
بسم الله الرحمن الرحيم

HYPOTHYROIDISM IN PREGNANCY

دکتر سید محمود میرحسینی

فوق تخصص غدد و متابولیسم

دانشیار دانشگاه علوم پزشکی شهرکرد

INTRODUCTION

- ***Diagnosis of thyroid disease during pregnancy requires an understanding of changes in thyroid physiology and TFTs that accompany normal pregnancy.***

- ***To meet increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered TFTs.***

- ***The major changes in thyroid function during pregnancy are:***

- ***I) Thyroxine-binding globulin (TBG):***
- ***During pregnancy, serum TBG rises ~ 2-fold because estrogen:***

  1) increases hepatic TBG production, and

  2) increases TBG sialylation which results in decreased clearance of TBG.

- ***In the setting of increased TBG, for maintenance of adequate free T3 and T4, thyroidal T4 and T3 production must be increased.***

- ***<u>TBG excess</u> leads to an increase in serum total T4 and T3 levels (but not free ones).***

- ***Levels of total T4 and T3 rise by ~ 50% during the 1st half of pregnancy, plateauing at ~ 20 weeks of gestation, at which time a new steady state is reached.***

- ***II) hCG is a member of glycoprotein hormones, (TSH, FSH, LH, hCG) with a common α-subunit and a unique β-subunit.***

- ***There is considerable structural homology between β-subunits of hCG and TSH, as a result, hCG has weak thyroid-stimulating activity (~1% of TSH activity).***

- ***Serum hCG increase soon after fertilization and peak at 10-12 weeks (2nd half of 1st trimester).***

- ***During this peak, free T4 and free T3 increase slightly, and TSH are appropriately reduced (all usually within the normal ranges), however, in 10-20% of pregnant women, TSH are transiently low (transient subclinical hypothyroidism [SCH]), this transient SCH, should be considered a normal physiologic finding.***

- ***In late pregnancy, as hCG declines, free T4 and free T3 decline and TSH normalizes.***

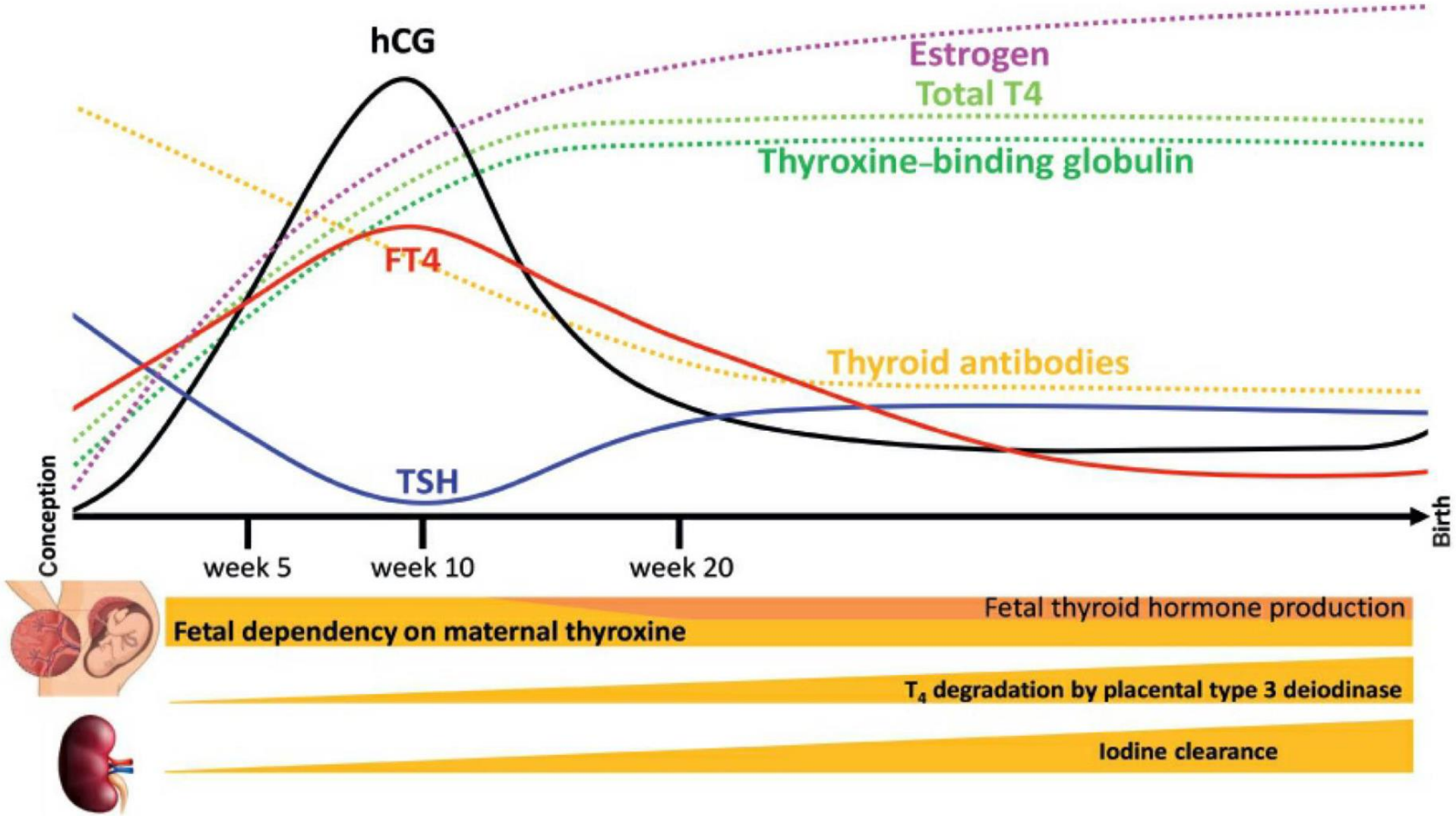


FIGURE 66-3. Shows the changes in thyroid physiology during pregnancy.

❖ *Trimester-specific reference ranges:*

- ***Because of changes in thyroid physiology, ATA guidelines use trimester-specific reference ranges for TSH and free T4.***

- ***Unfortunately, many laboratories currently do not provide these reference ranges.***

- ***When trimester-specific reference ranges for free T4 are not available, measurement of total T4 may be superior to free T4.***

FETAL THYROID FUNCTION

- During the 10-12 week of gestation, fetal serum TSH appears, and fetal thyroid is capable of concentrating iodine and synthesizing iodothyronines (MIT and DIT).

- Little fetal T4 and T3 synthesis occurs until 18-20 week, thereafter, fetal thyroid hormone secretion increases gradually.

- As such, maternal thyroid hormones are critical for growth and development during this priod.

ETIOLOGY

- In the absence of iodine deficiency, the most common cause of hypothyroidism during pregnancy is chronic autoimmune (Hashimoto's) thyroiditis.

- Other causes of hypothyroidism, such as:

  1) prior radioiodine ablation,

  2) prior total thyroidectomy, or

  3) disorders of pituitary or hypothalamus, can also occur in pregnant women.

CLINICAL FEATURES

- ***Clinical symptoms of hypothyroidism during pregnancy is similar to those that occur in nonpregnant patients (eg, fatigue, constipation, weight gain).***

- ***Hypothyroid symptoms may be attributed to pregnancy itself because some of symptoms of hypothyroidism are similar to those of pregnancy (although cold intolerance is not a normal clinical manifestation of pregnancy).***

- ***Many patients are asymptomatic.***

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Intellectual disability (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

LABORATORY FINDINGS

- ***If laboratory does not provide trimester-specific reference ranges for TSH, an upper reference limit of 4 mU/L can be used.***

- ***If trimester-specific reference ranges for free T4 is not available, measurement of total T4 may be superior to free T4, especially in the 2nd and 3rd trimesters.***

- ***Total T4 is 1.5-fold higher than in nonpregnant women.***

THYROID ANTIBODIES

- ***Thyroid peroxidase (TPO) antibodies are elevated in 30-60% of pregnant women with an elevated TSH.***

- ***Pregnant women who have SCH with positive TPO antibodies have higher risk of pregnancy complications and adverse outcomes occur at lower TSH than in those who are TPO antibodies-negative.***

- ***According to 2017 ATA guidelines, if serum TSH is >2.5 mU/L, TPO antibodies should be measured to inform treatment decision.***

- ***TPO antibody positivity may increase risk of:***
  - ***1) abortion, and***
  - ***2) premature delivery.***
- ***Certainly, the most known complication of TPO antibody positivity is postpartum thyroiditis.***
- ***TPO antibody positivity is NOT a contraindication to becoming pregnant.***
- ***Immunosuppressive treatment (eg, glucocorticoids and IVIG) has no persistent effect on lowering serum TPO antibody and is NOT recommended.***

DIAGNOSIS

- ***Diagnosis** of hypothyroidism during pregnancy is based upon **elevated TSH** using **trimester-specific TSH reference ranges**.*

- *Many centers use **upper normal limits** for TSH of **2.5** mU/L in the **1st trimester** and **3** mU/L in the **2nd** and **3rd trimesters**, these cutoffs may be **too low** and lead to considerable **overdiagnosis**.*

- *For women in the **1st trimester** with a **TSH above trimester-specific upper limit of normal** **or** **>4** mU/L when trimester-specific reference ranges are **not available**, it is recommended to **measure free T4** **or** **total T4**, if trimester-specific reference range for **free T4 is not provided**.*

PREGNANCY COMPLICATIONS

- ***Hypothyroidism can have adverse effects on pregnancy outcomes, depending upon the severity of biochemical abnormalities:***

  1) Overt hypoglycaemia (OH),

  2) SCH, and

  3) Isolated hypothyroxinemia (normal TSH with low free T4/total T4).

- ***Overt hypothyroidism in pregnancy is uncommon (0.3-0.5% of screened women), whereas SCH is more common than OH (2-2.5% of screened women).***

- ***Overt hypothyroidism** has been associated with an increased risk of several complications, including:*

  1) Preeclampsia** and **gestational hypertension

  2) Placental abruption

  ***3) Preterm delivery**, including **very preterm delivery** (**before 32 weeks**)*

  4) Low birth weight

  5) Increased rate of cesarean section

  6) Postpartum hemorrhage

  7) Perinatal morbidity** and **mortality

  ***9) Neuropsychological** and **cognitive impairment** in the child (up to 7-point lower child IQ).*

- ***Risk of complications during pregnancy is lower in women with SCH.***

- ***In some, but not all studies, women with SCH were also reported to be at increased risk for:***

  1) severe preeclampsia,

  2) pregnancy loss (abortion).

  3) preterm delivery,

  4) placental abruption, and

  5) neonatal respiratory distress syndrome (NRDS).

- ***It is uncertain if children of pregnant women with SCH are at risk for neuropsychological impairment, however, some, but not all studies suggest an association between SCH and impaired cognitive development in children.***

- ***It is uncertain if levothyroxine replacement reduces risk of adverse pregnancy, neonatal, and childhood cognitive outcomes in pregnant women with SCH.***

Isolated Hypothyroxinemia

- The effects of isolated maternal hypothyroxinemia (normal TSH, low T4) on perinatal and neonatal outcome are unclear.

- The 2017 ATA guidelines recommend against routine treatment of isolated hypothyroxinemia.

SCREENING

- ***Because OH and SCH are associated with pregnancy complications and TFTs are widely available and easy to perform, there is interest in screening for thyroid dysfunction in asymptomatic pregnant women.***

- ***Because there are insufficient data showing benefit of levothyroxine replacement, universal screening of asymptomatic pregnant women during the 1st trimester is controversial, therefor, there is wide variation in screening practices.***

- ***Pregnant women with any of the following are candidates for screening (case finding):***

1) Living in an area of moderate to severe iodine insufficiency

2) Symptoms of hypothyroidism

3) Family or personal history of thyroid disease

4) TPO antibody positivity

5) Goiter

6) Age >30 years

7) Type 1 diabetes

8) Head and neck irradiation

9) Recurrent miscarriage/preterm delivery

10) Multiple prior pregnancies (two or more)

11) Class 3 obesity (BMI ≥40 kg/m2)

12) Infertility

13) Prior thyroid surgery

14) Use of amiodarone, lithium, or recent administration of iodinated radiologic contrast agents.

Approach to Screened Women

- In women who meet case-finding criteria, suggestion is to measure TSH during the 1st trimester as screening test for hypothyroidism:

- 1) If TSH is between trimester-specific lower limit of normal and 2.5 mU/L, most women require no further testing.

- 2) In women at high risk for developing hypothyroidism during pregnancy (post-radioiodine treatment, post-hemithyroidectomy, history of irradiation of head or neck), TSH should be reassess every 4 weeks during the 1st trimester, and then at least once during each of the 2nd and 3rd trimesters.

- ***3) If TSH is >2.5 mU/L, measure TPO antibodies because TPO antibody positivity may be useful for:***

  a) making decision about levothyroxine treatment in women with TSH 2.5-4 mU/L, and

  b) predicting development of hypothyroidism and pregnancy complications including postpartum thyroiditis.

- ***4) If TSH is >4 mU/L, measure free T4 to determine the degree of hypothyroidism (OH vs. SCH).***

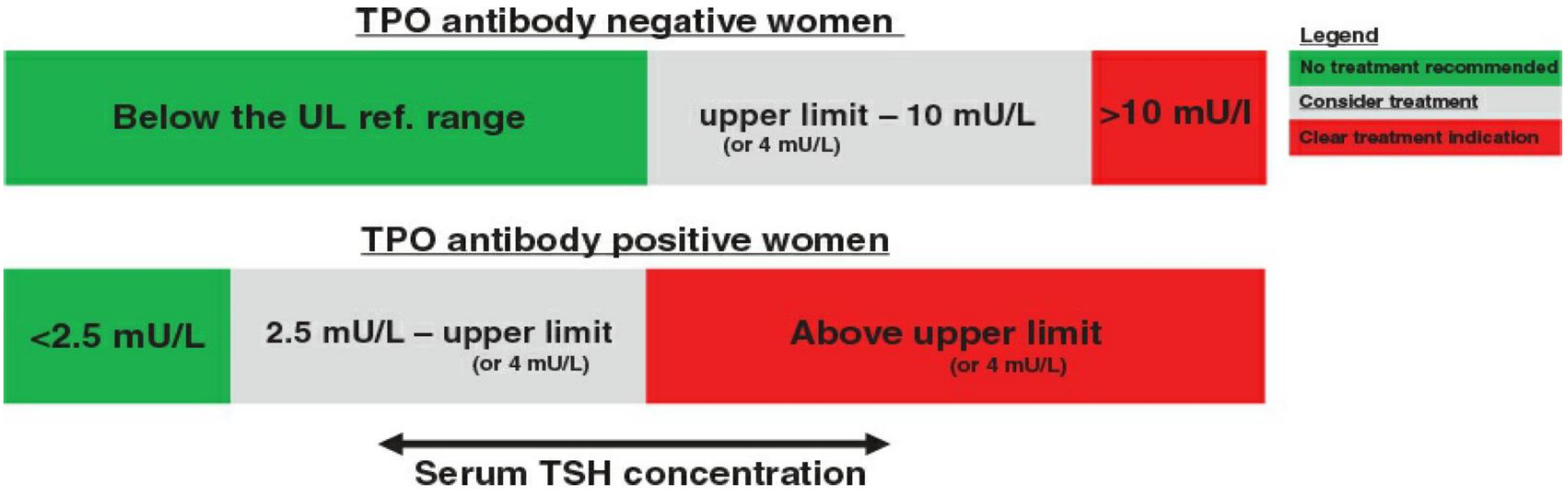


FIGURE 66-4. Shows a color-coded scheme for treatment recommendations based on TPOAb status and serum TSH concentration according to the 2017 ATA guidelines with *green* indicating no treatment indication, *yellow* indicating that treatment can be considered, and *red* indicating a clear treatment indication. (Based on Alexander E, Pearce E, Brett GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;27:315–389.)

Levothyroxine Initial Dosing

- ***Drug of choice for correction of hypothyroidism in pregnancy is synthetic levothyroxine.***

- ***The goal of levothyroxine replacement is to restore euthyroidism as soon as possible with target TSH <2.5 mU/L.***

- ***General initial levothyroxine dosing guidance:***
  - ***TSH >4 mU/L with low free T4: full replacement dose (~ 1.6 mcg/kg/day).***
  - ***TSH >4 mU/L, with normal free T4: Intermediate dose (~ 1 mcg/kg/day).***
  - ***TSH between 2.6-4 mU/L: if decision has been made to treat euthyroid women with positive TPO antibodies, low dose (typically 50 mcg/day).***
  - ***After starting levothyroxine, dose adjustment is done by measurement of TSH every 4 weeks until TSH becomes normal (<2.5 mU/L).***

- ***Another approach** is that hypothyroid women who are **newly pregnant** should **increase** their **levothyroxine dose** by **~ 30%**, it typically accomplish by increasing levothyroxine dose from **once-daily dosing** to a total of **9 doses/week (double daily dose 2 days each week)** and measure **TSH 4 weeks later**.*

Postpregnancy Levothyroxine Dose Adjustments

- Since treatment criteria for pregnant women with SCH differ from those for treating nonpregnant women, women who were started on levothyroxine for SCH do not need to continue levothyroxine treatment after delivery.

- After delivery, for women with OH, prepregnancy doses of levothyroxine are used and TSH is measured 4-6 weeks later to confirm that reduction was appropriate.

Preexisting Treated Hypothyroidism

- ***Women with preexisting hypothyroidism who are planning to become pregnant should optimize their levothyroxine dose before conception.***

- ***Preconception TSH goal is between lower reference limit and 2.5 mU/L, some experts prefer a lower preconception TSH level (<1.2 mU/L).***

- ***Approximately 50-85% (not all) of women with preexisting hypothyroidism need more levothyroxine during pregnancy.***

- ***Usual approach** is to measure TSH as soon as pregnancy is confirmed, then 4 weeks later, 4 weeks after any change in levothyroxine dose, and at least once in the 2nd and 3rd trimester.*

- ***Levothyroxine dose requirements** may increase by as much as 50% in midpregnancy, and increased need occurs as early as the 5th week of gestation.*

- ***Unlike normal women, those with preexisting OH or SCH may be unable to increase thyroidal T4 and T3 secretion appropriately.***

- ***This is especially true for athyreotic women (postradioiodine hypothyroidism or with history of total thyroidectomy who have NO residual functioning thyroid tissue).***

- ***Several factors are responsible for increased T4 requirement during pregnancy, they include:***

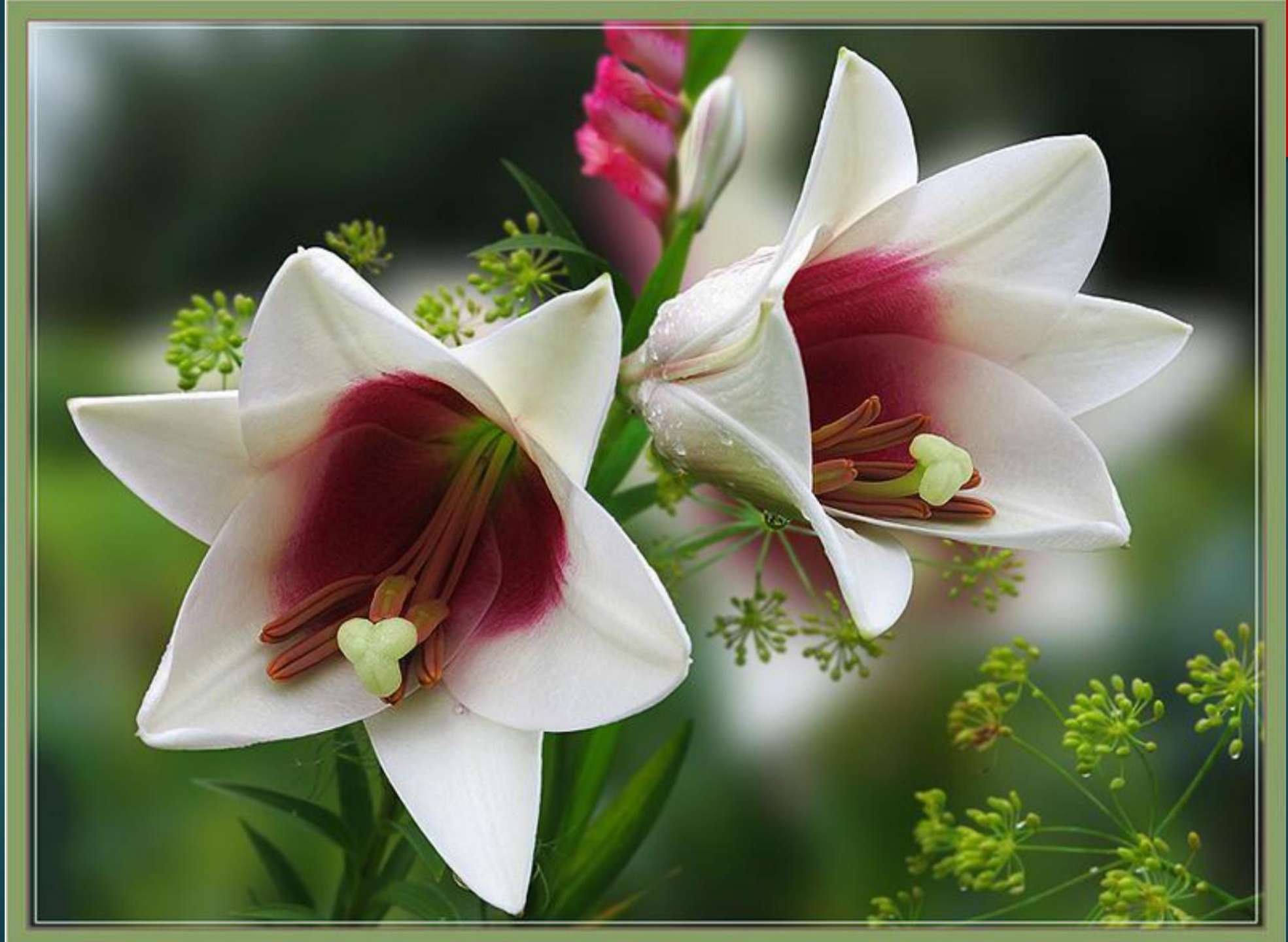
  1) weight gain and increased T4 pool size,

  2) high serum TBG levels,

  3) placental deiodinase (increases clearance of T4),

  4) transfer of T4 to fetus, and

  5) reduced intestinal absorption of levothyroxine due to iron in prenatal vitamin supplements.



Thank you for your attention and have a nice day