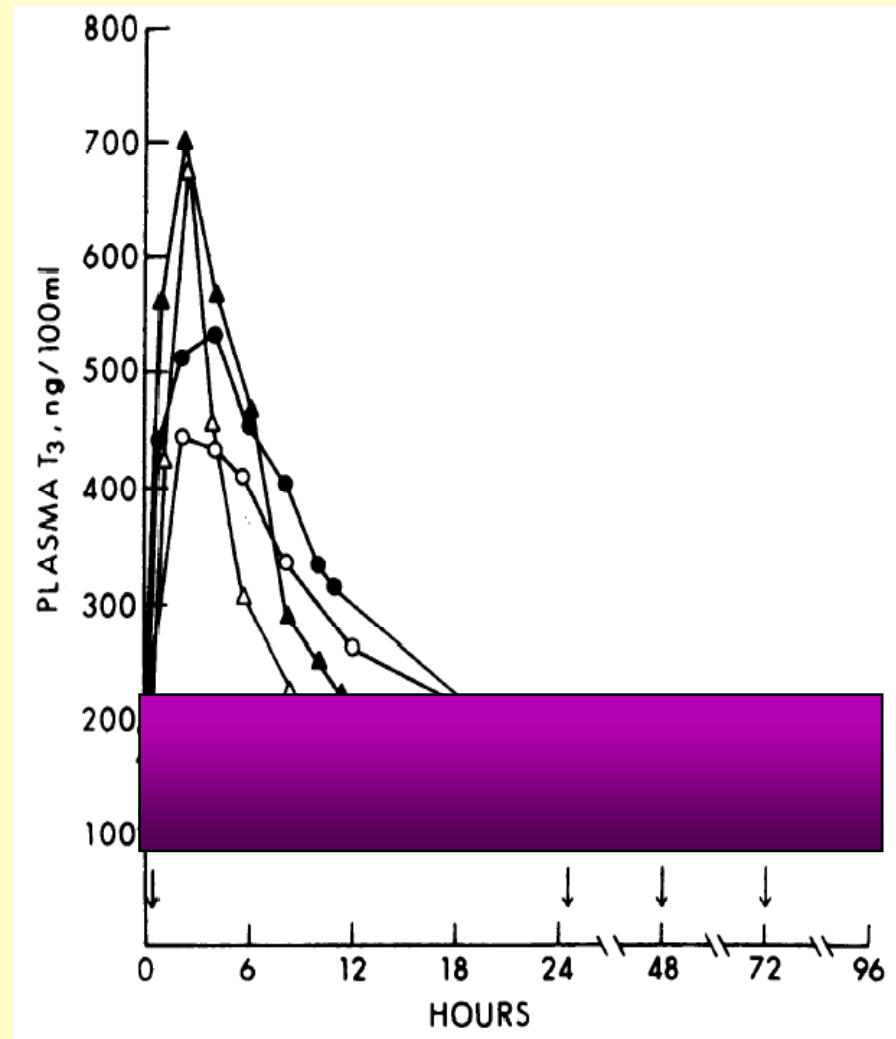
ATA Guidelines

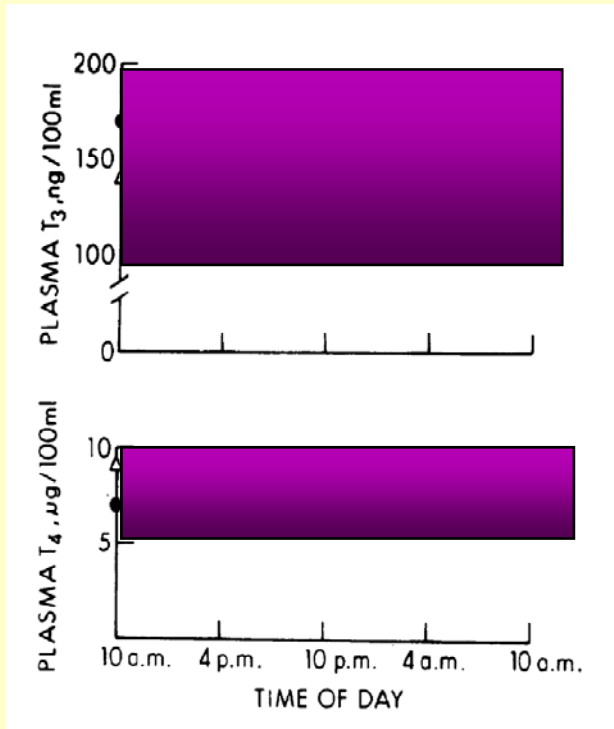
Chronic T3 (ie, Cytomel) for hypothyroidism is not recommended since its use is associated with a higher degree of hyperthyroidism. Some individuals, especially elderly individuals, are especially sensitive to the deleterious effects of T3.

Biological (ie, desiccated thyroid such as Armour thyroid) and synthetic preparations containing both T4 and T3 are also not recommended since they produce fluctuating and elevated T3 concentrations, although their use is not necessarily contraindicated

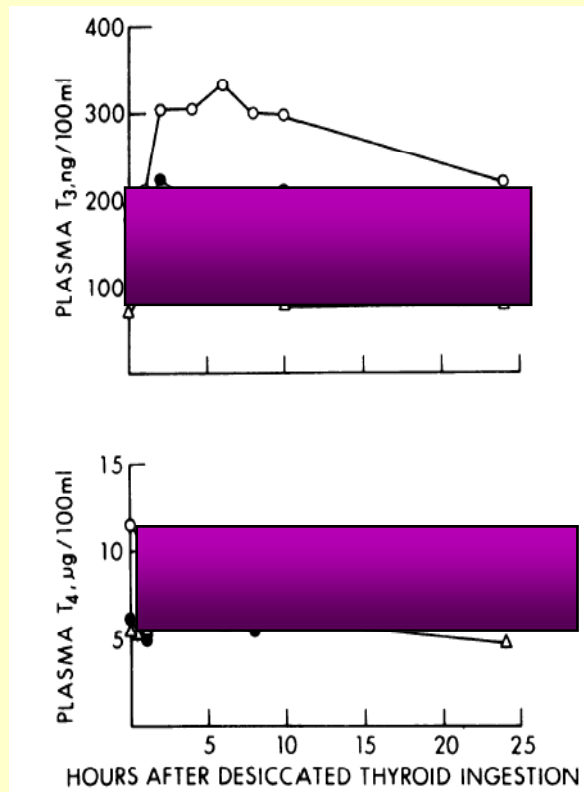
Athyrotic subjects given T3 once daily

75
mcg
in 3;
50
mcg
in one

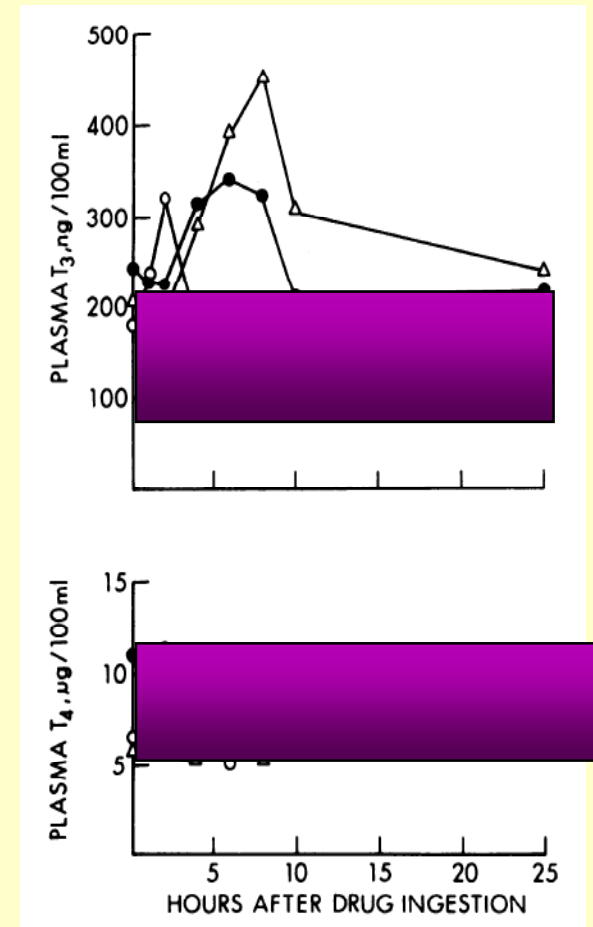




Normal, thyroid intact



120 mg/day in 2 and 60 mg/day in 1



L-T₄ 180 mcg and T₃ 45 mcg

TABLE 4. Summary of studies evaluating levothyroxine plus liothyronine combinations for the treatment of hypothyroidism

	Smith <i>et al.</i> (29)	Bunevicius <i>et al.</i> (30, 32) ^a	Walsh <i>et al.</i> (36)	Sawka <i>et al.</i> (37)	Clyde <i>et al.</i> (38)	Siegmund <i>et al.</i> (43)	Saravanan <i>et al.</i> (39)	Escobar-Morreale <i>et al.</i> (44)	Appelhof <i>et al.</i> (45)
Treatment approach	T ₄ 80 µg + T ₃ 20 µg vs. T ₄ 100 µg tablets ^b	T ₃ substitution	T ₃ substitution	T ₃ substitution	T ₃ substitution	Physiological T ₄ /T ₃ proportion	T ₃ substitution	Physiological T ₄ /T ₃ proportion	Supraphysiological T ₄ /T ₃ proportions
T ₄ /T ₃ doses	Variable	Variable	Variable	Variable	Variable	Variable	Variable	Fixed	Variable
Design	Crossover	Crossover	Crossover	Parallel	Parallel	Crossover	Parallel	Crossover	Parallel
Degree of hypothyroidism	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Overt hypothyroidism	Not specified
Prestudy period with stable T ₄ dose	>6 months	>3 months	>2 months	>6 months	>3 months	Not specified	>3 months	>12 months	>6 months
Treatment periods	8 wk	5 wk	10 wk	12–15 wk	16 wk	12 wk	12 months	8 wk	15 wk
Patients analyzed	87	33/26	101	39	44	23	573	26	130
Sample size analysis	No	No	Yes	No	Yes	Yes ^c	Yes	Yes	No
Outcomes ^d	Thyroid function	Thyroid function	Thyroid function	Thyroid function	Thyroid function	Thyroid function	Thyroid function	Thyroid function	Thyroid function
		QoL	QoL	QoL	QoL	QoL	QoL	QoL	QoL
		Mood	Mood	Mood	Mood	Mood	Mood	Mood	Mood
		Psycho	Psycho	Psycho	Psycho	Psycho	Psycho	Psycho	Psycho
	Preference	Preference	Preference					Preference	
		Few biological end-points	Few biological end-points		Few biological end-points	Pharmacokinetics	Several biological end-points	Multiple biological end-points	Few biological end-points
External euthyroid control group	No	No	No	No	No	No	No	Yes	No
Benefits of T ₄ + T ₃	No	Yes	No	No	No	No	No	No	No
Undesirable effects of T ₄ + T ₃	Yes (Hyperthyroid symptoms)	No	Not reported	Not reported	Not reported	Yes (serum TSH suppression and atrial arrhythmia)	No	Yes (serum TSH suppression and increased urinary bone remodeling markers)	Yes (serum TSH suppression and increased serum bone remodeling markers)
Patients' preference	T ₄	T ₄ + T ₃	T ₄ = T ₄ + T ₃	Not assessed	Not assessed	Not assessed	Not assessed	T ₄ + T ₃	T ₄ + T ₃

Psycho, Test of psychometric performance. [Modified with permission from H. F. Escobar-Morreale *et al.*: *Ann Intern Med* 142:412, 2005 (44). © American College of Physicians.]

^a A later study by Bunevicius *et al.* (34) has not been included in this table because the small sample size of 10 patients precluded reaching a definite conclusion. Also, this table does not contain information of a study by Cassio *et al.* (42) because it included infants with congenital hypothyroidism and the outcomes are not comparable with studies conducted in adults.

^b Patients received the prestudy number of tablets (two or three) throughout the study.

^c A *priori* sample size calculation gave a minimum of 24 patients for an 80% power at the *P* < 0.05 significance level, but only 23 patients completed the study.

^d Thyroid function tests: serum thyroid hormone levels, except in Ref. 29 in which serum PBI and T₃-resin uptake were measured.

Special Populations

Pregnancy and Hypothyroidism

Cretinism



Iodine treatment
at birth does not
prevent endemic
neurological
cretinism

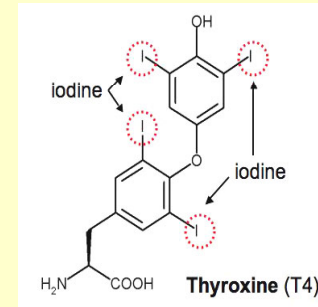
Neurological – strabismus, deaf-mutism (50%), proximal spasticity, disordered gait and coordination

During pregnancy and breast feeding, women should increase their daily iodine intake to 250 mcg/day on average

USPSTF A, evidence good, Grade 1 +++-

WHO Recommended daily intake of iodine

- 90 mcg for preschool children (0-59 months)
- 120 mcg for schoolchildren (6-12 yrs)
- 150 mcg for adults (> 12 yrs)
- 200-250 mcg for pregnant and lactating women



Severity of Iodine deficiency

Severe < 20 mcg/day

Moderate 20-49 mcg/day

Mild 50-99 mcg/day

Iodine deficiency becomes significant in pregnancy when iodine intake < 100 mcg/day

Treatment of
sporadic congenital hypothyroidism
with thyroid hormone
beginning in the neonatal period
permits
normal neurological development.

IQ scores in children born to mothers with hypothyroxinemia

	Children born to		
	Healthy control mothers	Mothers with hypo-T4	P value
Average IQ score	107	(overall) 103	0.06
Average IQ score	107	(untreated) 100	0.004
Average IQ score	107	(T4-treated) 111	0.259
IQ scores > 2 SD below the mean of controls	4 %	13 %	0.08

TABLE 2. MEASUREMENTS OF THYROID FUNCTION IN THE STUDY WOMEN DURING PREGNANCY.*

VARIABLE	WOMEN WITH HYPOTHYROIDISM (N= 62)	CONTROL WOMEN (N= 124)
Serum thyrotropin concentration (mU/liter)	13.2±0.3†	1.4±0.2
Serum thyroxine concentration (μg/dl)	7.4±0.1†	10.6±0.1
Serum free thyroxine concentration (ng/dl)	0.71±0.1†	0.97±0.07
High serum concentrations of anti-thyroid peroxidase antibodies (%)‡	77†	14

*Plus-minus values are geometric means ± the logarithmic SD. To convert values for serum thyroxine and free thyroxine to nanomoles per liter and picomoles per liter, respectively, multiply by 12.87.

†P<0.001 for the comparison with the control women.

‡Concentrations of more than 2 U per milliliter were considered high.

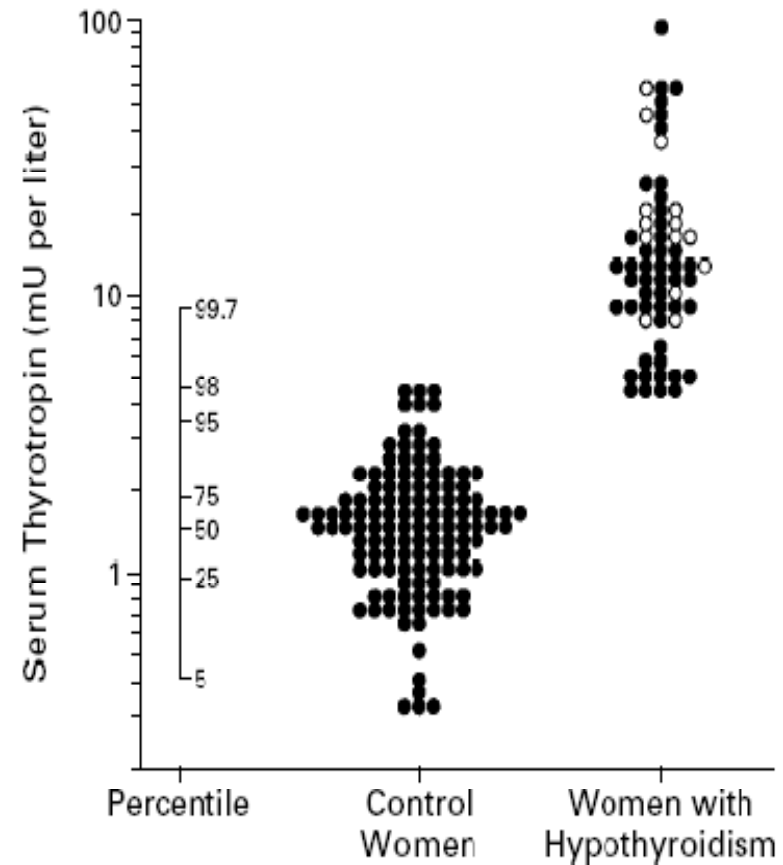


Figure 1. Distribution of Serum Thyrotropin Concentrations during Pregnancy in the 62 Women with Hypothyroidism and the 124 Matched Control Women.

Open circles indicate the 14 women who were treated for hypothyroidism during the pregnancy under study. Selected percentiles are shown for the entire cohort of 25,216 pregnant women.

Hypothyroidism & Pregnancy

- Maternal hypothyroidism should be avoided
- USPSTF level A, evidence fair, Grade 1 +++-

Repercussions of Hypothyroidism on pregnancy: Maternal aspects

- Decreased fertility
- Increased prevalence of
 - Abortion
 - Anemia
 - Gestational HTN
 - Placental abruption
 - Postpartum hemorrhage
- Adequate L-T₄ treatment greatly decreases the risk of a poorer obstetrical outcome

Repercussions of Hypothyroidism on pregnancy: Fetal aspects

- Premature birth
- Low birth weight
- Neonatal respiratory distress

Overt Hypothyroidism diagnosed during pregnancy

- TFTs should be normalized as rapidly as possible to **trimester specific normal TSH ranges**.
 - TSH < 2.5 in the first trimester
 - < 3 in the 2nd and 3rd trimester
- TFTs can be **re-measured within 30-40 days**
 - USPSTF A, evidence good, Grade 1 ++++

Median and 95% TSH confidence limits (Hong Kong)

Panesar et al, Ann Clin Biochem 38:329, 2001

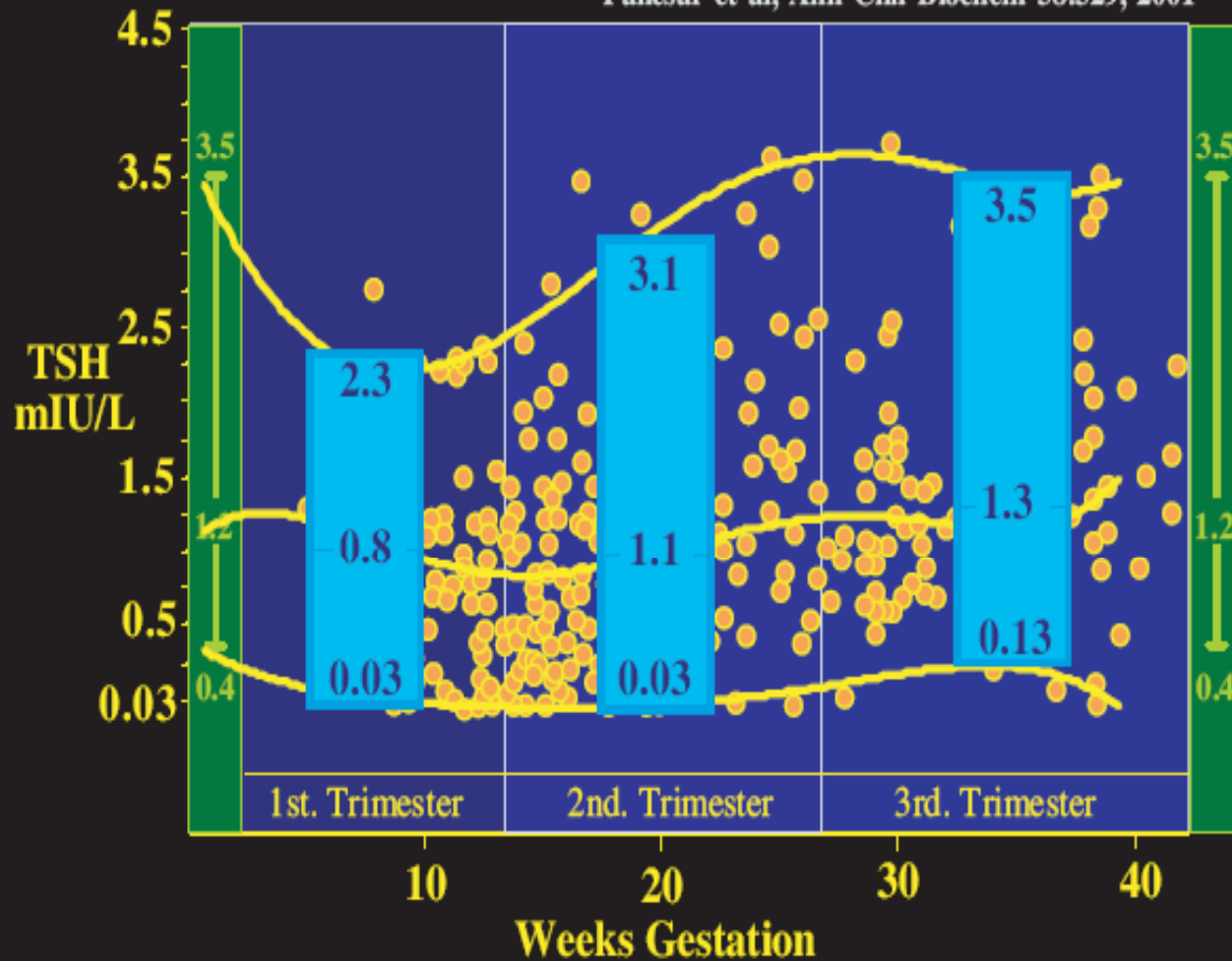
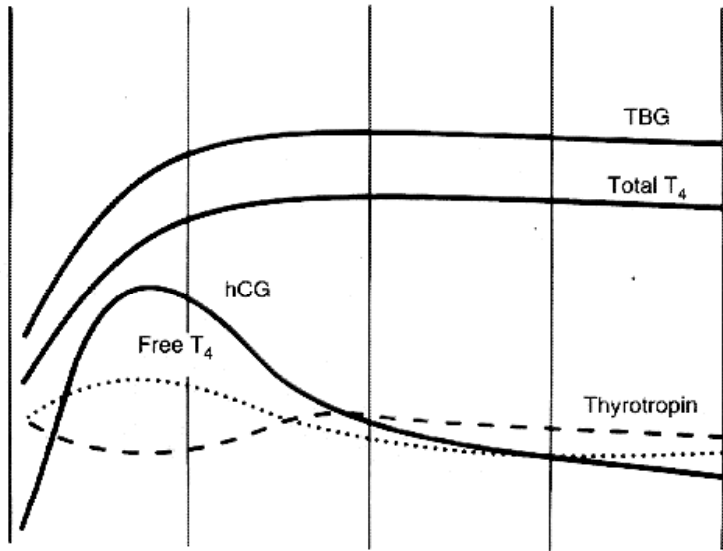
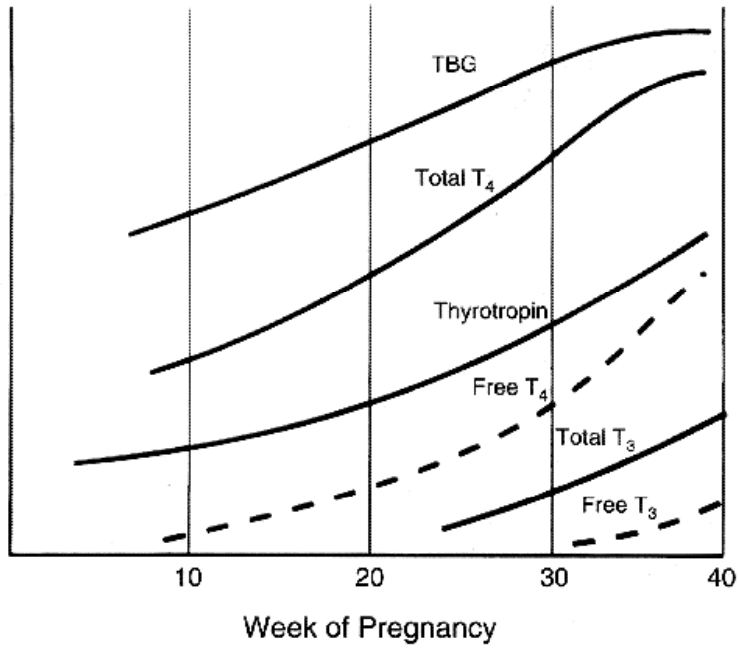


FIG. 1. Median and 95% confidence levels for TSH during pregnancy.

Mother

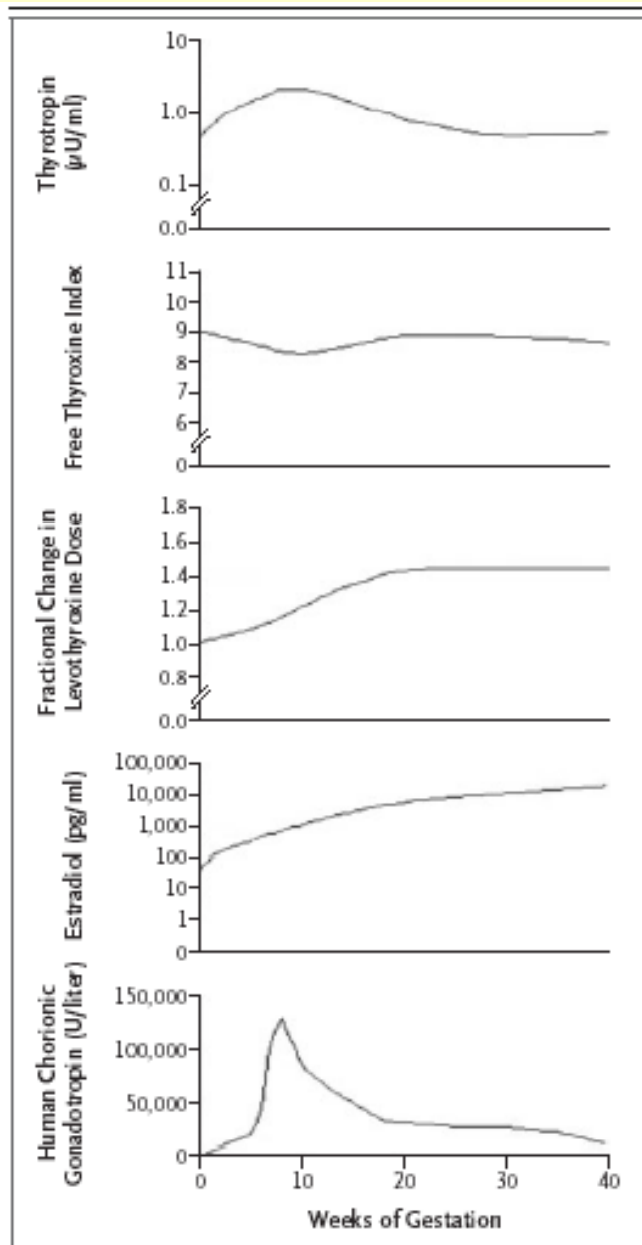


Fetus



Hypothyroidism Treatment

- L-T4 dose needs to be incremented by 4-6 weeks gestation and may require a 30-50% increase in dosage
- USPSTF A, evidence good, Grade 1 (++++)



At 10 weeks, the L_t4 dose had increased by 29 +/- 5 %

At 20 weeks, the L_T4 dose had increased by 48%

Time at which increased TSH was first observed varied between 4.4 and 16 weeks (median 8 weeks).

Women who are currently being treated for hypothyroidism should be given written instruction to increase their current dose of L_T4 by taking 2 extra daily doses each week (to increase dose by 29%) beginning the week pregnancy is confirmed

ATA Guideline- Pregnancy

Check TSH each trimester

After delivery, most hypothyroid women need a decrease in the LT4 dosage they received during pregnancy

- USPSTF A, evidence good, Grade 1 ++++

Return L-T4 dose to pre-pregnancy dose immediately after pregnancy and check TSH again in 6-8 weeks

Thyroid Autoimmunity

- Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for elevation of TSH above the normal range
- USPSTF A, evidence good, Grade 1 (+++)

Post Partum Thyroiditis

- Women known to be thyroid peroxidase antibody positive should have a TSH performed at 3 and 6 months postpartum
- USPSTF A, evidence good, grade 1 +++-

References

- American Thyroid Association Guidelines for detection of Thyroid dysfunction. Paul W. Ladenson, Peter A. Singer, Kenneth B. Ain, Nandalal Bagchi, S. Thomas Bigos, Elliot G. Levy, Steven A. Smith, Gilbert H. Daniels. *Archives of Internal Medicine (Arch Intern Med)* 2000;160:1573–1575.
- Treatment guidelines for patients with hyperthyroidism and hypothyroidism Peter A. Singer, David S. Cooper, Elliot G. Levy, Paul W. Ladenson, Lewis E. Braverman, Gilbert Daniels, Francis S. Greenspan, I. Ross McDougall, Thomas F. Nikolai. *Journal of the American Medical Association (JAMA)* 1995;273:808–812.
- AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE EVALUATION AND TREATMENT OF HYPERTHYROIDISM AND HYPOTHYROIDISM AACE Thyroid Task Force
 - http://www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf
- Management of Thyroid Dysfunction during Pregnancy and Postpartum:An Endocrine Society Clinical Practice Guideline
 - <http://www.endo-society.org/guidelines/final/upload/Clinical-Guideline-Executive-Summary-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.pdf>
 - <http://www.endosociety.org/guidelines/final/upload/Clinical-Guideline-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.pdf>
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