
بسم الله الرحمن الرحيم

- **Hypothyroidism and**

  Subclinical Hypothyroidism

- **Subclinical Hypothyroidism**

  in pregnancy

Euthyrox®

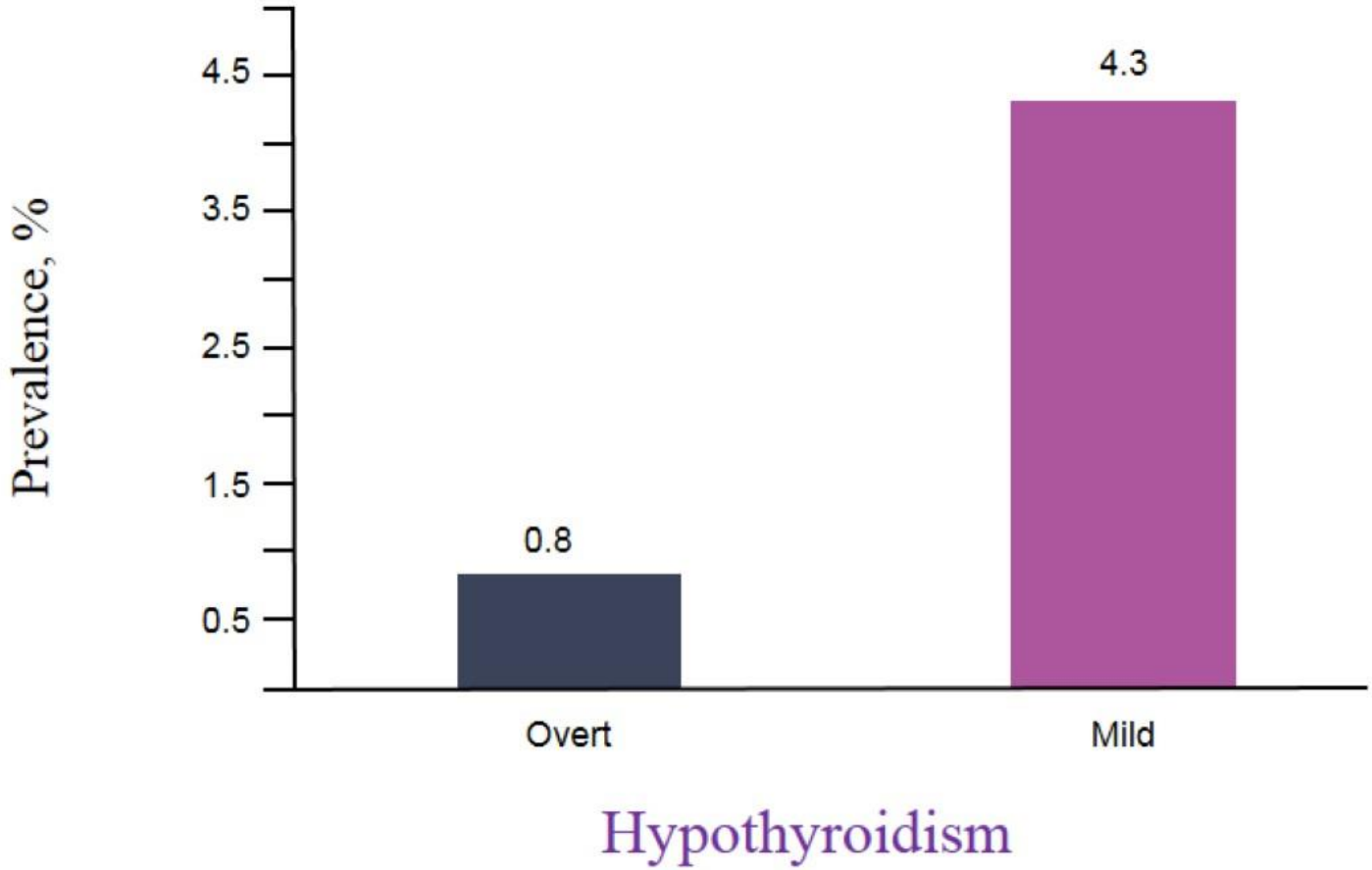
MERCK

Prevalence

Overt hypothyroidism varies from 0.1 to 2 percent.

Hypothyroidism much (5 to 8 times) more common in women than men.

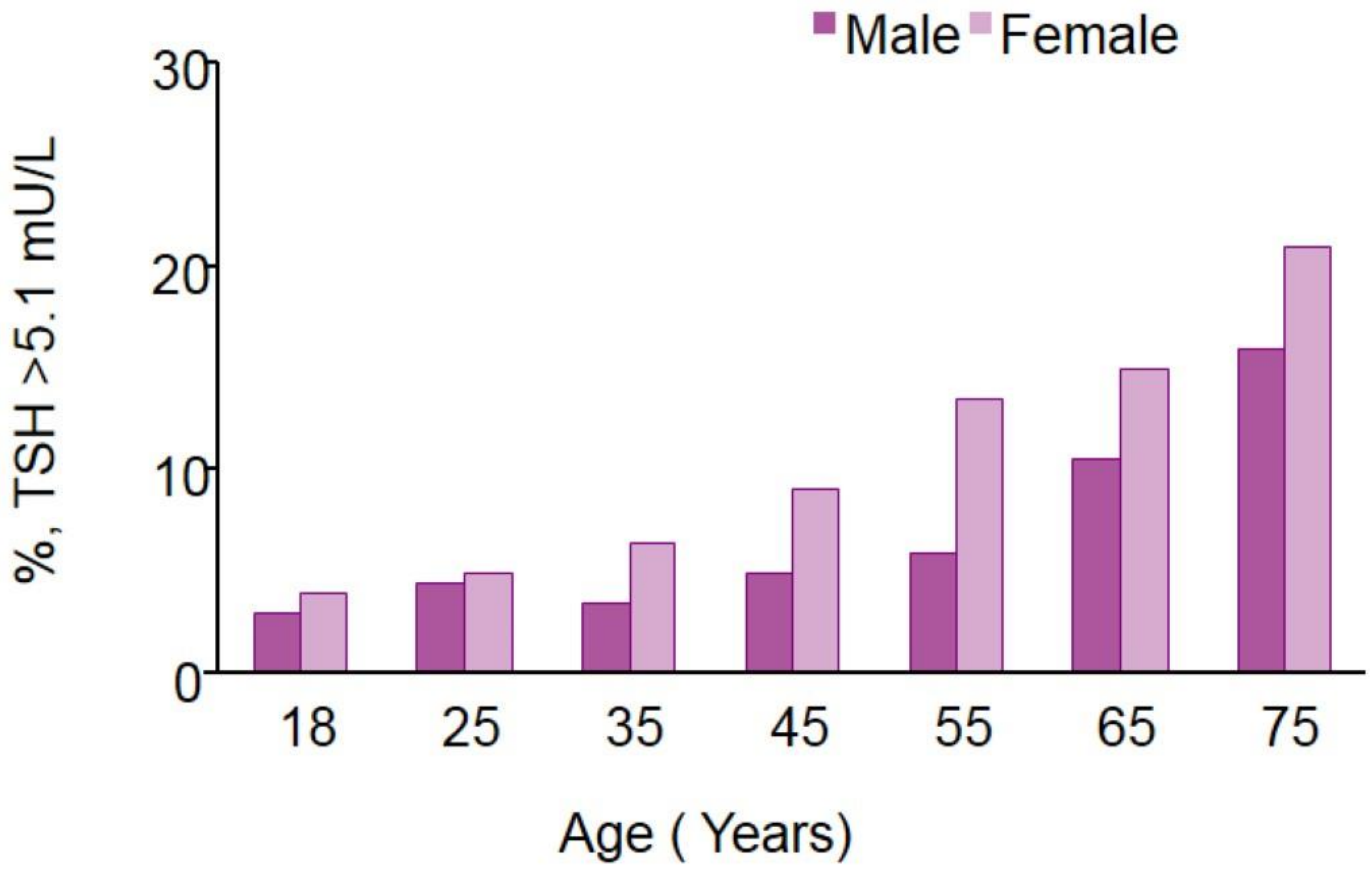
Prevalence of Hypothyroidism



J Clin Endocrinol Metab 2002;87:489–499

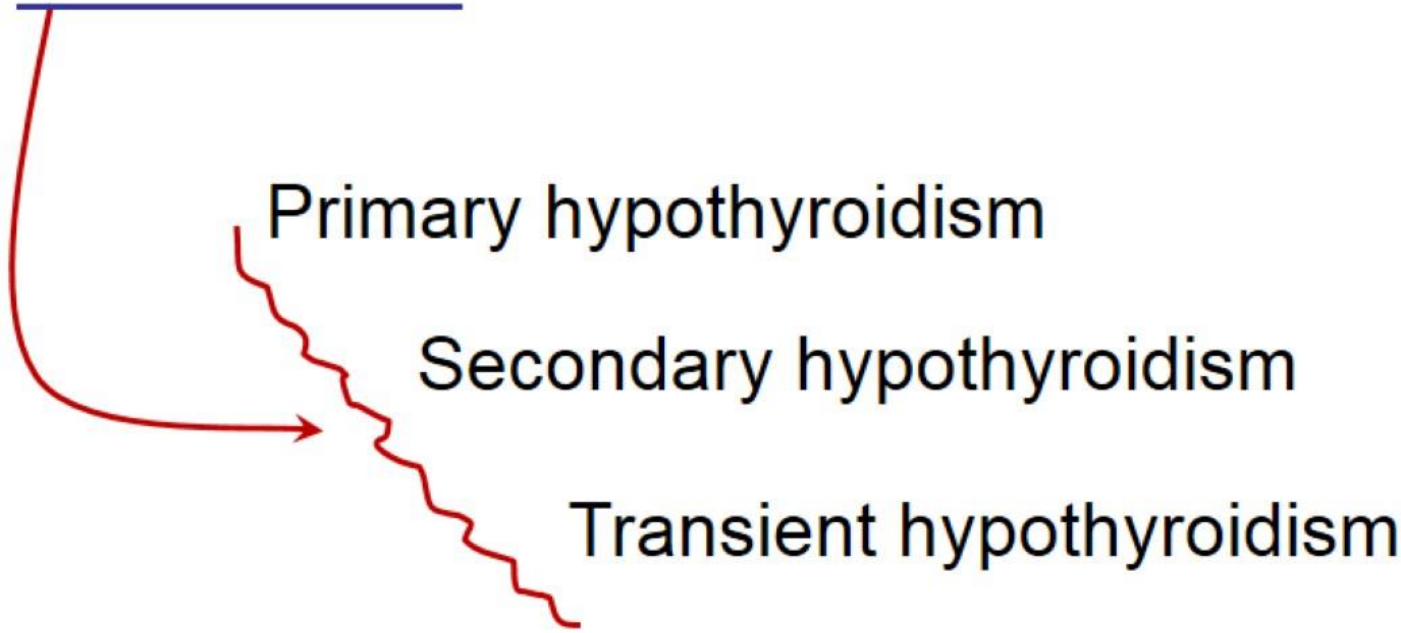
Kravets American Family Pysiciann 2016;93:363-373

Prevalence of hypothyroidism by age



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

Causes of hypothyroidism



Primary Hypothyroidism

Worldwide, **iodine deficiency** is the most common cause of hypothyroidism, but in areas of iodine sufficiency, **Hashimoto's** disease is the most common cause of thyroid failure.

شایعترین علت کمکاری تیروئید در کل دنیا کدام است؟

الف: هاشیماتو

ب: کمبود ید

ج: جراحی

د: ید رادیواکتیو

اولین یافته ی آزمایشگاهی بیماری هاشیماتو کدام است؟

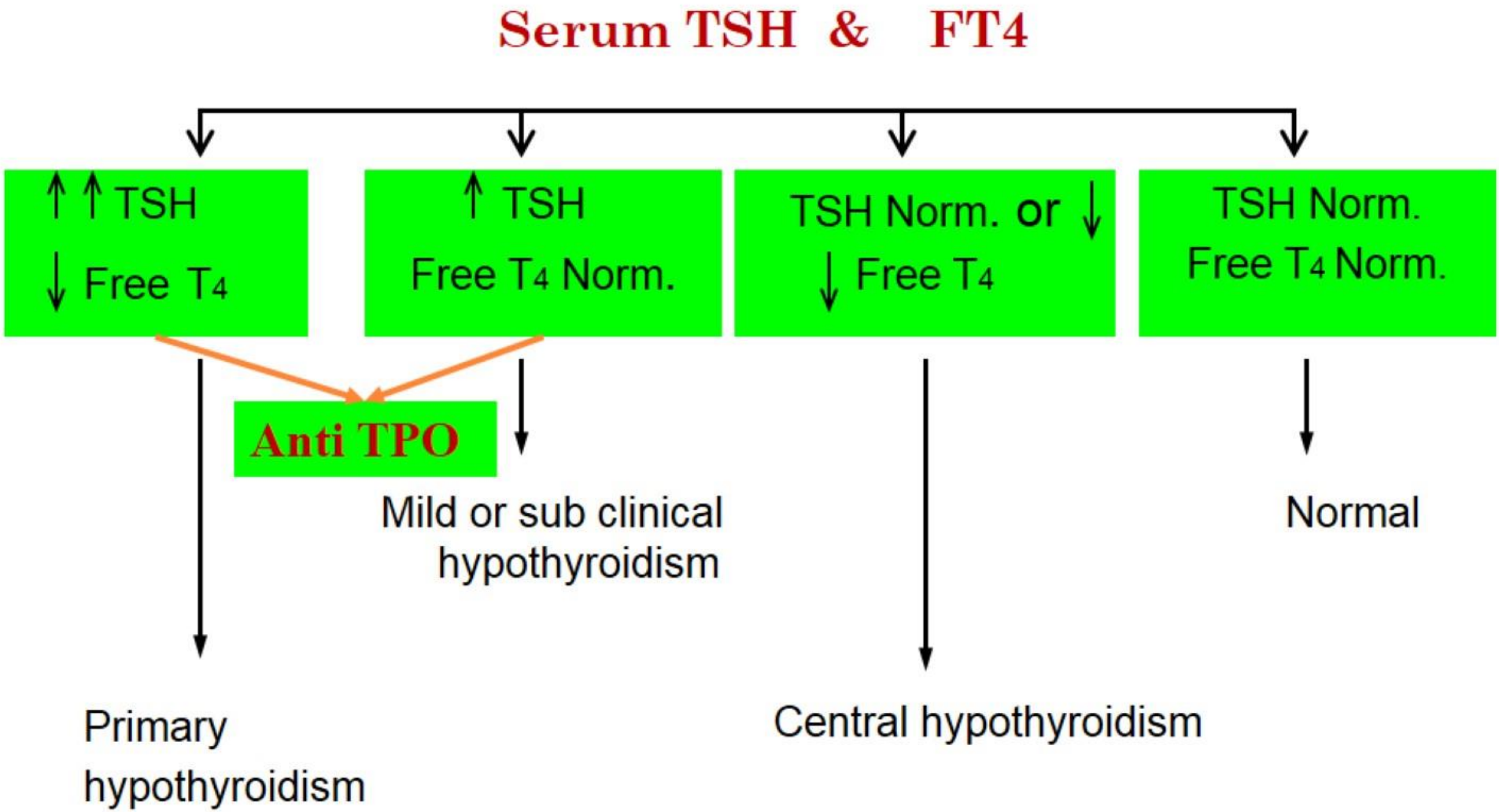
الف: افزایش TSH

ب: کاهش FT_4

ج: کاهش T_3

د: مثبت شدن Anti TPO

Laboratory Assessment of Hypothyroidism



آقای 45 ساله ای با ضعف و بی حالی مراجعه کرده است. در بررسی اولیه آنمی مشهود بود.

تستهای تیروییدی به شرح زیر گزارش شد

FT4= 0.4 ng/dL (0.8 – 1.8) TSH= 2 mIU/L (0.5 – 4.2)

کدام تشخیص برای وی مطرح است؟

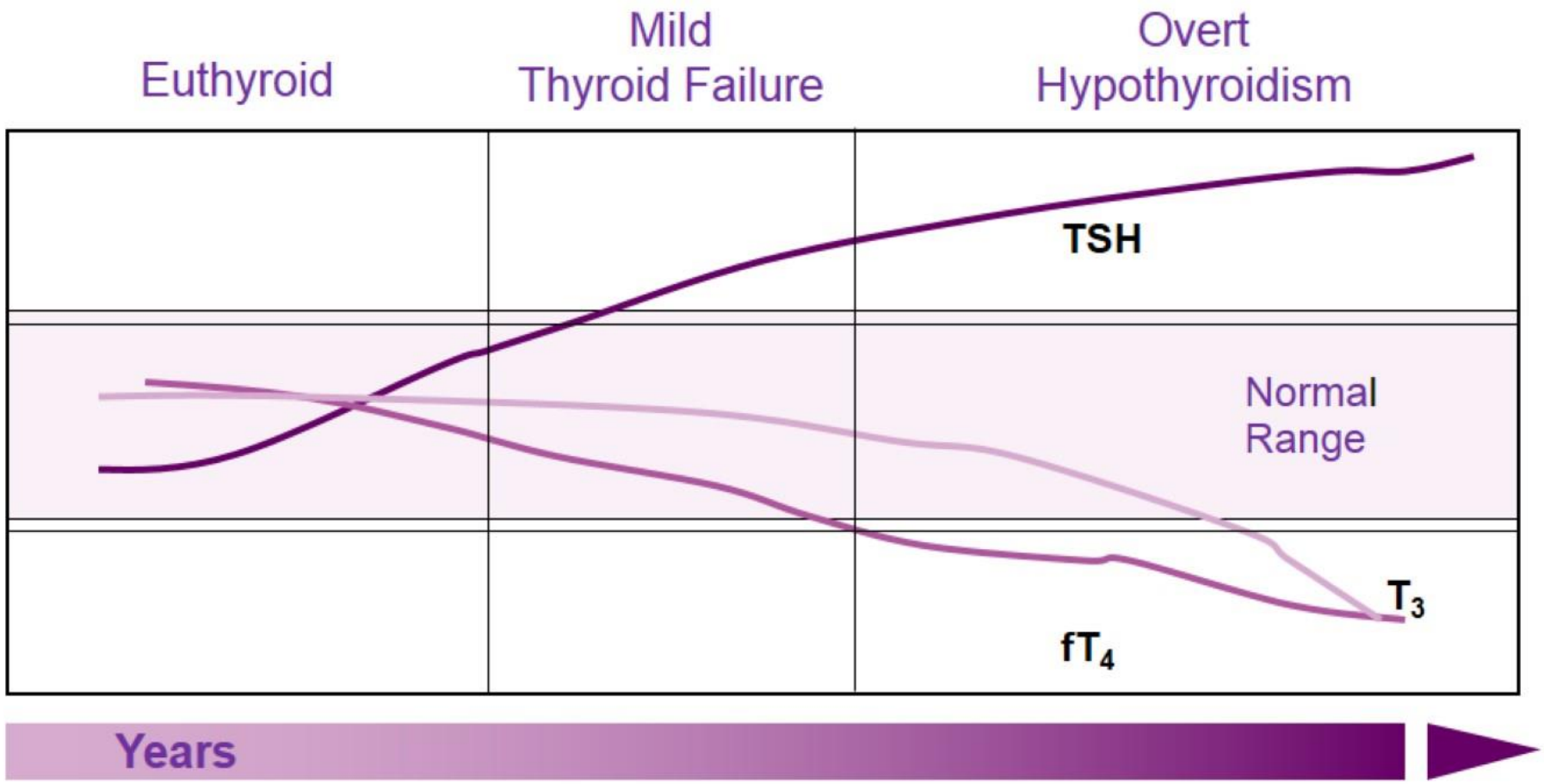
الف هیپوتیرویییدی اولیه

ب هیپوتیرویییدی ثانویه (مرکزی)

ج هیپوتیرویییدی ساب کلینیکال

د نرمال است

Progression of Hypothyroidism



Adapted from Ayala AR, et al. *Endocrinologist* 1997;7:44–50

Sings and Symptoms

Generalised slowing of metabolic processes
Fatigue or Feeling slowed down
Sensitive to cold
Weight gain
Constipation
Sadness or Depression
Slow movements and thoughts
Muscle aches, weakness cramps
Dry skin, brittle hair and nails
Irregular menses
Joint or muscle pain

Medline Plus. 2014 Hypothyroidism

Cardiovascular Effects of Hypothyroidism

Haemodynamic changes

- Increase in vascular resistance
- Impaired ventricular performance
- Increased systolic time interval

Increased cardiovascular risk

- Increased risk for functional cardiovascular abnormalities
- Increased risk for atherosclerosis

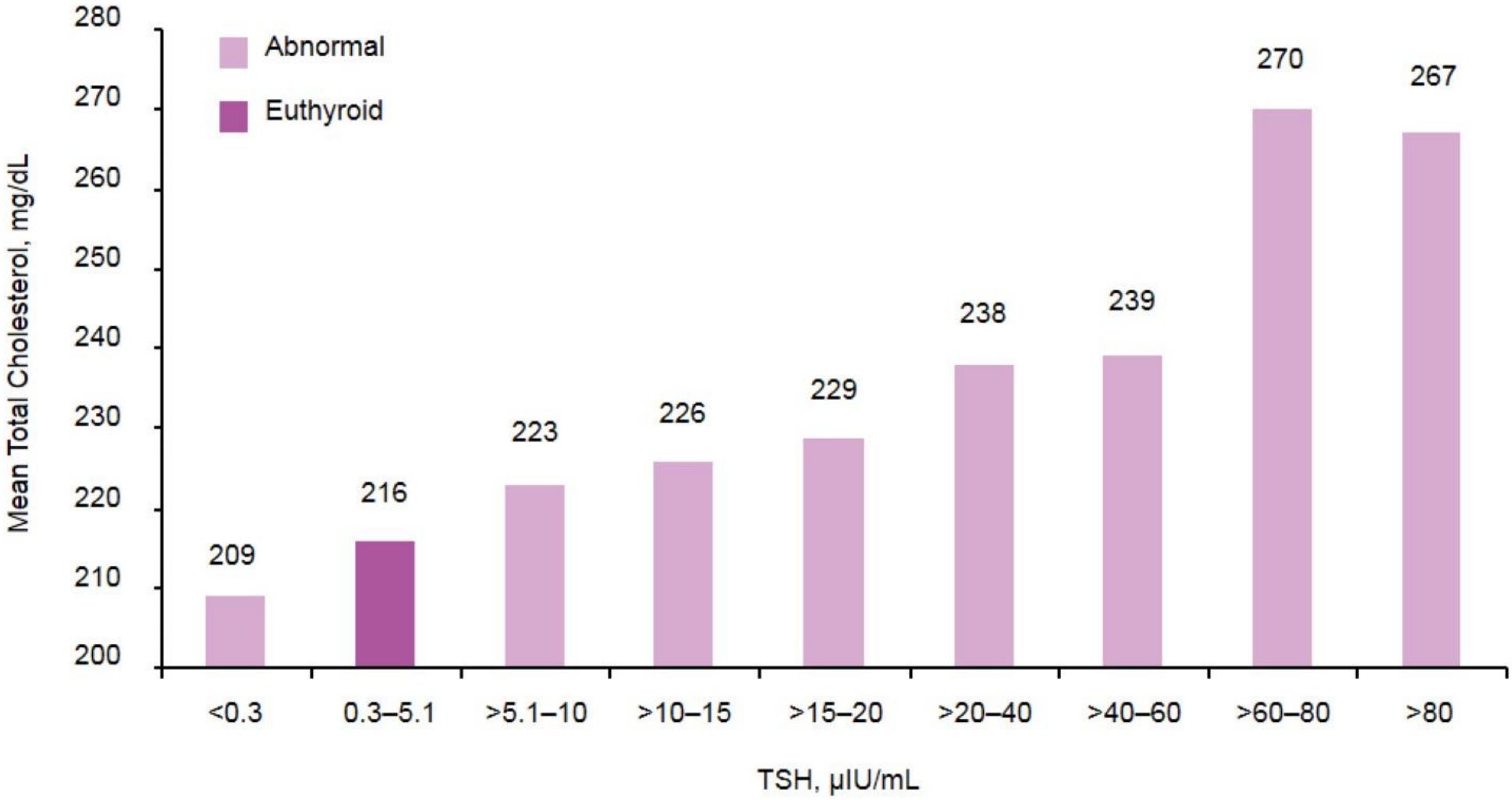
Lippincott Williams & Wilkins; 2005:774–780
Biondi B, et all. *Endocrine* 2004;24:1–13

Hypothyroidism and Changes in Lipid Profile

- Hypercholesterolemia
- Increased LDL-C and apoB levels
- Decreased fractional clearance of LDL-C by a reduced number of LDL receptors in the liver
- Normal or elevated HDL-C levels

Duntas LH. *Thyroid* 2002;12:287–293

Cholesterol Levels Rise with Increasing TSH Levels



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

Changes in Renal Function in Hypothyroidism

Endocrine-metabolic changes

Plasma catecholamines changes
Plasma renin activity ↓
Serum aldosterone ↓
Serum atrial natriuretic peptide ↓

Hypertension

Plasma catecholamines ↑
α-adrenergic response ↑
Salt sensitivity ↑

Hyponatraemia

Glomerular filtration ↓
Free water delivery to distal tubule↓

Hyperuricaemia/gout

Cardiovascular changes

Cardiac output ↓
Peripheral vascular resistance ↑

Changes in renal function

Renal blood flow ↓
Glomerular filtration ↓
Sodium conservation during sodium restriction ↓
Potassium excretion ↓
Free water and osmolar clearance ↓

Oedema

Total body sodium and water ↑
Capillary permeability ↑

Hypertension and electrolyte disturbances

Kaptein EM. *The Thyroid*, 9 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:789–795

Gastrointestinal Effects of Hypothyroidism

Reduced intestinal motility

- Dysphagia
- Prolonged gastric emptying
- Constipation; in severe cases paralytic ileus

Comorbidity of hypothyroidism with other concomitant autoimmune disorders

- Immune gastritis
- Autoimmune liver diseases (chronic active hepatitis, primary biliary cirrhosis)

Wasan SM, et al. *The Thyroid*, 9 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:796–802

Abnormal thyroid status impairs female fertility

Hypothyroidism
Changes of cycle length and amount of bleeding: oligomenorrhea, hypomenorrhea, amenorrhea, hypermenorrhea/menorrhagia
Diminished libido
Failure of ovulation
Abortions in the first trimester, stillbirths, prematurity

Silva et al. 2018 Negro 2006

Abnormal thyroid status impairs male fertility

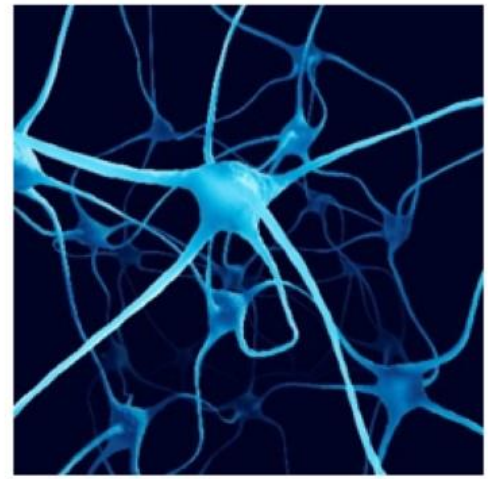
Hypothyroidism
Reduced libido
Impaired ejaculatory reflex
Altered sperm motility

Lombardo F et al. Int J Androl 2005;28 Suppl 2:53-5; Maggi M et al. J Sex Med 2013;10:661-77; Krassas GE et al. Endocr Rev 2010;31:702-55.

Effects of Hypothyroidism on the Neuromuscular System

Hypothyroid myopathy (Very common)

Stiffness, cramps, myalgia, muscle fatigue, slow movements, muscle aches, weakness cramps



Neurological disorders

Neuropathic symptoms

Paresthesia, painful dysesthesias

Carpal tunnel syndrome

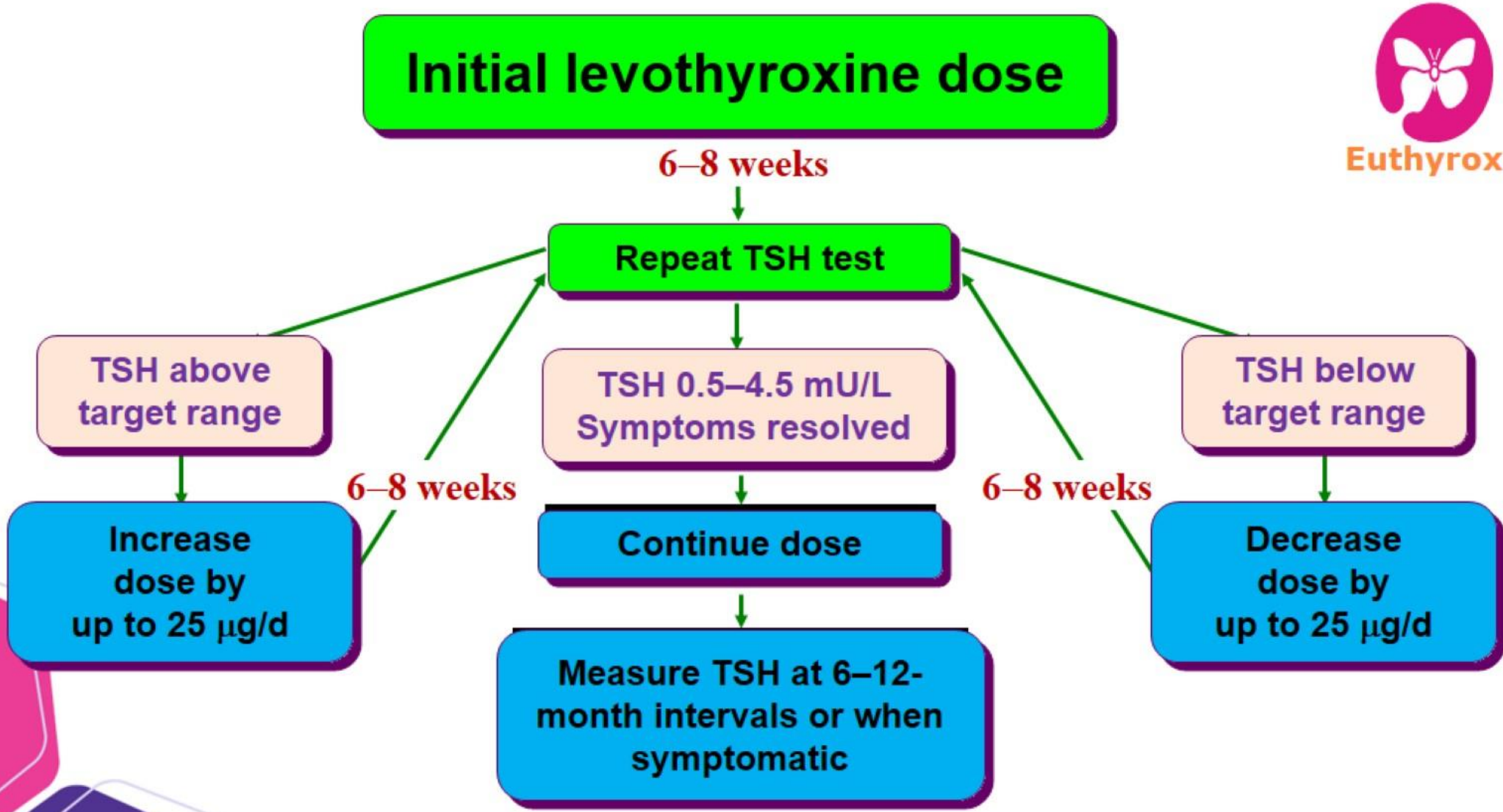
Ataxia

Neurocognitive impairment, particularly in elderly patients

Slowness in comprehension, diminished attention, poor recent memory, difficulty with word fluency

Gardner DF. *The Thyroid*, 9 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:836–841

Treatment algorithm of Primary Hypothyroidism



Euthyrox®

Demers LM, et al. *Clin Endocrinol (Oxf)* 2003;58:138–140

Subclinical Hypothyroidism

Mild thyroid failure / subclinical hypothyroidism

TSH ↑, FT_4 normal

Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*, 9th ed. 2005
Vanderpump MP, et al. *Clin Endocrinol (Oxf)* 1995;43:55–68

It is important to **confirm** that any elevation of TSH is sustained over a 3-month period before treatment is given.

Natural History of Sub Clinical Hypothyroidism

First TSH	% with normal TSH at end of 38 months	Rate of overt hypothyroidism per 100 patient-years
5-9.9	52 %	1.76
10-14.9	13 %	19.67
15-19.9	5 %	73.47

Diez et al. JCEM 89: 4890,2004

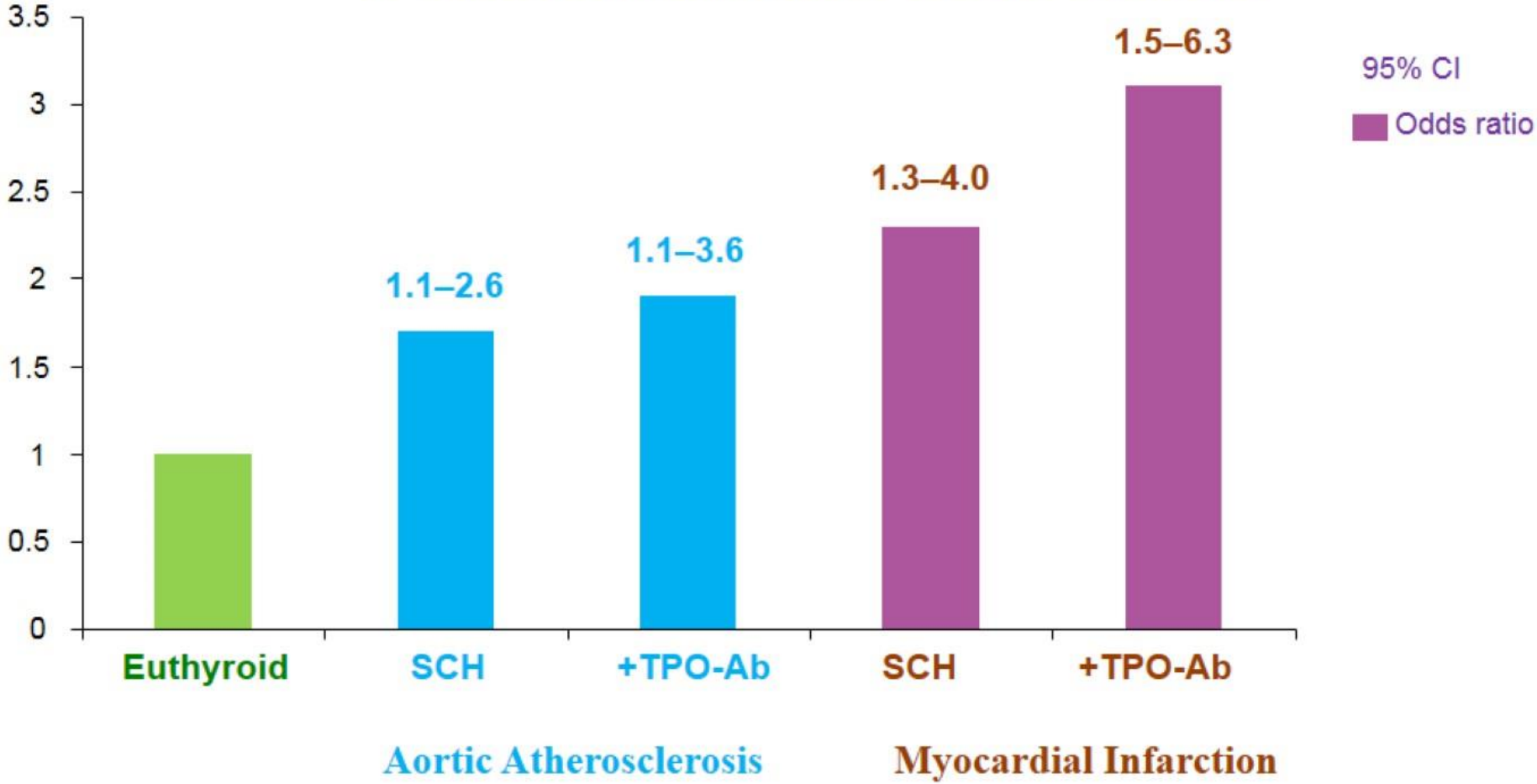
Subclinical Hypothyroidism
Progression to Overt Hypothyroidism

2.6% of patients each year **if** Anti-TPO Ab **are absent**

4.3% of patients each year **if** Anti-TPO Ab **are present**

Fatourechi V. *Mayo Clin Proc 2009;84:65-71*

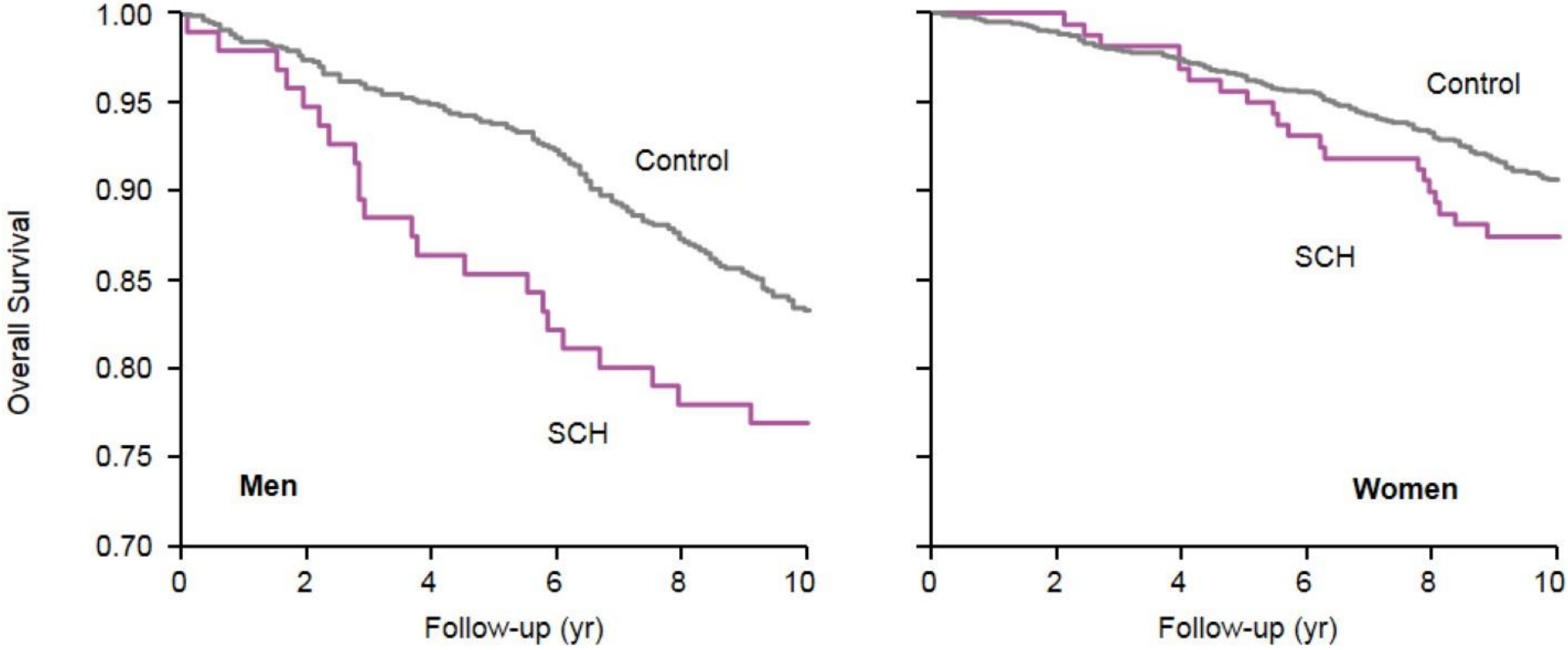
Subclinical Hypothyroidism a Cardiovascular Risk Factor



Subclinical Hypothyroidism is also associated with an increased risk of coronary heart disease

Rodondi N et al. *Am J Med* 2006;119:541–551
Hak AE, et al. *Ann Intern Med* 2000;132(4):270–278

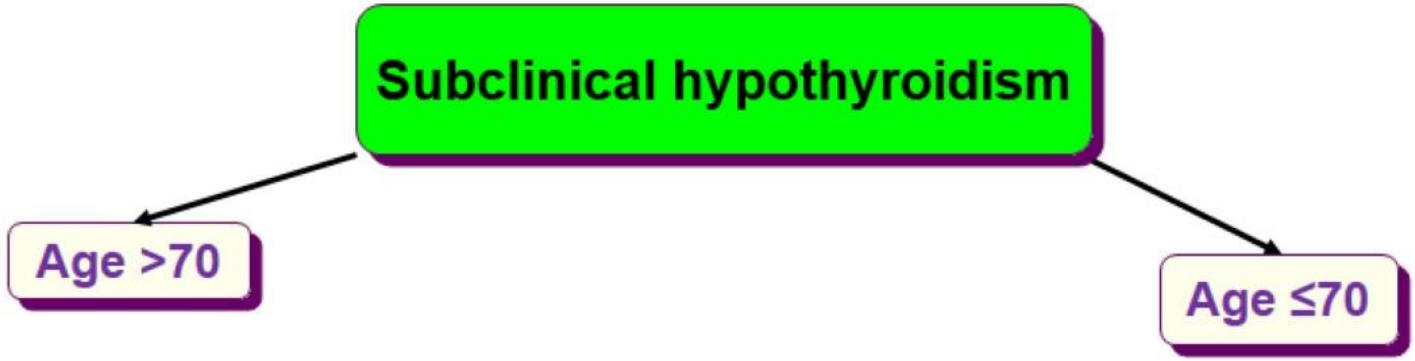
Subclinical Hypothyroidism
Mortality Due to Coronary Heart Disease



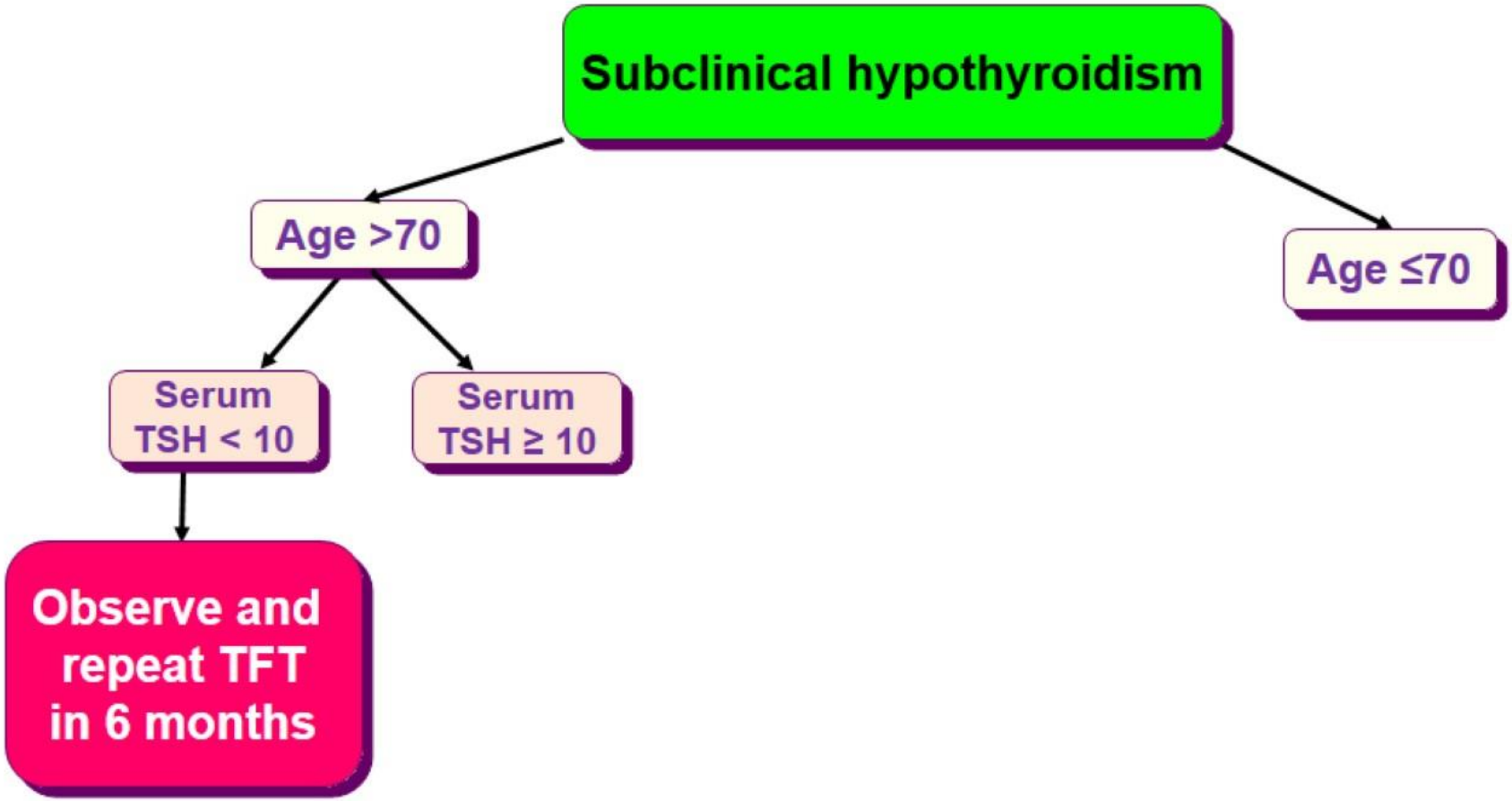
257 pts with SCH, TSH >5.0
2293 controls, TSH <5.0

Imaizumi M. *J Clin Endocrinol Metab* 2004;89:3365–3370

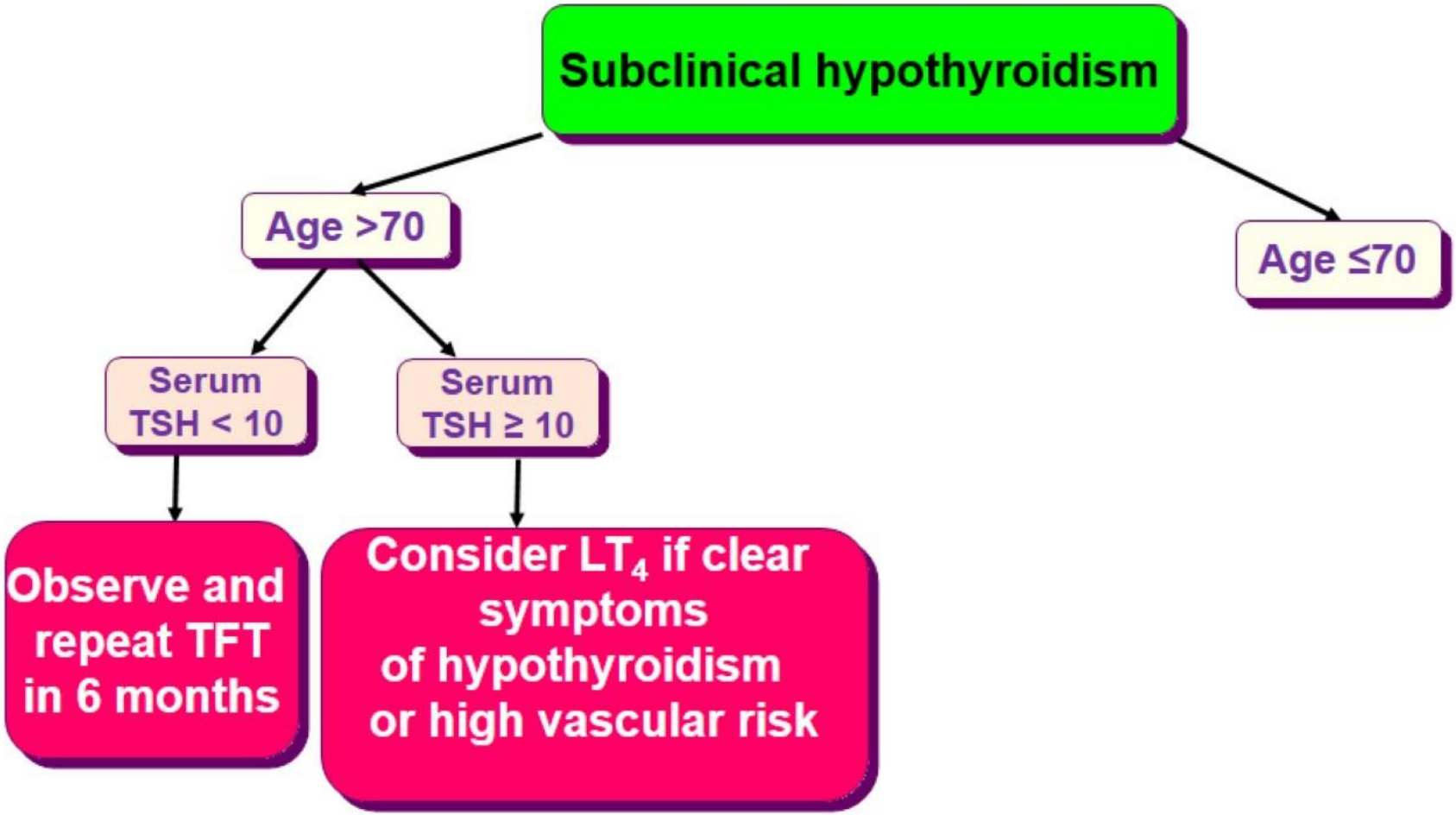
Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



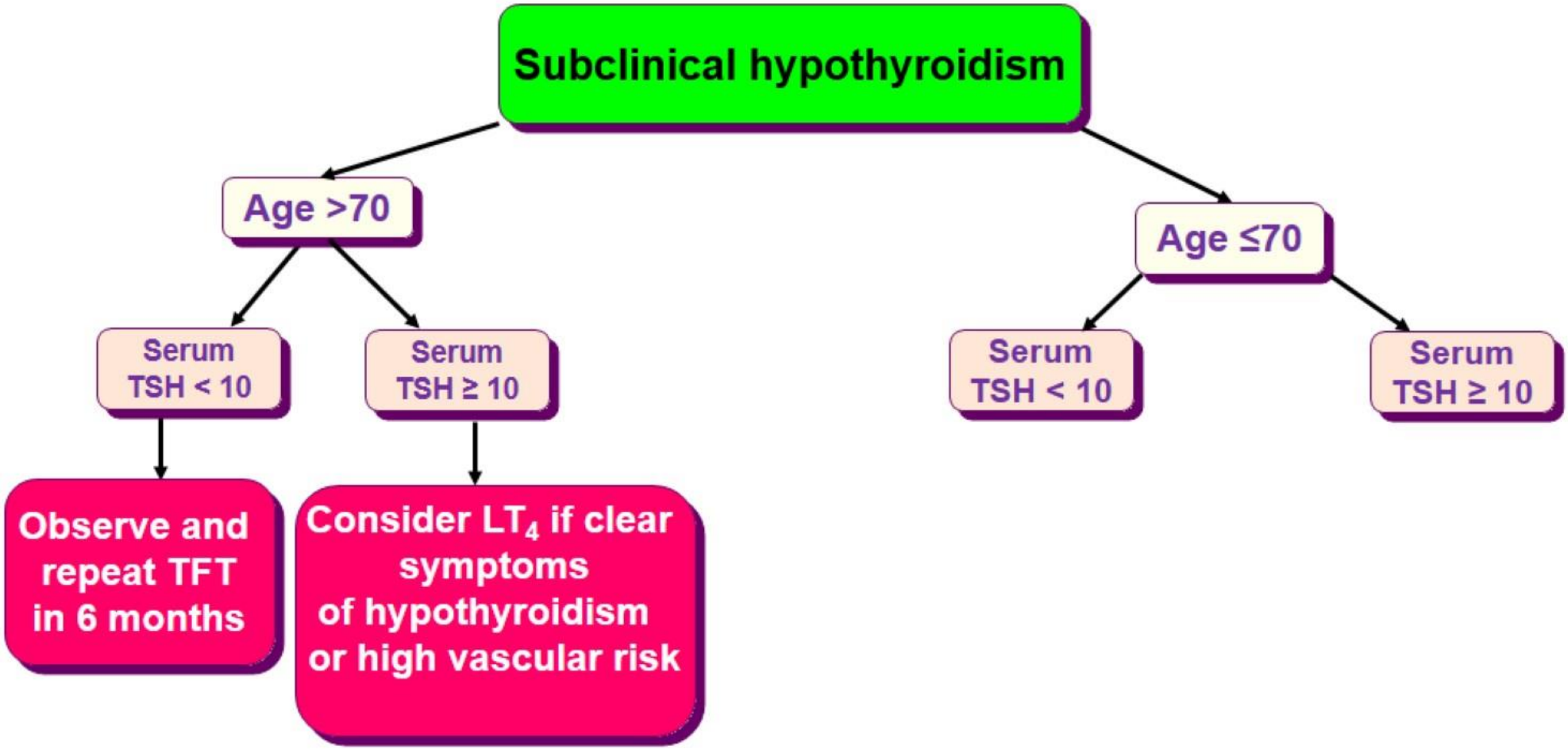
Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



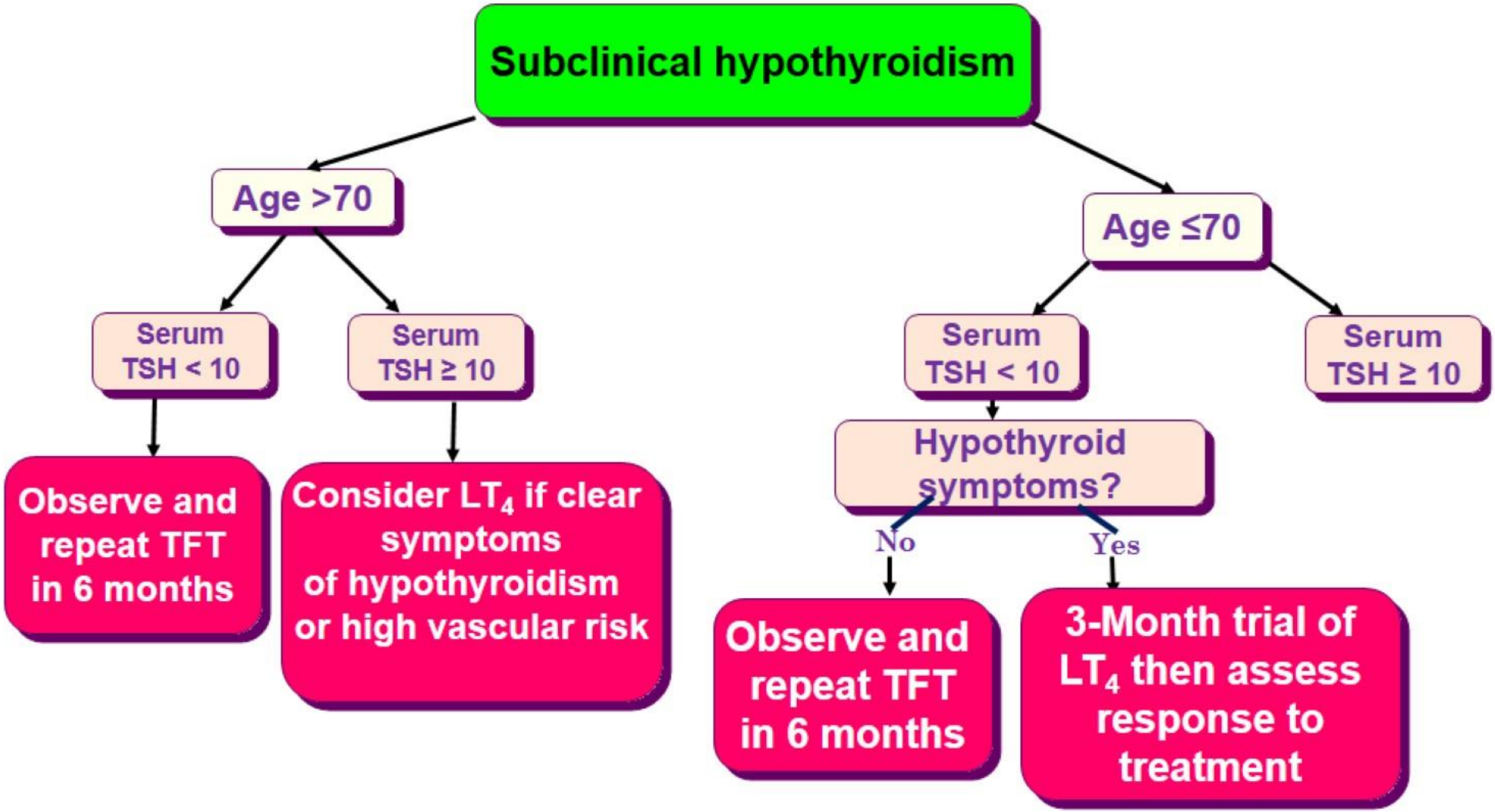
Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



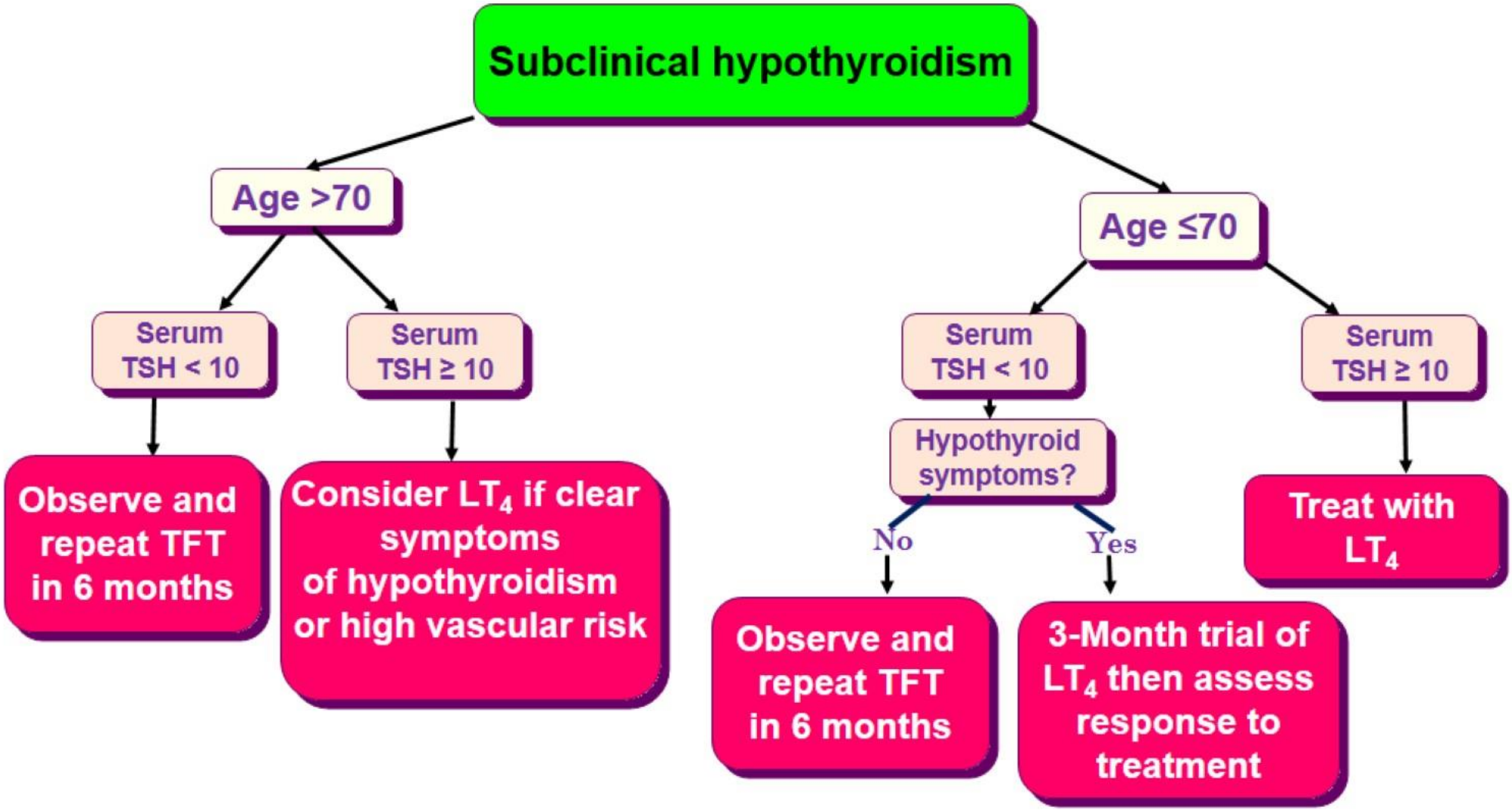
Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



Subclinical Hypothyroidism Recommendations for Therapy ETA Guidelines 2013



To Treat or Not to Treat Subclinical Hypothyroidism, What Is the Evidence?

- In subclinical hypothyroidism with TSH >10 mIU/L, treatment is indicated.
- In milder subclinical hypothyroidism, a **wait-and-see** strategy is advocated to see if normalization occurs.
- However, individuals with **cardiovascular risk** and subclinical hypothyroidism may benefit from levothyroxine treatment.

Medicina (Kaunas). 2020 Jan; 56(1): 40.

Hypothyroidism

and

Subclinical Hypothyroidism

In pregnancy

Euthyrox®

Prevalence

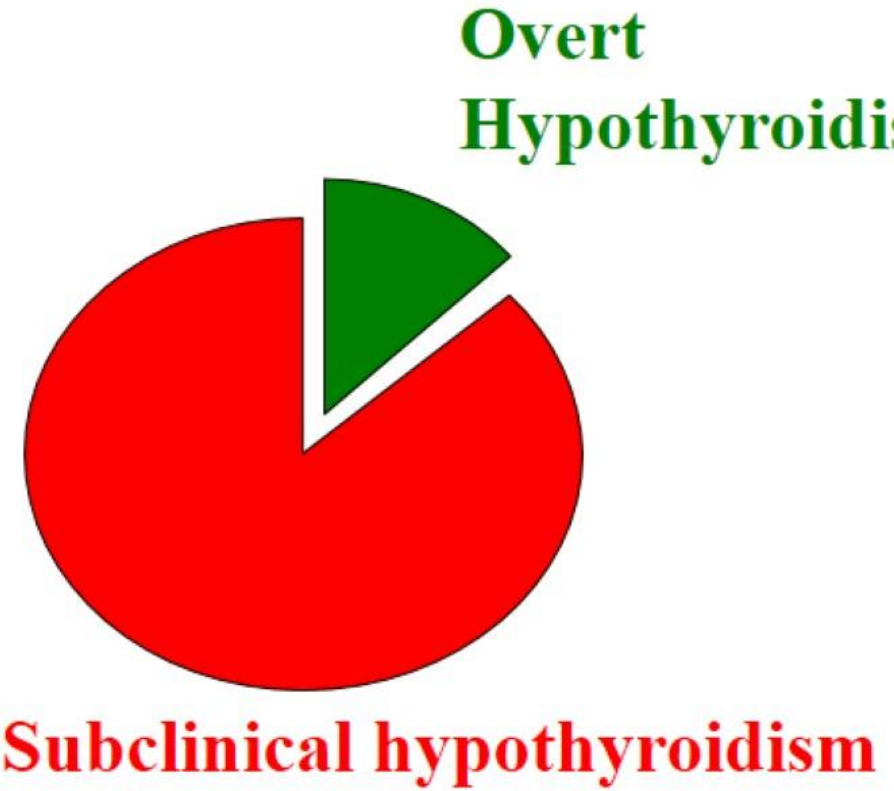
Overt hypothyroidism complicating pregnancy is unusual (0.3 to 0.5 percent of screened women).

Subclinical hypothyroidism is far more common than overt hypothyroidism, occurring in 2 to 2.5 percent of screened women. Although in China the incidence has been reported to be 4.0%, in Belgium 6.8% and in Northern Spain as high as 13.7%.

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

How common is hypothyroidism during pregnancy?

- Up to **3%** of pregnancies are complicated by hypothyroidism
- Most cases (**2.0–2.5%** of all pregnancies) are due to subclinical hypothyroidism
- **0.3–0.5%** of cases are due to overt hypothyroidism



Männistö T. Expert Rev Endocrinol Metab 2013;8:537-47.

Overlapping Complaints

Symptoms	Hypothyroidism	Pregnancy
Fatigue	✖	✖
Constipation	✖	✖
Hair Loss	✖	
Dry Skin	✖	
Brittle Nail	✖	
Weight Gain	✖	✖
Fluid Retention	✖	✖
Bradycardia	✖	
Carpel Tunnel Syndrome	✖	✖

Adverse Outcomes Of Maternal Hypothyroidism

MATERNAL DISORDERS

- Abortion
- Gestational hypertension
- Increased cesarean section
- Anemia
- Placental abruption
- Preterm labor
- Postpartum hemorrhage
- Gestational diabetes

FETAL DISORDERS

- Premature birth
- Fetal and perinatal death
- Disorders of brain development
- Low IQ Scores
- Fetal respiratory distress
- Low birth weight
- Cretinism

Adverse Effects of SCH on Mother and Child

- Pre-eclampsia
- Gestational hypertension
- Preterm labor
- Gestational diabetes
- Low-birth-weight
- Pregnancy loss
- Fetal death

Screening for Thyroid Hypo function in Pregnancy

The American Thyroid Association and the American Endocrine Society guidelines recommends measurement of serum TSH in pregnant women if they are **symptomatic, from an area of known moderate to severe iodine insufficiency,** or **have a family or personal history of thyroid disease, type 1 diabetes, history of miscarriage, preterm delivery, infertility, TPO antibodies, history of head and neck radiation** or **obesity.**

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

All current recommendations support a **targeted screening strategy,** but such a strategy may miss **at least from 33 to 81%** of women with hypothyroidism.

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

Therefore some endocrinologists have argued for **universal screening** for thyroid dysfunction in pregnant women or those planning to become pregnant.

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

Because maternal hypothyroidism may both adversely affect fetal neural development and be associated with adverse gestational outcomes (miscarriage, preterm delivery), thyroid function should be monitored to preserve euthyroidism in women **with a history or high risk** of hypothyroidism.

پیشنهادات انجمن غدد ایران در هیپوتیروئیدی تحت بالینی خانمهای باردار

شواهدی به نفع یا به ضرر توصیه به اندازه گیری TSH قبل از بارداری برای عموم زنان وجود ندارد و فقط در زنان با ریسک بالا باید انجام شود.

در مورد غربالگری بیماری تیروئید در خانم 20 ساله که قصد حامله شدن دارد همه موارد زیر صحیح است بجز؟

الف: اگر وی سابقه سقط های مکرر داشته باشد باید TSH اندازه گیری شود.

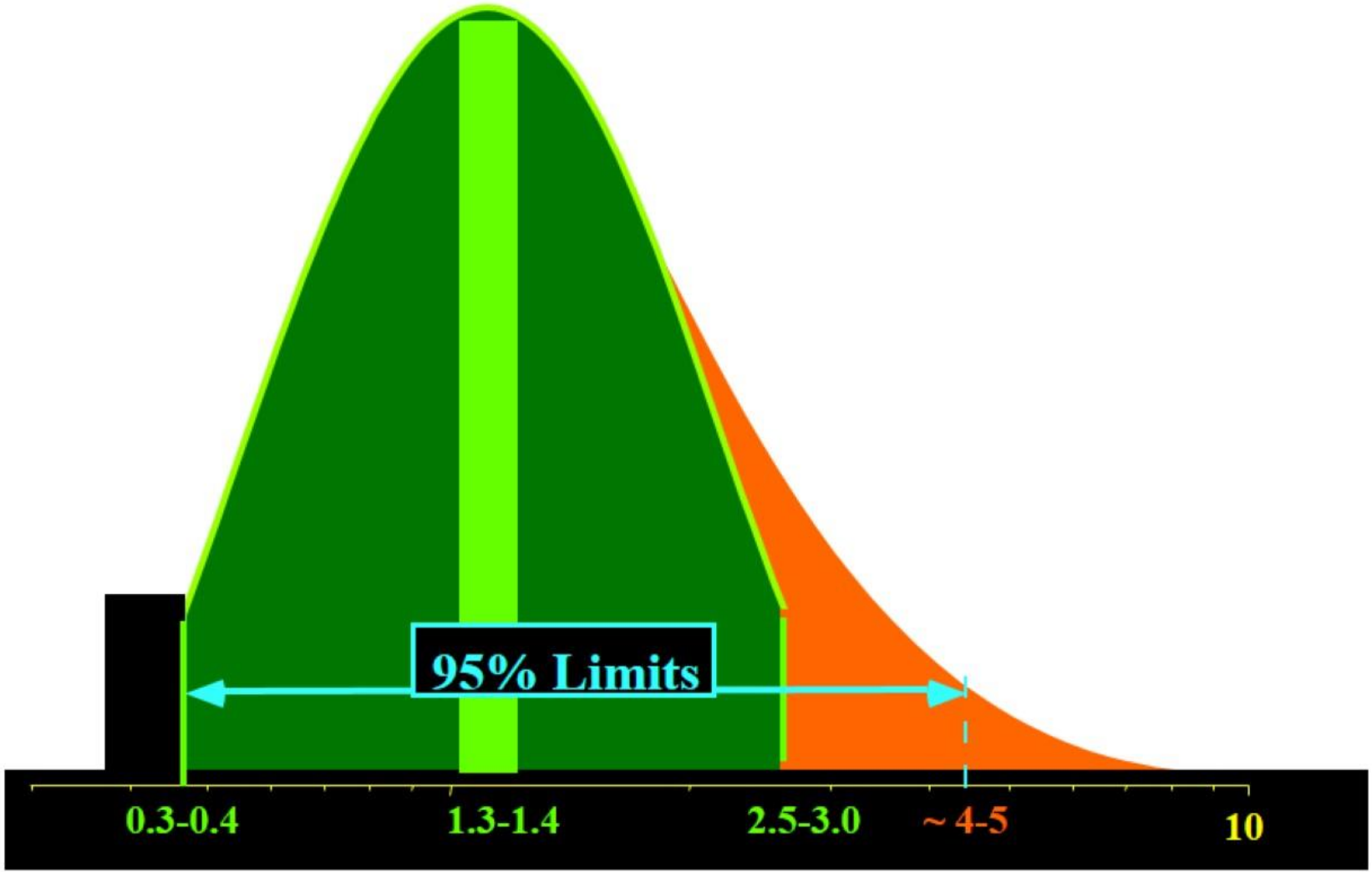
ب: اگر وی سابقه نازایی داشته باشد باید TSH اندازه گیری شود.

ج: اگر وی سابقه بیماری تیروئید داشته باشد باید TSH اندازه گیری شود.

د: در همه خانمها قبل از حاملگی باید TSH اندازه گیری شود.

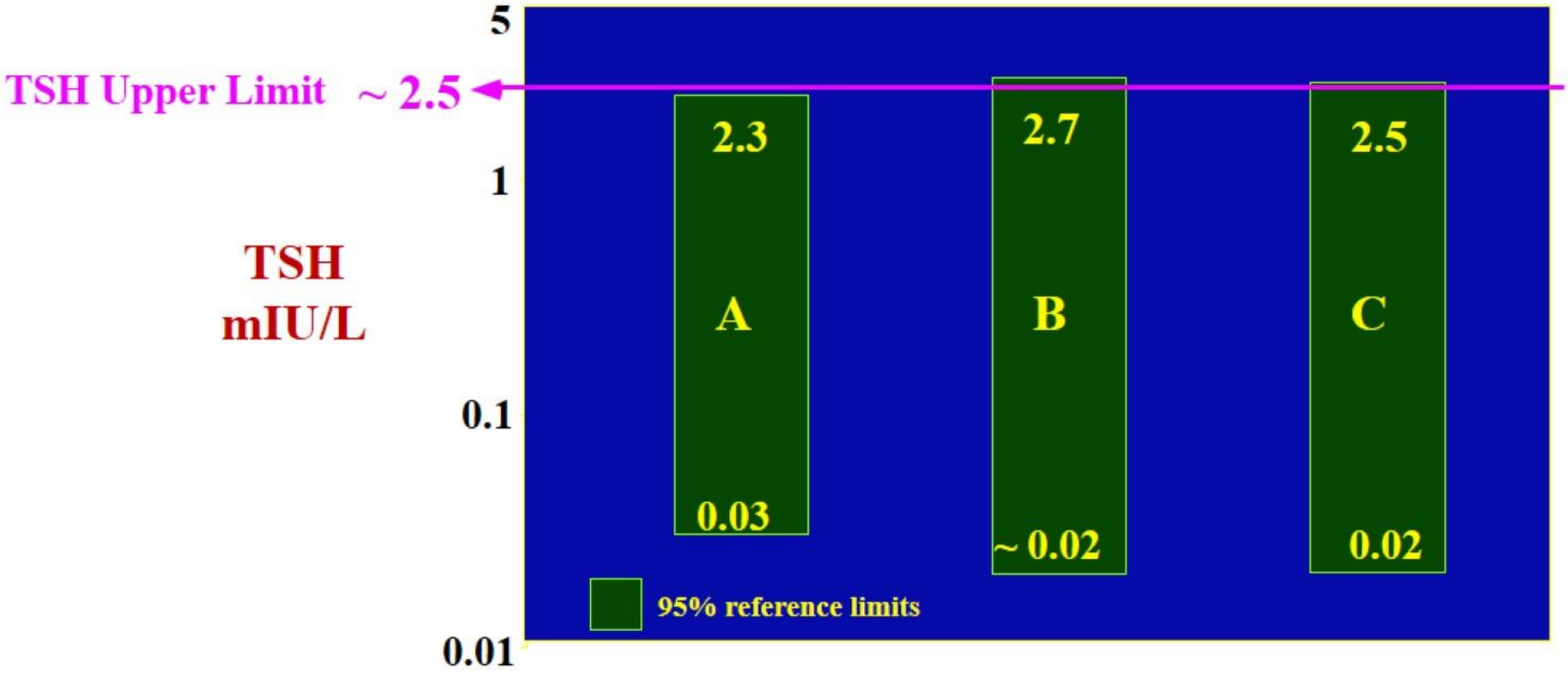
Diagnosis of SCH in Pregnancy

TSH Population Reference Range



TSH mIU/L

1st trimester TSH norms during pregnancy



A n = 343 (Hong Kong) Panesar et al Ann Clin Biochem 38:329, 2001

B n = 17,298 (USA) Casey et al Obstet Gynecol 105:239, 2005

C n = 115 Mestman (USA) ITC, Buenos Aires, Argentina, 10/2005

American Thyroid Association and the **American Endocrine Society** suggested the following reference range:

- First trimester, 0.1 to 2.5 mu/l
- Second trimester, 0.2 to 3.0 mu/l
- Third trimester, 0.3 to 3.0–3.5 mU/l

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

It is a matter of discussion whether these reference ranges should be used worldwide.

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

Recommendations

1- Trimester-specific reference ranges for TSH and T4 (total or free) should be established in each antenatal hospital setting.

2- If TSH trimester-specific reference ranges are not available in that laboratory, the following reference range upper limits are recommended: **first trimester**, 2.5 mU/l; **second trimester**, 3.0 mU/l; **third trimester**, 3.5 mU/l.

3- If TSH is elevated, **FT4 and TPOAb** should be determined.

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy

پیشنهادات انجمن غدد ایران در هیپوتیروئیدی تحت بالینی خانمهای باردار

محدوده طبیعی TSH در زنان باردار ایرانی:

- سه ماهه اول: ۳/۹ mu/l
- سه ماهه دوم و سوم : ۴/۱ mu/l

Maternal SCH and Child Cognition

Controlled Antenatal Thyroid Study (CATS)

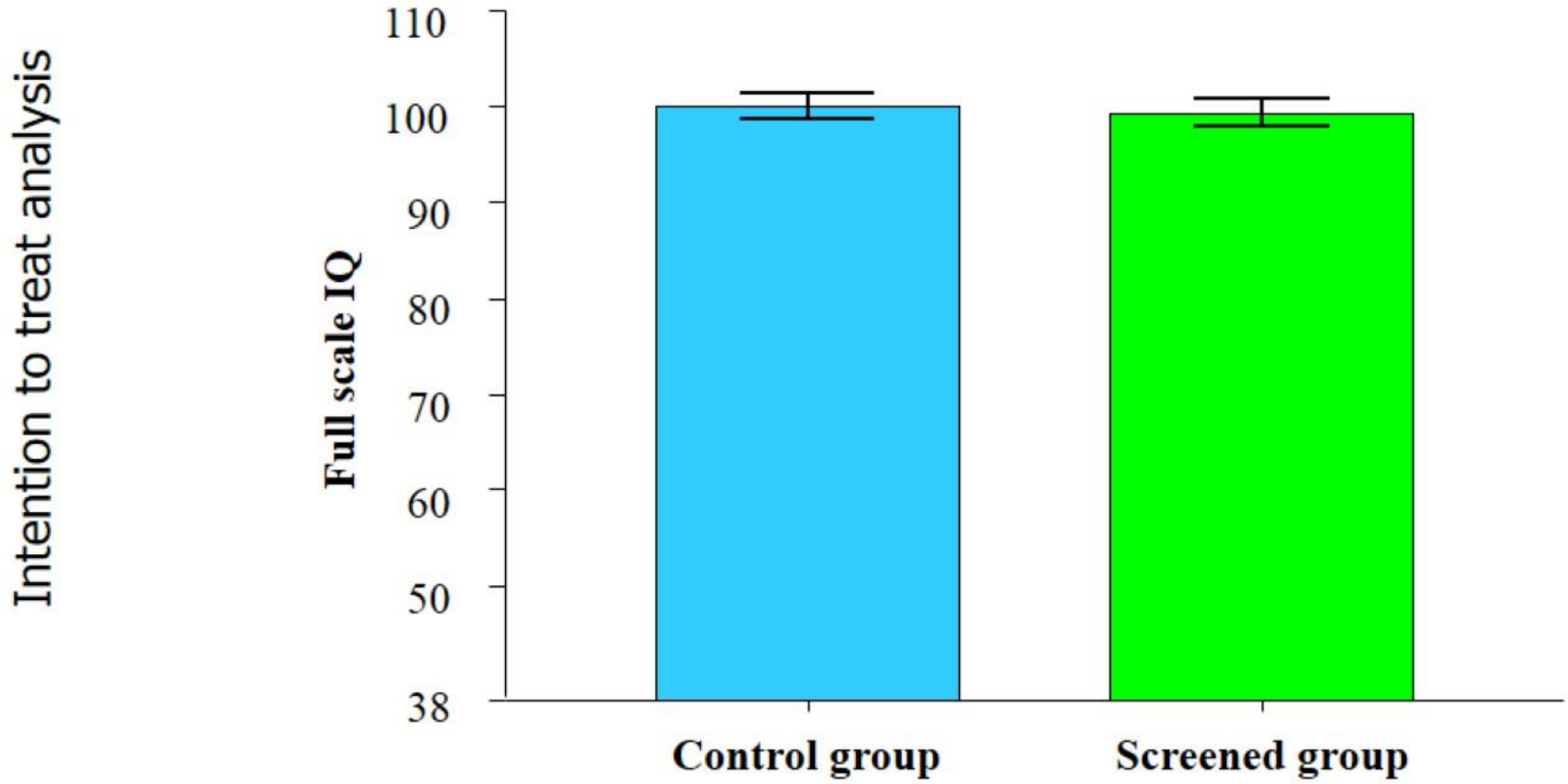
Effect of Treating Maternal Suboptimal Thyroid Function on Child Cognition

Large prospective randomized controlled trial of **L-thyroxine treatment** vs. **no treatment** in subclinical hypothyroid mothers starting in the 1st trimester.

Outcome: Maternal Levothyroxine during pregnancy did not improve child cognition at age 9.5 years.

JCEM 2018 Apr 1;103(4):1583-1591

CATS conclusion: No benefit of screening for hypothyroidism in pregnancy with respect to intellectual development of the child



From John Lazarus CATS PI

Subclinical hypothyroidism in pregnancy: intellectual development of offspring

Dr Azizi

IQ level and cognitive performance of children born to **Levothyroxin-treated hypothyroid** mothers is similar in those whose mothers have maternal **subclinical hypothyroidism** during pregnancy compared with those whose mothers have **normal serum TSH** concentrations during pregnancy.

Thyroid. 2011 Oct;21(10):1143-7

The association between **sub clinical hypothyroidism** in pregnancy and **impaired neuropsychological development** of the offspring is inconsistent.

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

Subclinical hypothyroidism and **thyroid autoimmunity** are not associated with fecundity, pregnancy loss, or live birth.

J Clin Endocrinol Metab, June 2016

Is subclinical hypothyroidism associated with infertility in women?

Levothyroxine treatment is recommended for infertile women with **overt hypothyroidism** who desire pregnancy.

Evaluation of serum TSH concentration is recommended for all women seeking care for **infertility**.

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

There is **insufficient evidence** to determine if levothyroxine therapy **improves fertility in subclinically hypothyroid**, Anti TPO - women who are attempting natural conception.

However, administration of levothyroxine may be considered in this setting given its ability **to prevent progression to more significant hypothyroidism** once pregnancy is achieved. Furthermore, **low dose levothyroxine** therapy (25-50 mcg daily) carries minimal risk.

The presence of thyroid autoantibodies alone, in a euthyroid patient, is also associated with **miscarriage** and **preterm delivery.**

Subclinical hypothyroidism in pregnancy should be approached as follows:

a) Levothyroxine therapy is recommended for

- TPO **antibody positive** women with a TSH greater than the pregnancy specific reference range.

- TPO **antibody negative** women with a TSH greater than 10.0 mU/L.

b) Levothyroxine therapy may be considered for:

- TPO **antibody positive** women with TSH concentrations > 2.5mU/L and below the upper limit of the pregnancy specific reference range.

- TPO **antibody negative** women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L.

c) Levothyroxine therapy is not recommended for:

- TPO **antibody negative** women with a normal TSH (TSH within the pregnancy specific reference range, or < 4.0 mU/L if unavailable).

پیشنهادات انجمن غدد ایران در هیپوتیروئیدی تحت بالینی

خانمهای باردار

با توجه به کمبود شواهد، توصیه ای به نفع و یا به ضرر درمان کم کاری تیروئید تحت بالینی در مادران با آنتی TPO منفی وجود ندارد. ولی در کم کاری تیروئید تحت بالینی در مادران با آنتی TPO مثبت درمان باید صورت گیرد.

خانم ۲۵ ساله ای که قصد حاملگی دارد به شما ارجاع شده است. نامبرده تا کنون حامله نشده است و سابقه بیماری خاصی را ذکر نمی کند. در معاینه تیروئید نرمال است. آزمایشات تیروئید وی بدین شرح میباشد:

TSH = 6.5 mIU/L (0.5 – 4.2) FT4 = 1 ng/dL (0.8 – 1.8)

Anti-TPO = 85 IU (0 – 35)

اقدام بعدی در وی کدام است:

الف: درمان با لووتیروکسین

ب: پیگیری بیمار بعد از حاملگی

ج: تجویز یدوفولیک

د: اقدام خاصی نیاز نمی باشد

پیشنهادات انجمن غدد ایران در هیپوتیروئیدی تحت بالینی

خانمهای باردار

شواهد کافی برای پیشنهاد یا مخالفت با درمان توسط لووتیرکسین

در مادران Euthyroid با آنتی TPO مثبت وجود ندارد.

Is there an association between thyroid antibodies and sporadic spontaneous pregnancy loss in euthyroid women?

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

Patients who were positive for TPOAb demonstrated a **two-fold increase** in the risk for pregnancy loss (17 % vs. 8.4 %, p=0.01)

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

Is there an association between thyroid antibodies and recurrent spontaneous pregnancy loss in euthyroid women?

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In a case-control study reported that patients with recurrent pregnancy losses (3 or more) had a **higher incidence of TPOAb positivity**.

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

خانم ۲۸ ساله ای با سقط های مکرر و آزمایشات زیر مراجعه کرده است.

TSH = 2.3 mIU/L (0.5 – 4.2) FT4 = 0.9 ng/dL (0.8 – 1.8)

Anti-TPO = 585 IU (0 – 35)

اقدام بعدی کدام است؟

الف: تجویز IVIG

ب: تجویز کورتون

ج: تجویز لووتیروکسین

د: تجویز ید

Does treatment with Levothyroxin or IVIG decrease the risk for pregnancy loss in euthyroid women with thyroid autoimmunity?

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

Intravenous immunoglobulin treatment of euthyroid women with a history of recurrent pregnancy loss **is not recommended.**

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum.

There is **insufficient evidence** to conclusively determine whether **levothyroxine** therapy decreases pregnancy loss risk in **TPOAb positive**, euthyroid women who are **newly pregnant.**

However, administration of levothyroxine to TPOAb positive, euthyroid pregnant women with a **prior history of loss** may be considered given its potential benefits in comparison to its minimal risk. In such cases, 25-50 mcg of levothyroxine is a typical starting dose.

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Treatment

If the hypothyroidism is apparent **prior to pregnancy**, it should be **corrected before conception**.

If discovered **during pregnancy**, treatment with levothyroxine should be started **as soon as possible**.

In a **hypothyroid patient** on substitutive treatment before conception, a **25–50% increase in levothyroxine** dosage is required.

Pregnant women not on Levothyroxine before pregnancy

First trimester TSH > 2.5 mIU/L (especialy if Anti TPO +) → Levothyroxine

First trimester TSH 2.5 - 5 mIU/L → Start Levothyroxine 50 µ / day

First trimester TSH 5 - 8 mIU/L → Start Levothyroxine 75 µ / day

First trimester TSH > 8 mIU/L → Start Levothyroxine 100 µ / day

Monitoring TSH during pregnancy

During pregnancy: Each 4 weeks until 16-20 weeks gestation.

At least once between 26-32 weeks gestation.

Following delivery the levothyroxine dose should be reduced to the preconception dose. Women diagnosed with SCH during pregnancy with **TSH less than 5 mU/l and negative TPOAb** could stop levothyroxine after delivery and have thyroid function checked **6 weeks after delivery**.

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