

Hypot  **yroidism**

&

Pre  **nancy**

The 2017 American Thyroid Association Guidelines for Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

An Expert Panel Discussion

Moderators

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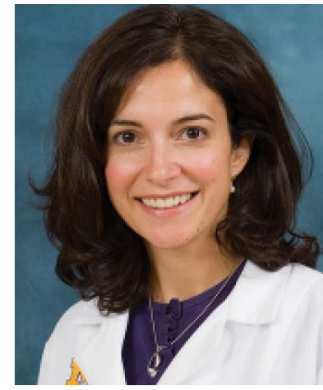
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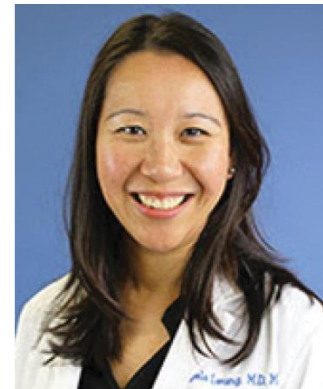
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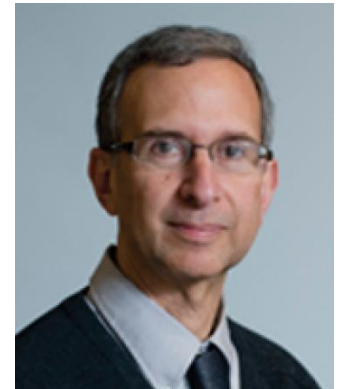
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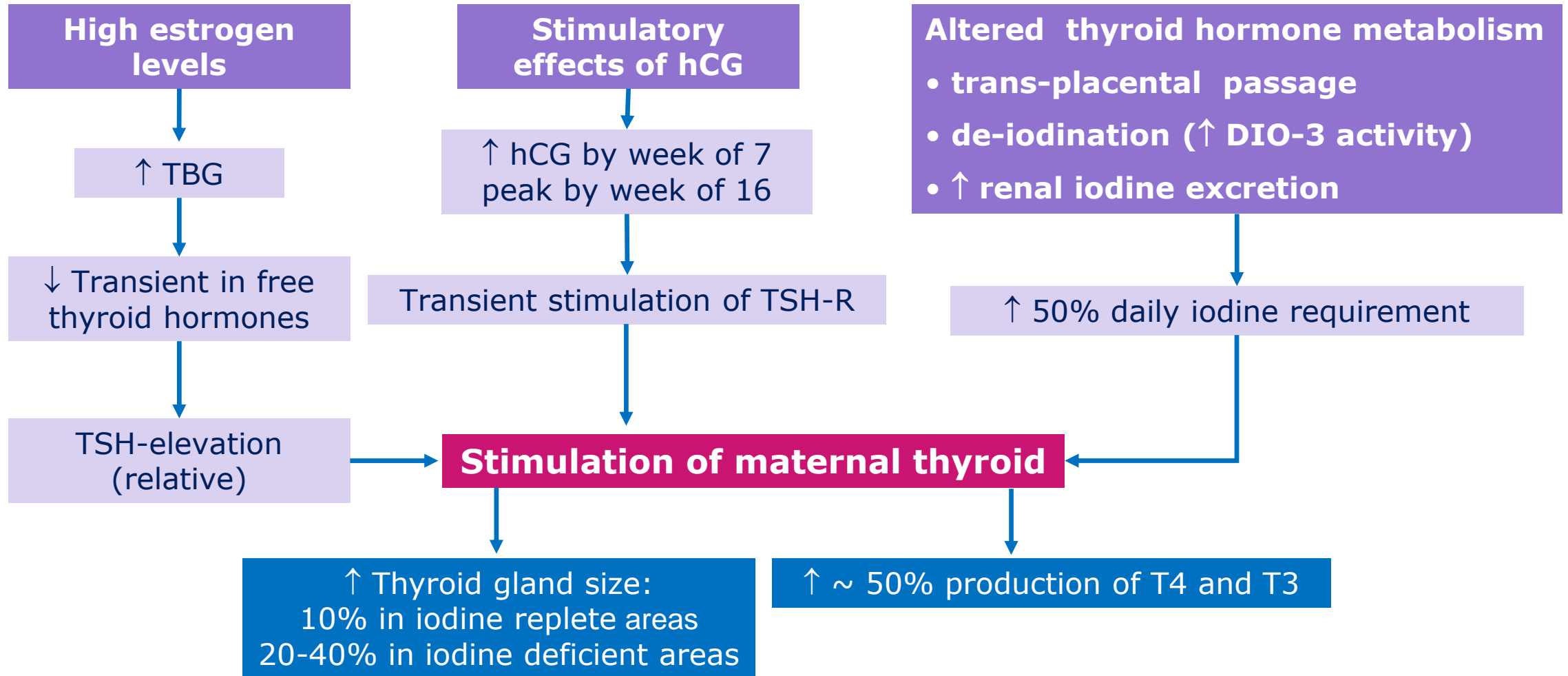


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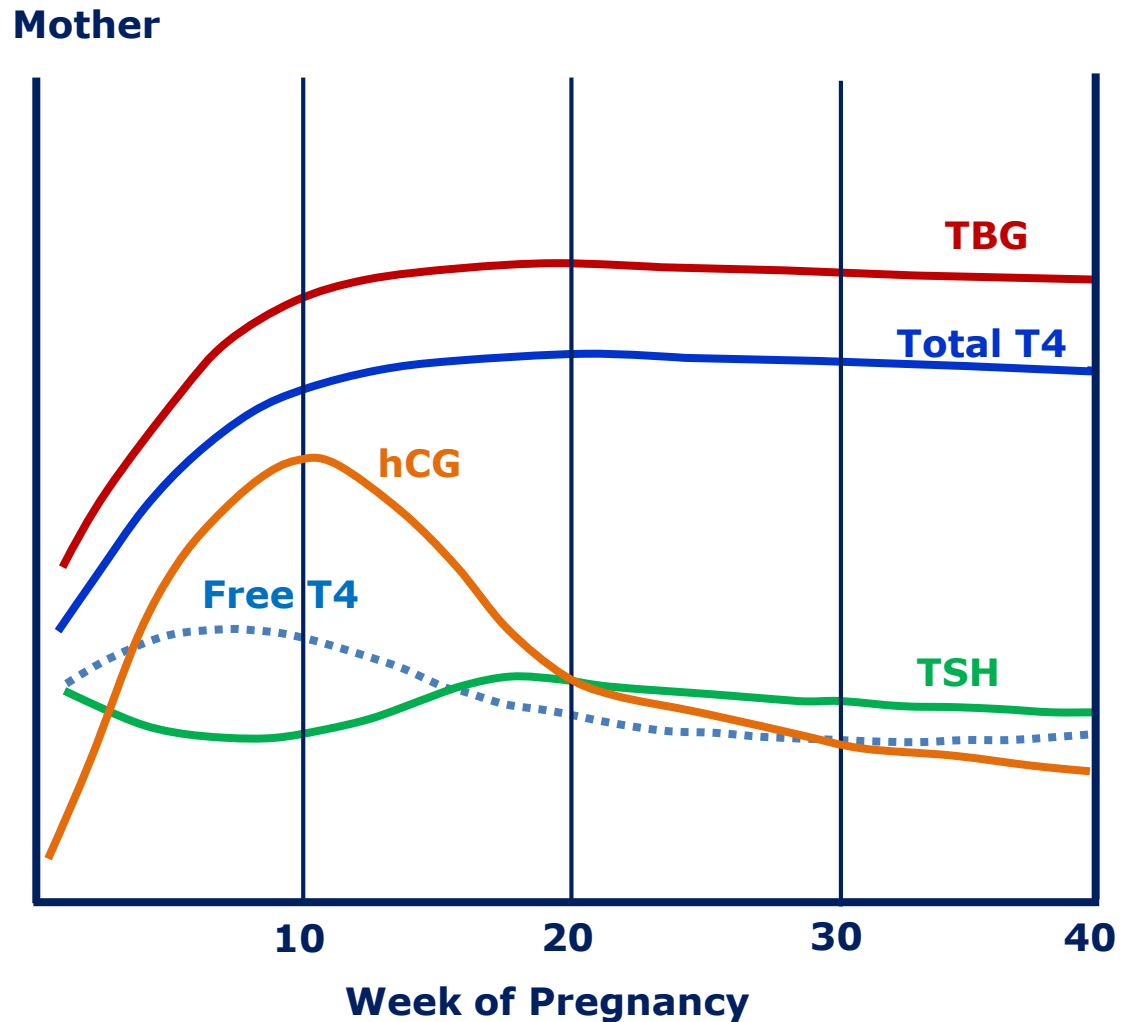


Dr. Douglas S. Ross

Thyroid adaption to pregnancy



Changes in thyroid physiology during pregnancy



Case 1

- 31 y/o women seeks your opinion for pre-pregnancy thyroid evaluation
- **PMHx:** regular menses with no prior pregnancy or infertility
- **FHx:** hypothyroidism in mother
- **P/E:** within normal limit



What of the following do you recommend?

A. TSH

B. TSH – FT4

C. TSH - T4 – T3RU

D. Anti TPO Ab and/or Anti Tg Ab

E. Anti TPO Ab and TSH

F. No need for thyroid function tests

31 y/o 

Hypo in
mother



Screening

What to do



Should women be universally tested for thyroid function before or during pregnancy?

Recommendation 96

- All pregnant women should be verbally screened at the initial prenatal visit for any Hx of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or anti-thyroid medications (MMI, CM, or PTU).

Strong recommendation, high-quality evidence

Should women be universally tested for thyroid function before or during pregnancy?

Recommendation 94

- Insufficient evidence to recommend for or against universal screening for abn TSH preconception, with the exception of women planning ART or known to have TPO Ab positivity.

No recommendation, insufficient evidence

Recommendation 93

- Insufficient evidence to recommend for or against universal screening for abn TSH in early pregnancy.

No recommendation, insufficient evidence

Should women be universally tested for thyroid function before or during pregnancy?

Recommendation 97

All patients seeking pregnancy, or newly pregnant, if **any of the following risk factors** are identified, **testing for serum TSH** is recommended:

1. Hx of hypo~/hyperthyroidism or current symptoms/signs of thyroid dysfunction
2. Known thyroid antibody positivity or presence of a goiter
3. Hx of head or neck radiation or prior thyroid surgery
4. Age >30 years
5. Type 1 diabetes or other autoimmune disorders
6. Hx of pregnancy loss, preterm delivery, or infertility
7. Multiple prior pregnancies (≥ 2)
8. F Hx of autoimmune thyroid disease or thyroid dysfunction
9. Morbid obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$)
10. Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
11. Residing in an area of known moderate to severe iodine insufficiency

Strong recommendation, moderate-quality evidence

Screening for thyroid dysfunction during pregnancy

Recommendation 8.3 a

- Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is not recommended.

USPSTF recommendation level: C; evidence, fair (2⊕000)

Case 1 - F/U after one year

- She has not conceived naturally
- She is asking ART for conception
- TSH: 1 mU/L
- Anti TPO Ab: 250 (nl<40)

32 y/o ♀

**Hypo in
mother**



What of the following do you recommend?

A. Low dose LT4

B. Low dose glucocorticoid

C. Low dose LT4 + glucocorticoid

D. Selenium supplement

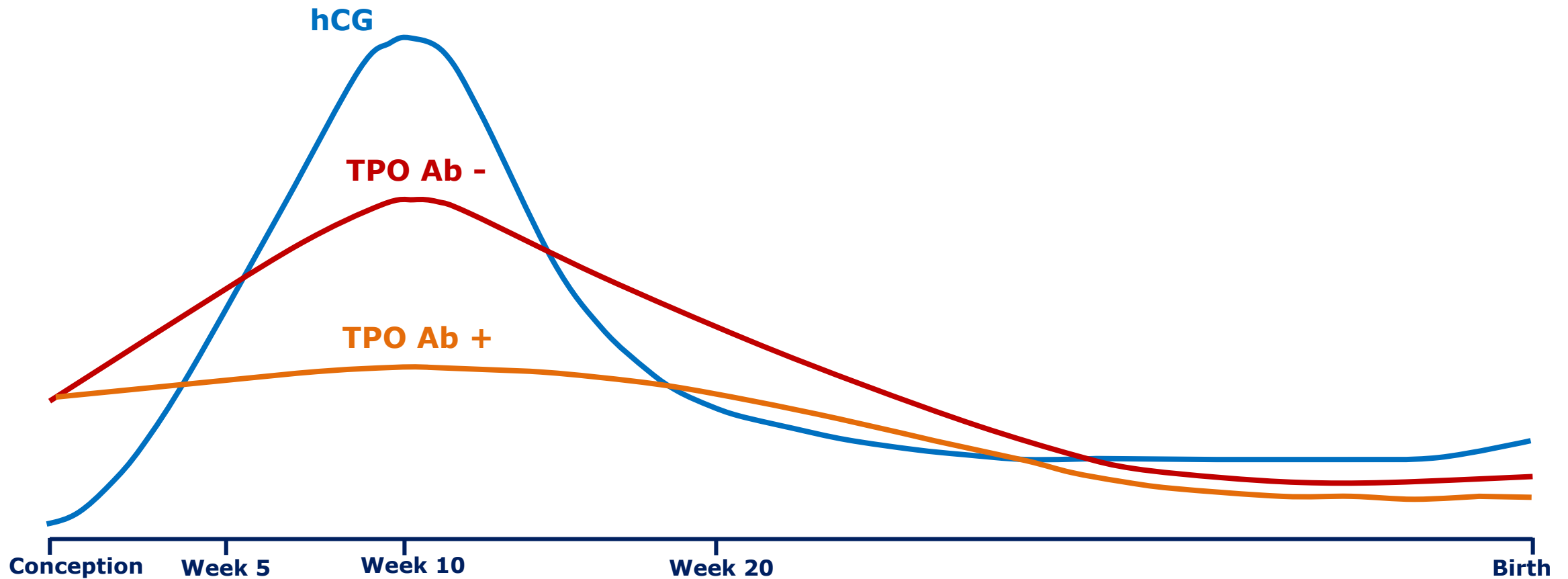
32 y/o 

Hypo in
mother

TSH: 1
Anti TPO +

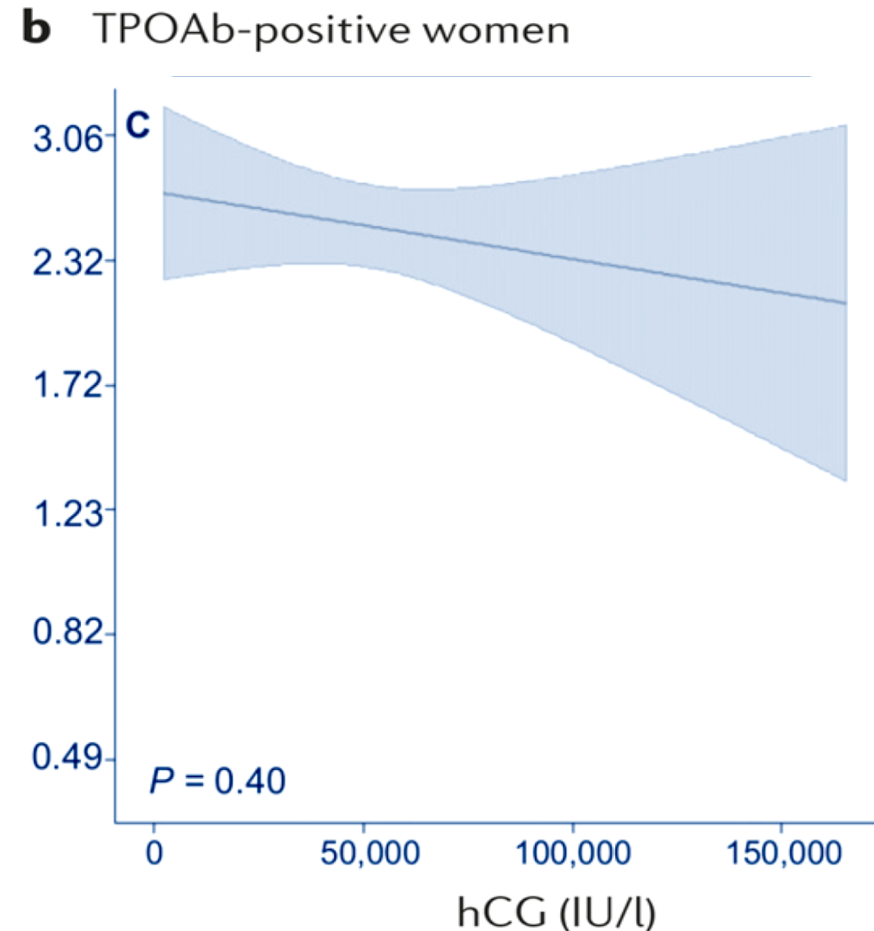
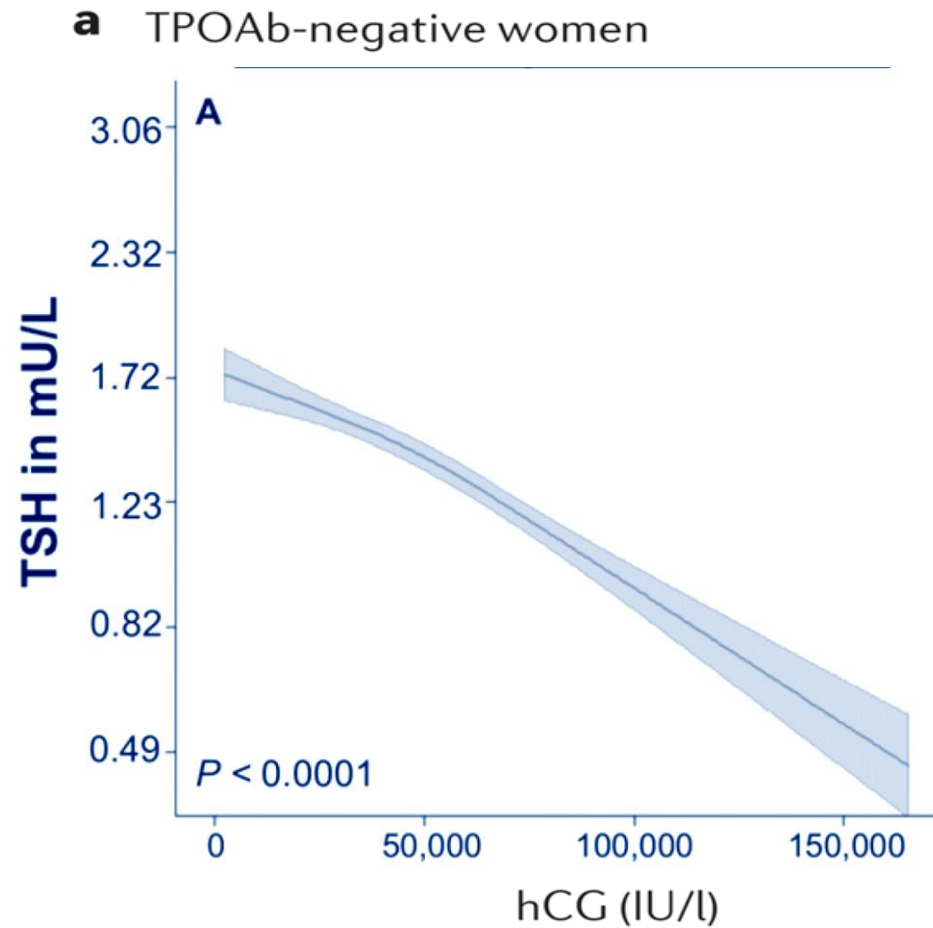


↓ **Total thyroid hormone availability in early pregnancy**
(area under the curve) in women who are TPO Ab positive



Thyroidal response to hCG in women with TPO Ab

Up to 18% of all pregnant women are TPO-Ab or Tg-Ab positive



Generation R Study

2002-2006, population-based prospective cohort from early fetal life onward in Rotterdam, The Netherlands; N: 5924

Does LT4 treatment of women with thyroid dysfunction improve ART outcomes?

Meta-analysis of the effects of LT4 treatment for TPO Ab-positive euthyroid women undergoing ART:

- No effect on clinical pregnancy rate (pooled RR 1.75 [95% CI 0.90–3.38])
- Higher delivery rate (pooled RR 2.76 [95% CI 1.20–6.44])

Is thyroid dysfunction associated with infertility in women?

Recommendation 16

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

Weak recommendation, moderate-quality evidence

Recommendation 17

- LT4 treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy.

Strong recommendation, moderate-quality evidence

Is thyroid dysfunction associated with infertility in women?

Recommendation 19

- Insufficient evidence exists to determine if LT4 improves fertility in non-pregnant, thyroid autoantibody-positive euthyroid women who are attempting natural conception (not undergoing ART). No recommendation can be made for LT4 therapy in this setting.

No recommendation, insufficient evidence

Recommendation 18

- Insufficient evidence exist to determine if LT4 improves fertility in sub-clinically hypothyroid, thyroid autoantibody-negative women who are attempting natural conception (not undergoing ART).
- LT4 may be considered to prevent progression to more significant hypothyroidism once pregnancy is achieved. Low dose LT4 (25–50 µg/d) carries minimal risk.

Weak recommendation, low-quality evidence

Does LT4 treatment of women with thyroid dysfunction improve ART outcomes?

Recommendation 20

- Sub-clinically hypothyroid women undergoing IVF or ICSI should be treated with LT4. The goal of treatment is to achieve a TSH <2.5 mU/L.

Strong recommendation, moderate-quality evidence

Recommendation 21

- LT4 therapy to TPO Ab-positive euthyroid women undergoing ART may be considered given its potential benefits in comparison to its minimal risk. 25–50 µg/d of LT4 is a typical starting dose

Weak recommendation, low-quality evidence

Recommendation 22

- Glucocorticoid therapy is not recommended for thyroid auto Ab-positive euthyroid women undergoing ART.

Weak recommendation, moderate-quality evidence

Is thyroid dysfunction associated with infertility in women?

- Selenium daily did not affect TPO concentrations or TPO Ab positivity.
- Patients treated with selenium could be at higher risk for developing type 2 diabetes mellitus.

Recommendation 12

- Selenium supplementation is not recommended for the treatment of TPO Ab-positive women during pregnancy.

Weak recommendation, moderate-quality evidence

Case 1 - F/U after one year

- She became pregnant naturally (GA 6th week)
- She has not taken LT4
- She is worried about pregnancy loss
- TSH: 2 mU/L

33 y/o 

Hypo in
mother

Anti TPO +



What of the following do you recommend?

- A. Low dose LT4 + Check TSH at 14th week
- B. Low dose LT4 + Check TSH at 10th week
- C. Check TSH 4 weeks later
- D. Check FT4 + TSH at 12th week



33 y/o ♀
GA 6 week

Hypo in
mother

Anti TPO +

TSH: 2

How should euthyroid women who are thyroid antibody (Ab)-positive be monitored during pregnancy?

Recommendation 11

Euthyroid pregnant women who are TPOAb or TgAb positive should have measurement of serum TSH concentration performed at time of pregnancy confirmation and every 4 weeks through mid-pregnancy.

Strong recommendation, high-quality evidence.

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

- Spontaneous pregnancy loss- occurring at <20 weeks of gestation (17-31% of all gestations).
- Recurrent pregnancy loss- 2 consecutive spontaneous losses or ≥ 3 spontaneous losses (1% of all gestations).
- Meta-analysis in thyroid Ab-positive women:
Spontaneous pregnancy loss
 - OR 3.90 for cohort studies [95% CI 2.48–6.12]
 - OR 1.80 for case control studies [95% CI 1.25–2.60]
- Recurrent pregnancy loss (OR 2.3 [95% CI 1.5–3.5])

Thangaratinam S, et al. *BMJ* 2011; 342:d2616.

van den Boogaard E, et al. *Hum Reprod Update* 2011; 17:605–619.

Does treatment with LT4 decrease the risk for pregnancy loss or premature delivery in euthyroid women with thyroid autoimmunity?

Recommendation 14

- LT4 therapy to TPOAb-positive euthyroid pregnant women with a prior history of pregnancy loss may be considered given its potential benefits in comparison with its minimal risk. 25–50 µg of LT4 is a typical starting dose.

Weak recommendation, low-quality evidence

Recommendation 15

- Thyroid autoantibody positivity is associated with ↑ risk for preterm delivery.
- Insufficient evidence exists to recommend for or against treating euthyroid pregnant women who are thyroid autoantibody positive with LT4 to prevent preterm delivery.

No recommendation, insufficient evidence

Case 1 - F/U

- She is at 10th week pregnancy
- She does not take LT4
- TSH: 2.4 mU/L (non-pregnant ♀: 0.3-4.5)
- FT4: 0.7 ng/dL (non-pregnant ♀: 0.8-1.7)

33 y/o ♀

Hypo in
mother

Anti TPO +



What of the following do you recommend?

- A. Low dose LT4
- B. Measure TT4
- C. Measure T3RU
- D. Check TSH at 14th week



33 y/o ♀
GA 10 week

**Hypo in
mother**

Anti TPO +

TSH: 2.4
FT4: 0.7

What is the optimal method to assess serum T4 concentration during pregnancy?

- FT4 measurement is prone to **inaccuracy** in the setting of pregnancy
- TT4 measurements may be **superior**
- TT4 increase from **weeks 7–16** of gestation, ultimately reaching **~50%** above the pre-pregnancy level.
- Calculation can be made for the upper reference range based on increasing the non-pregnant upper reference limit by **5% per week**, beginning with **week 7**

⇒ 11 weeks of gestation (**4 weeks beyond week 7**), the upper reference range for T4 is increased by **20%** (**4 weeks × 5%/week**)

Should women with isolated hypothyroxinemia be treated with LT4 in pregnancy?

- Normal TSH with FT4 in the lower 2.5th–5th percentile of a given population.
- Investigations failed to show any beneficial effect of LT4 therapy.

Recommendation 30

- Isolated hypothyroxinemia should **not be routinely treated** in pregnancy.

Weak recommendation, low-quality evidence

Case 1 - F/U

- She is at 16th week pregnancy
- She does not take LT4
- TSH: 4.3 mU/L (non-pregnant ♀: 0.3-4.5)
- TT4: 12.7 µg/dL (non-pregnant ♀: 4.5-12.5)

33 y/o ♀

Hypo in
mother

Anti TPO +



What of the following do you recommend?

A. Prescribe LT4

B. Prescribe Liothyronine (T3)

C. Prescribe LT4 + Liothyronine (T3)

D. Check TSH and TT4 at 20th week



33 y/o ♀
GA 16 week

Hypo in
mother

Anti TPO +

TSH: 4.3
TT4: 12.7

Trimester-specific reference ranges for TSH during pregnancy

- Population-based trimester-specific reference ranges for serum TSH should be defined.
- Serum TSH reference range determinants: iodine intake, TPO positivity, BMI, race, ethnicity, hCG concentrations (multiple pregnancies).

Trimester	ATA - guideline (reference range)
1 st	Relative to the typical non-pregnant TSH reference range: ✓ Lower limit decreased ~0.1–0.2 mU/L ✓ Upper limit decreased ~0.5–1.0 mU/L (~ 4 mU/L can be used)
2 nd	
3 rd	

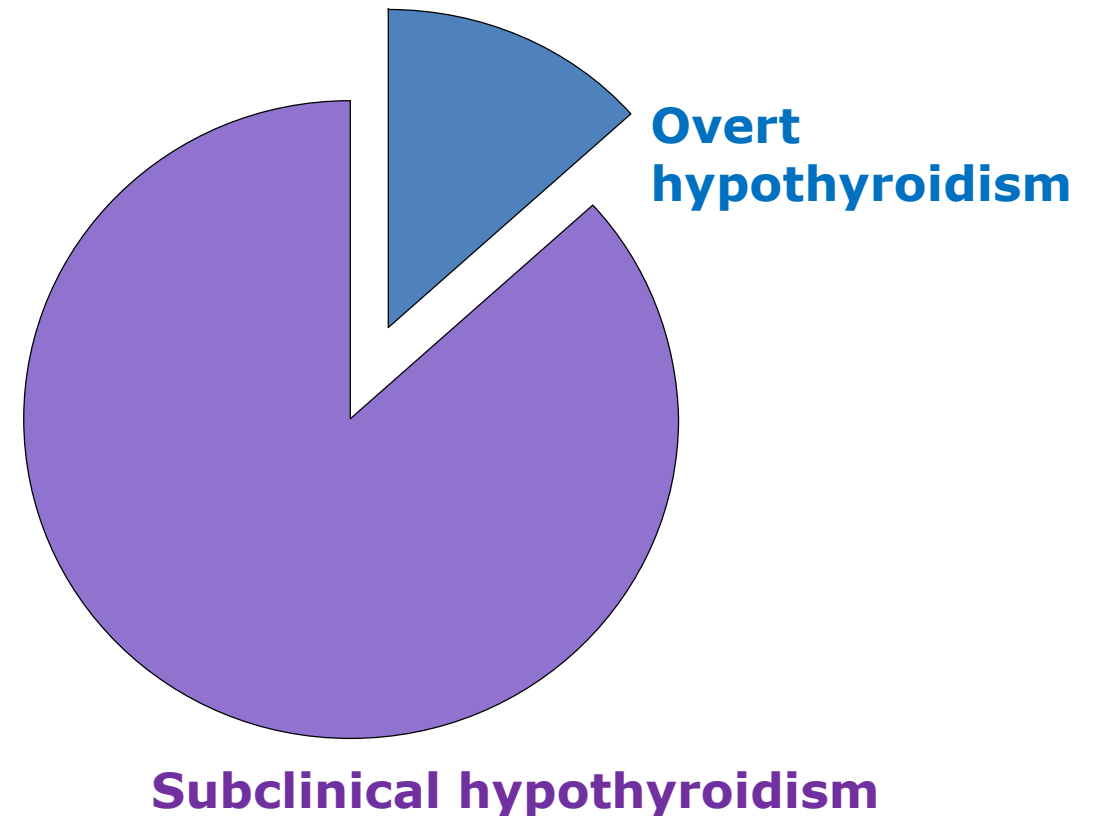
Trimester-specific reference intervals for TSH*

Reference	Year	1st trimester	2nd trimester	3rd trimester
Stricker	2007	1.04 (0.09-2.83)	1.02 (0.20-2.79)	1.14 (0.31-2.90)
Haddow	2004	0.94 (0.08-2.73)	1.29 (0.39-2.70)	
Panesar	2001	0.80 (0.03-2.30)	1.10 (0.03-3.10)	1.30 (0.13-3.50)
Soldin	2004	0.98 (0.24-2.99)	1.09 (0.46-2.95)	1.20 (0.43-2.78)
Bocos-Terraz	2009	0.92 (0.03-2.65)	1.12 (0.12-2.64)	1.29 (0.23-3.56)
Blatt	2012	1.01 (0.10-2.50)	1.14 (0.35-2.75)	1.26 (0.43-2.91)
Azizi	2013	1.7 (0.2-3.9)	1.9 (0.5-4.1)	1.8 (0.6-4.1)
* median TSH mIU/L with 5 th and 95 th percentiles or P 2.5 and P 97.5 between brackets.				

Soldin OP et al. Clin Chem Acta 2004; 349: 181
 Haddow JE et al. J Med Screen 2004; 11:170-174.
 Panesar NS et al. Ann Clin Biochem 2001; 34: 67
 Stricker R, et al. Eur J Endocrinol 2007; 157: 509
 Bocos-Terraz JP, et al. BMC Res Notes 2009; 2: 237
 Blatt AJ, et al. J Clin Endocrinol Metab 2012; 97: 777
 Azizi f, et al. Thyroid 2013; 23:354

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**
- ✓ Thyroid autoantibodies can be detected in **30%–60%** of pregnant women with **elevated TSH**



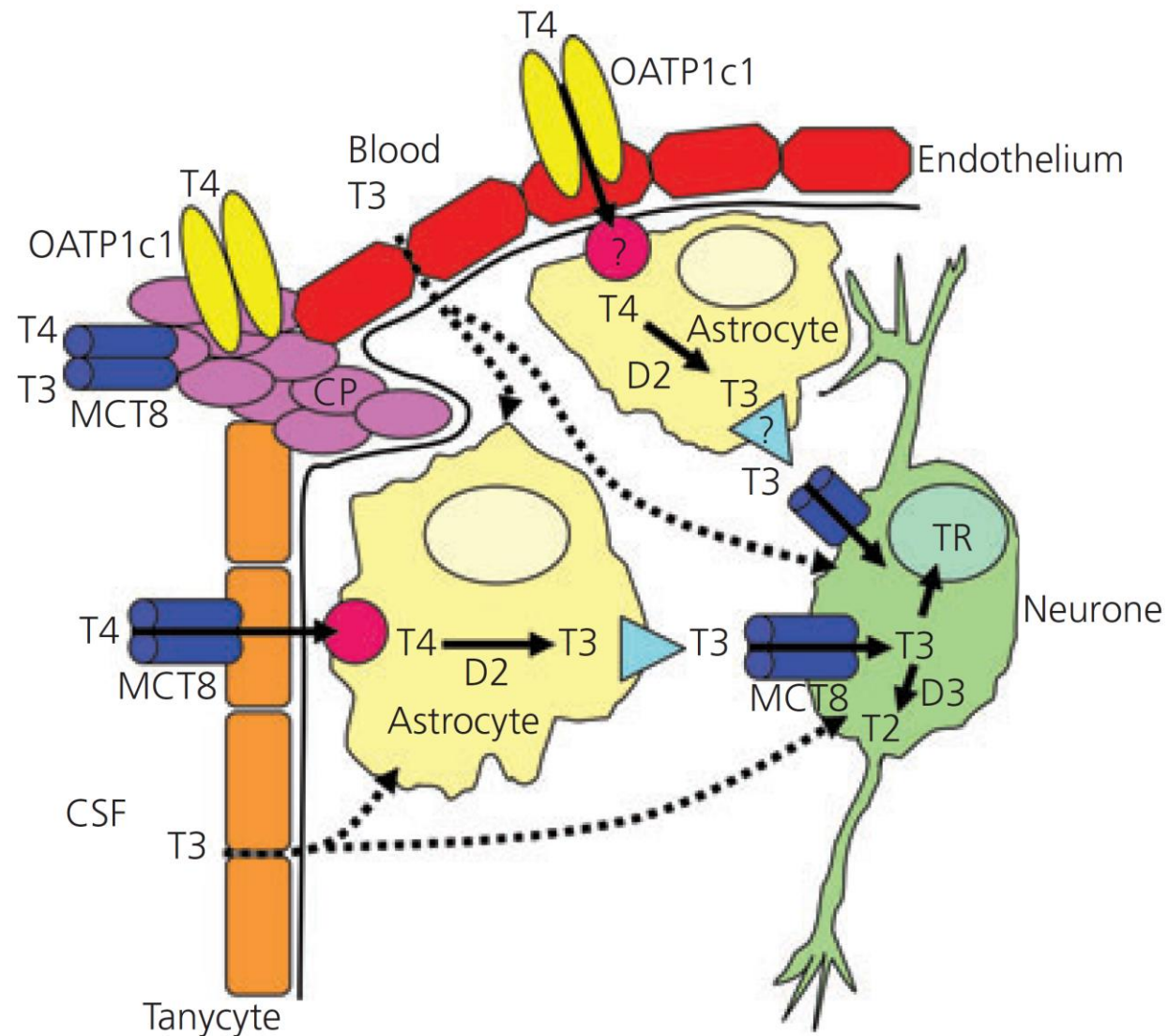
What if the mom's thyroid doesn't work?

	Subclinical	Overt
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“Maternal hypothyroidism is associated with **increased** rate of **pregnancy complications**, and the risk is **greatest in overt** hypothyroidism compared to subclinical hypothyroidism.”

La Franchi, Thyroid 2005

Delivery of thyroid hormones to neurons



What is the optimal method of treating hypothyroidism in pregnant women?

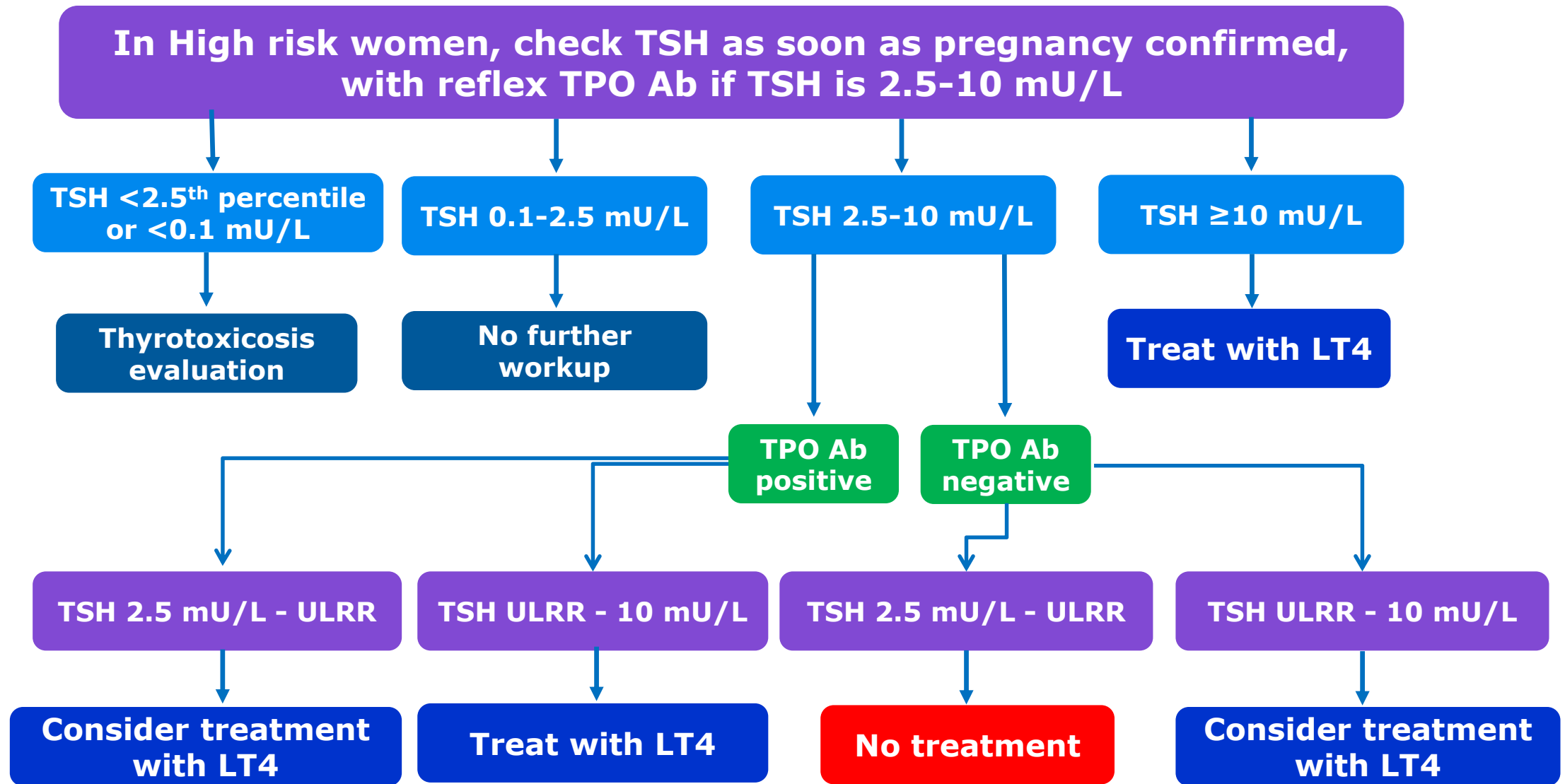
- The fetal CNS is relatively impermeable to T3.
- The majority of fetal T3 in the CNS is derived from maternal T4.

Recommendation 31

- The recommended treatment of maternal hypothyroidism is administration of oral LT₄. Other thyroid preparations such as T₃, should not be used in pregnancy.

Strong recommendation, low-quality evidence

Testing for thyroid dysfunction in pregnancy



Case 1 - F/U

- She is at 20th week pregnancy
- She has taken LT4 500 µg/week
[50 µg (4 days/week) and 100 µg (3 days/week)]
- TSH: 3.3 mU/L (non-pregnant ♀: 0.3-4.5)
- TT4: 13 µg/dL (non-pregnant ♀: 4.5-12.5)

33 y/o ♀

Hypo in
mother

Anti TPO +



What of the following do you recommend?

A. ↑ LT4 dose to 550 µg/week

B. ↓ LT4 dose to 450 µg/week

C. Continue & check TSH at 24th week



33 y/o ♀
GA 20 week

Hypo in
mother

Anti TPO +

TSH: 3.3
TT4: 13

What changes can be anticipated in treated hypothyroid women during gestation?

- ↑Requirement for LT4 occurs as early as 4–6 weeks of pregnancy
- Requirements gradually increase through 16–20 weeks of pregnancy and plateau thereafter until the time of delivery.
- 50-85% of LT4-treated hypothyroid women need to increase exogenous LT4 dosing during pregnancy.

What is the biochemical goal when treating hypothyroidism in pregnant women?

Recommendation 32

- TSH target is in the lower half of the trimester-specific reference range.
- When this is not available, target maternal TSH <2.5 mU/L.

Weak recommendation, moderate-quality evidence

What changes can be anticipated in treated hypothyroid women during gestation?

Recommendation 35

- In hypothyroid women treated with LT4 who are planning pregnancy, serum TSH should be evaluated preconception, and LT4 dose adjusted to achieve lower reference limit $\text{TSH} < 2.5 \text{ mU/L}$.

Strong recommendation, moderate-quality evidence

Recommendation 36

- Hypothyroid patients receiving LT4 treatment with a suspected or confirmed pregnancy should independently increase their dose of LT4 by $\sim 20\% - 30\%$.

Strong recommendation, high-quality evidence

Case 1 - F/U

- She had delivery last week
- Full term, without complication
- She has taken LT4 550 µg/week
- TSH: 0.6 mU/L (non-pregnant ♀: 0.3-4.5)
- TT4: 11 µg/dL (non-pregnant ♀: 4.5-12.5)

33 y/o ♀

Hypo in
mother

Anti TPO +



What of the following do you recommend?



33 y/o ♀
Post-partum

**Hypo in
mother**

Anti TPO +

TSH: 0.6
TT4: 11

- A. Continue LT4 & check TSH 6 week later
- B. Discontinue LT4 & check TSH 6 week later
- C. ↓ LT4 to 50 µg/day & check TSH 6 week later

How should LT4 be adjusted postpartum?



Recommendation 37

- Following delivery, LT4 should be reduced to the patient's preconception dose. Additional TFT should be performed at ~ 6 weeks post partum.

Strong recommendation, moderate-quality evidence

Recommendation 38

- Women in whom LT4 is initiated during pregnancy, are candidates for D/C LT4, especially when the LT4 dose ≤ 50 $\mu\text{g}/\text{d}$. If LT4 is D/C, serum TSH should be evaluated in ~ 6 weeks.

Weak recommendation, moderate-quality evidence

2017 American Thyroid Association Recommendations for the Management of in Pregnancy

Laboratory Data	Levothyroxine Therapy	Recommendation Strength	Evidence Quality
TSH >10 mU/L	Yes	Strong	Low
Anti-TPO–positive & TSH > ULRR	Yes	Strong	Moderate
Anti-TPO–positive & 2.5 mU/L > TSH < ULRR	Consider	Weak	Moderate
Anti-TPO–negative & ULRR > TSH <10 mU/L	Consider	Weak	Low
Anti-TPO–negative & 2.5 mU/L > TSH < ULRR or < 4 mU/L	No	Strong	High
Isolated maternal hypothyroxinemia	No	Weak	Low

SUGGESTION



COMMENT