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Thyroid Diseases in Pregnancy

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- Clinical focus: Thyroid diseases and general endocrinology
- Research focus: Metabolism and genetics of thyroid cancer

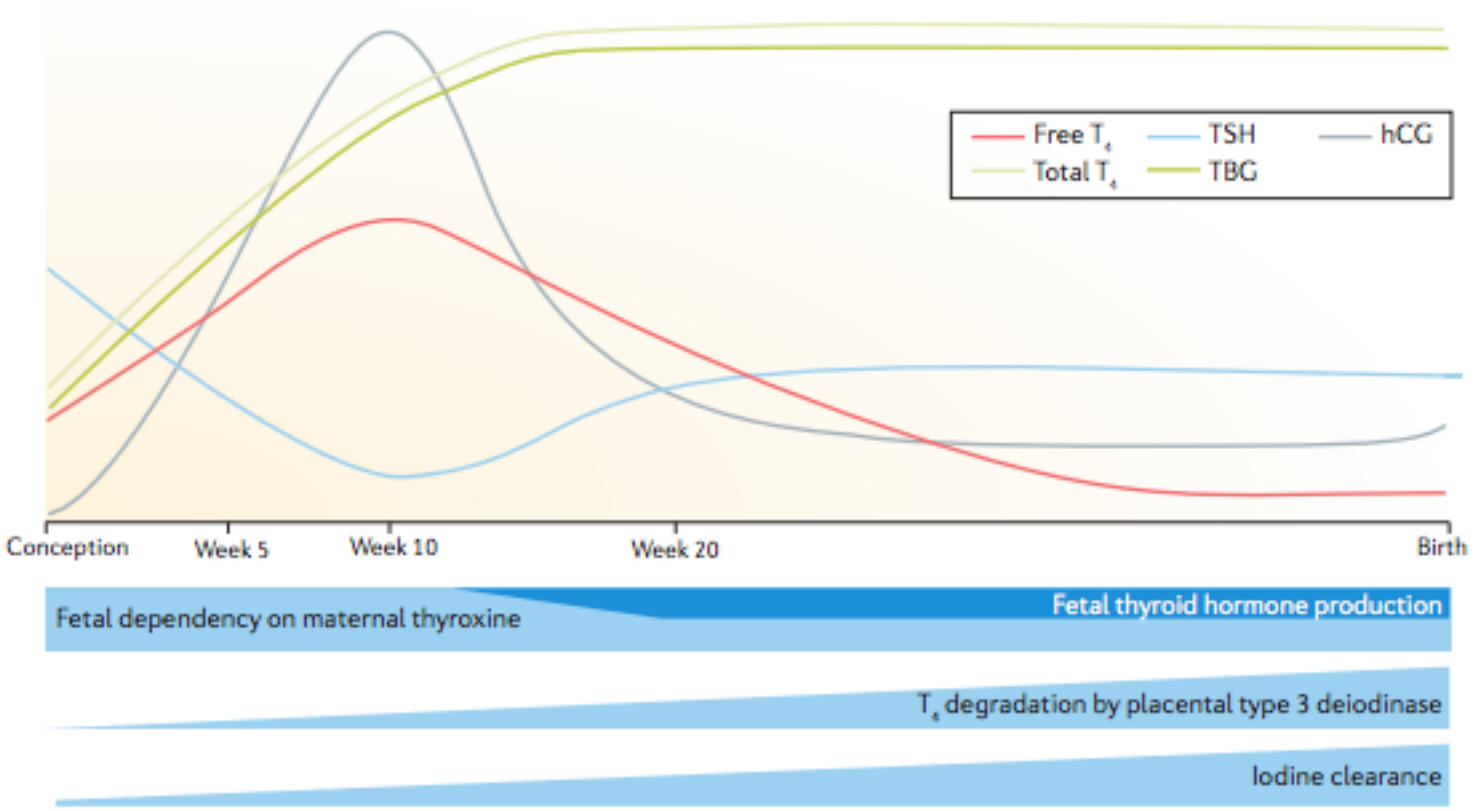
DISCLOSURES

- None

OBJECTIVES

At the end of this activity, participants will be able to:
-understand the physiology of hypothalamic-pituitary-thyroid axis in pregnancy
-treat hypothyroidism and hyperthyroidism in pregnancy
-manage thyroid nodules and thyroid cancer in pregnancy

Changes in Thyroid Physiology during Pregnancy



Korevaar TI et al. Nat Rev Endo 2017;13: 610.

TSH Reference Range in Normal Pregnancy
2017 ATA Guidelines

- Downward shift of both lower and upper limit of TSH
- Use population based trimester specific reference range if available
- Otherwise use TSH 4.0mIU/L as the upper ref limit in 1st trimester with gradual return to non-pregnant ref range in 2nd and 3rd trimester
  - Note: Previously ATA guidelines in 2011 used TSH 2.5mIU/L

Alexander et al. Thyroid 2017; 27: 315.

Case #1

- A 25-year-old female presents with a history of Hashimoto’s thyroiditis on Levothyroxine presents to the Endocrine clinic as she just recently found out she is pregnant. That is her first pregnancy, and she reports no current symptoms.
- No other medical issues
- Medications include Levothyroxine and a prenatal multivitamin
- On physical examination, vital signs are normal. The patient's thyroid gland is nontender and diffusely enlarged without nodules. Pregnancy test is positive.
- Serum thyroid-stimulating hormone level measured 2 months ago was 1.5 µU/mL (1.5 mU/L).

Case #1

- Which of the following is the best next step in management?

  A. Decrease Levothyroxine dose by 30%

  B. Increase Levothyroxine dose by 30%

  C. Stop Levothyroxine and start Liothyronine

  D. Check serum TSH in 2 months

Case #1 (answer)

❖ Which of the following is the best next step in management?

A. Decrease Levothyroxine dose by 30%

B. <u>Increase Levothyroxine dose by 30%</u>

C. Stop Levothyroxine and start Liothyronine

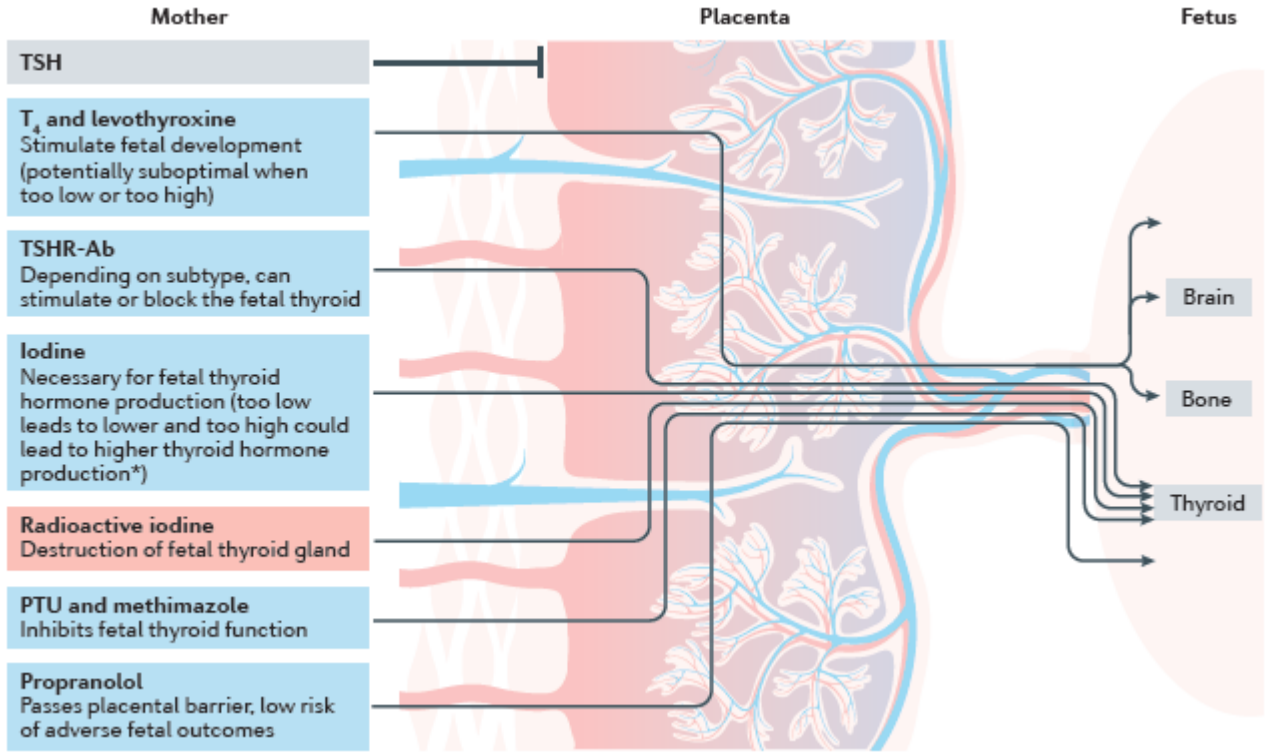
D. Check serum TSH in 2 months

Case #1

- In euthyroid women without thyroid disease, the total body thyroxine pool increases by 40% to 50% during pregnancy → mediated by the stimulatory effects of TSH and placental human chorionic gonadotropin.
- Pregnant women with hypothyroidism are unable to augment thyroidal production of T4 and T3 → LT4 needs to be adjusted
- Because T4 requirements may begin to increase as early as 4 to 6 weeks of pregnancy, **women with hypothyroidism should increase their levothyroxine dose or serum TSH should be measured as soon as pregnancy is confirmed.**
- **TSH should be measured every 4 weeks for the first half of pregnancy and around 30 weeks of gestation in all women with hypothyroidism**.

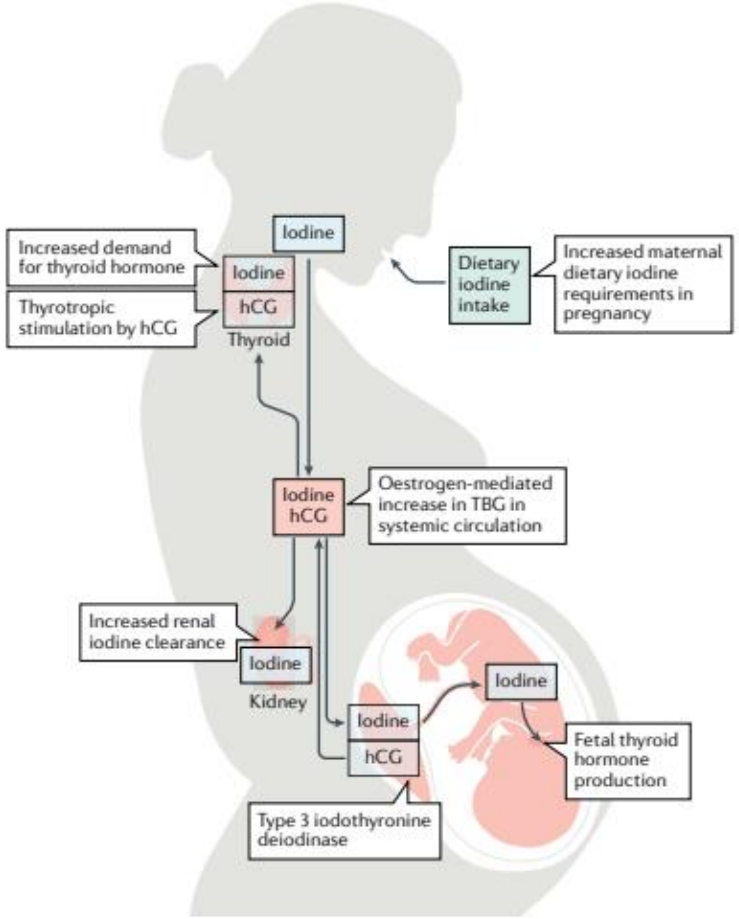
Case #1

- **<u>Do not use T3 in pregnancy.</u>**
- Fetal neurodevelopment dependent on maternal free T4 in early gestation.
- Use of dessicated T3 has a higher T3;T4 ratio than human normal thyroid and leads to excess T3 and low T4 as FETAL CNS relatively impermeable to T3!



Korevaar TI et al. Nat Rev Endo 2017;13: 610.

Iodine Requirements during Pregnancy



- Daily intake
  - WHO 250 mcg daily during pregnancy and lactation.
  - NAM 220 mcg during pregnancy and 290 mcg during lactation.
- Supplementation
  - ATA 150 mcg daily during pregnancy and lactation
- Maximum
  - WHO 500 mcg daily for pregnant women
  - NAM 1100 mcg daily for adults and pregnant women >19 years of age.

Lee SY, Pearce EN. Nat Rev Endo 2022;18: 159.

Iodine Deficiency Prevention

TABLE 1. MEDIAN URINE IODINE VALUES FOR POPULATION OF UNITED STATES—PAST 30 YEARS

	NHANES years of sample collection			
	1971–1974 (10)	*1988–1994 (10)*	*2000 (12)*	*2001–2002 (13)*
Total population (age 6–74 years)	321 (±6)[a]	145 (±3)	161 (±6)	168 (±7)
Women of reproductive age (age 15–44 years)				
Pregnant	373 (±35)	141 (±14)	Not available	173 (±38)
Nonpregnant	293 (±10)	127 (±4)		132 (±9)

NHANES, National Health and Nutrition Examination Survey.
[a]Urine iodine in μg/L (±SE).

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Marginal Iodine Status and High Rate of Subclinical Hypothyroidism in Washington DC Women Planning Conception

Alex Stagnaro-Green,[1,*] Emmerita Dogo-Isonaige,[2] Elizabeth N. Pearce,[3] Carole Spencer,[4] and Nancy D. Gaba[2]

Discussion: The present cohort exhibited the lowest median urinary iodine concentration levels to date reported in the United States for women in their childbearing years. One out of every nine women (11%) had thyroid function tests consistent with subclinical hypothyroidism.

UIC 100 ug/L, should be 150-200 ug/L

Case #2

- A 25-year-old female with obesity, asthma presents to the Endocrine clinic as she just recently found out she is pregnant. That is her first pregnancy, and she reports no current symptoms.

- Medications include a prenatal multivitamin, and an inhaler

- On physical examination, vital signs are normal. The patient's thyroid gland is nontender and diffusely enlarged without nodules. Pregnancy test is positive.

- Serum thyroid-stimulating hormone level is 5.7 µU/mL (1.5 mU/L), FT4 is 0.8 ng/dl (normal 0.9-1.7) and she has positive TPO antibodies.

Case #2

- Which of the following is the best next step in management?
  A. Recheck TSH and FT4 in 4 weeks
  B. Start Levothyroxine
  C. Start dessicated thyroid
  D. Recheck TPO antibodies in 4 weeks

Case #2 (answer)

❖ Which of the following is the best next step in management?

A. Recheck TSH and FT4 in 4 weeks

B. <u>Start Levothyroxine</u>

C. Start dessicated thyroid

D. Recheck TPO antibodies in 4 weeks

Primary hypothyroidism in pregnancy – obstetric outcomes

Primary hypothyroidism was associated with increased odds of

- preeclampsia (OR = 1.47, 99% CI = 1.20 –1.81),
- superimposed preeclampsia (OR = 2.25, 99% CI = 1.53–3.29)
- gestational diabetes (OR = 1.57, 99% CI = 1.33–1.86)
- preterm birth (OR = 1.34, 99% CI = 1.17–1.53)
- induction (OR = 1.15, 99% CI = 1.04 –1.28)
- cesarean section (prelabor, OR = 1.31, 99% CI = 1.11–1.54; after
- spontaneous labor OR = 1.38, 99% CI = 1.14 –1.66),
- ICU admission (OR = 2.08, 99% CI = 1.04 – 4.15)

Mannisto T, et al. JCEM 2013;98: 2725-2733.

Case #2

- Women with overt hypothyroidism are at risk for several complications including preeclampsia, preterm delivery, neuropsychological and cognitive impairment in the child.
- Risk of complications in subclinical hypothyroidism is lower than overt, however some studies show complications can still happen
- Controversial topic, awaiting new ATA Guidelines

Thyroid Hypofunction in Pregnancy

Table 1 | **Current US recommendations for treatment of thyroid hypofunction in pregnancy**

Laboratory data	ATA guidelines[8]	ACOG guidelines[13]
TPO antibody-negative and TSH >10 mIU/l	Treat with levothyroxine	Treat with levothyroxine only if free T_4 is low
TPO antibody-positive and TSH greater than the pregnancy-specific range (or >4 mIU/l)	Treat with levothyroxine	Treat with levothyroxine only if free T_4 is low
TPO antibody-positive and TSH >2.5 mIU/l but less than the pregnancy-specific reference range (or <4 mIU/l)	Consider treatment with levothyroxine	No treatment
TPO antibody-negative and TSH greater than the pregnancy-specific range (or >4 mIU/l) but <10 mIU/l	Consider treatment with levothyroxine	Treat with levothyroxine only if free T_4 is low
Isolated hypothyroxinaemia	No treatment	Not discussed

ACOG, American College of Obstetricians and Gynecologists; ATA, American Thyroid Association; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Lee SY, Pearce EN. Nat Rev Endo 2022;18: 159.

Case #3

- A 32-year-old female presents to the Endocrine clinic after a referral from her OB team. Currently at 12 weeks of gestation. This is her first pregnancy. She reports weight loss of 5 lbs, +anxiety, +palpitations. Bowel movements are normal. She does have nausea and vomits 2-3x/week.

- Medications include a prenatal multivitamin

- On physical examination, she is tachycardic to 97 bpm. The patient's thyroid gland is nontender, and no nodules are palpated.

- Serum thyroid-stimulating hormone level is 0.03 mU/L.

Case #3

- Which of the following is the best next step in management?
  A. Start PTU 50 mg TID
  B. Start Methimazole 10 mg daily
  C. Recheck TSH in 4 weeks
  D. Check FT4 and TSHr antibodies

Case #3 (answer)

- Which of the following is the best next step in management?

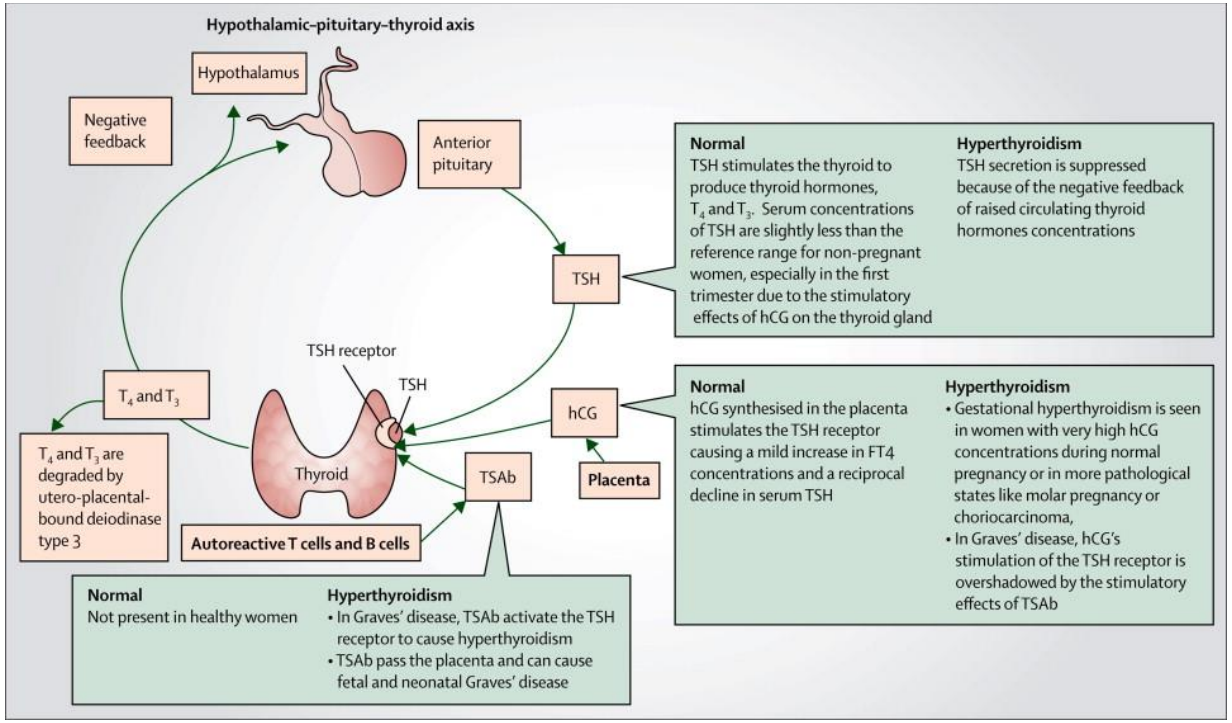
A. Start PTU 50 mg TID

B. Start Methimazole 10 mg daily

C. Recheck TSH in 4 weeks

D. <u>Check FT4 and TSHr antibodies</u>

Hyperthyroidism in pregnancy



- Differential diagnosis
  - Graves' disease
  - Gestational hyperthyroidism
  - Toxic nodule
  - Subacute thyroiditis
- Gestational transient thyrotoxicosis
  - hCG peaks at 10-12 weeks
  - More common with multiple gestation pregnancies, as well as hyperemesis gravidarum
  - Correlation with hCG levels (higher hCG→ lower TSH and higher T4 levels)
  - Usually resolves without intervention after 12-15 weeks

Cooper DS et al. Lancet Diabet and Endo 2013;1: 238-249

Case #3 (continued)

- Patient returns for labs on week 13 of gestation.

- Serum thyroid-stimulating hormone level is 0.01 mU/L, FT4 is 3 ng/dl (normal 0.9-1.7), TT3 300 ng/dl (normal 90-150), TSI and TBII are high.

Case #3

- Which of the following is the best next step in management?
  A. Start PTU 50 mg TID
  B. Start Methimazole 10 mg daily
  C. Recheck TSH in 4 weeks
  D. Refer for radioactive iodine ablation

Case #3

❖ Which of the following is the best next step in management?

A. **Start PTU 50 mg TID**

B. Start Methimazole 10 mg daily

C. Recheck TSH in 4 weeks

D. Refer for radioactive iodine ablation

Hyperthyroidism in pregnancy

- Overt hyperthyroidism can cause
  - pre-eclampsia, pregnancy loss, maternal and fetal congestive heart failure, maternal thyroid storm, preterm labour, intrauterine growth retardation, low birthweight, and fetal and/or neonatal hyperthyroidism
- Subclinical hyperthyroidism is NOT associated with those outcomes

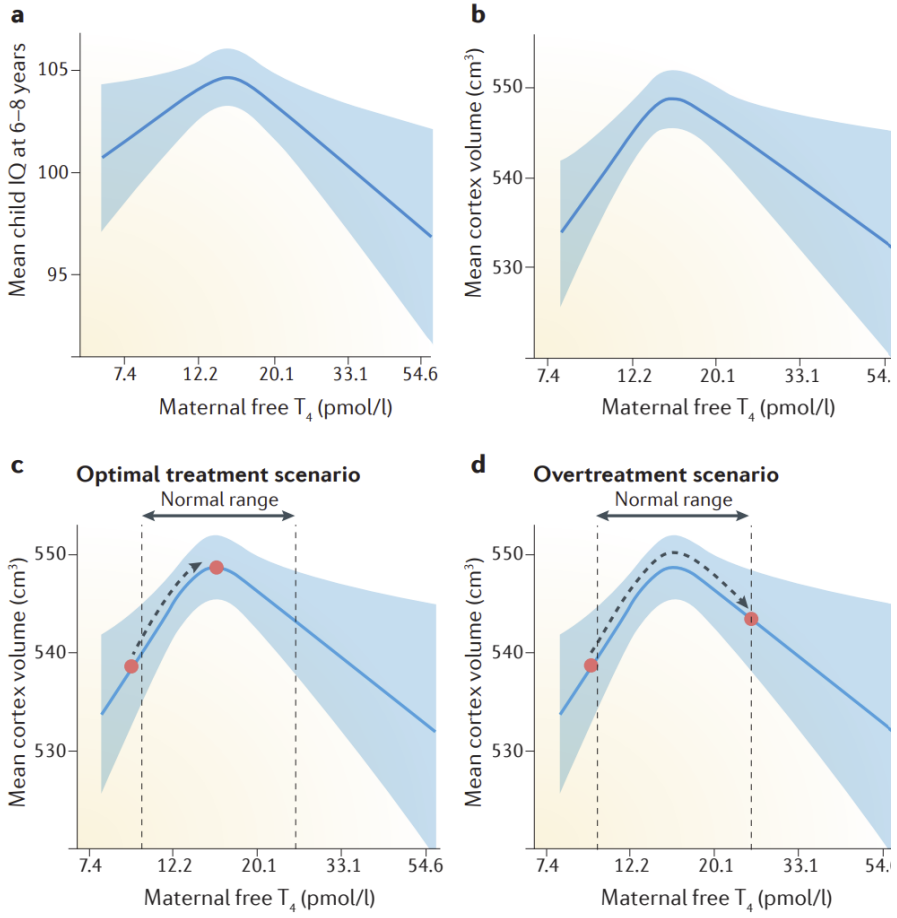


Figure 4 | **Association between maternal free T_4 concentrations during early pregnancy and child IQ and cortical volume as well as postulated treatment**

Korevaar TI et al. Nat Rev Endo 2017;13: 610.

Hyperthyroidism in pregnancy

Gestational transient thyrotoxicosis

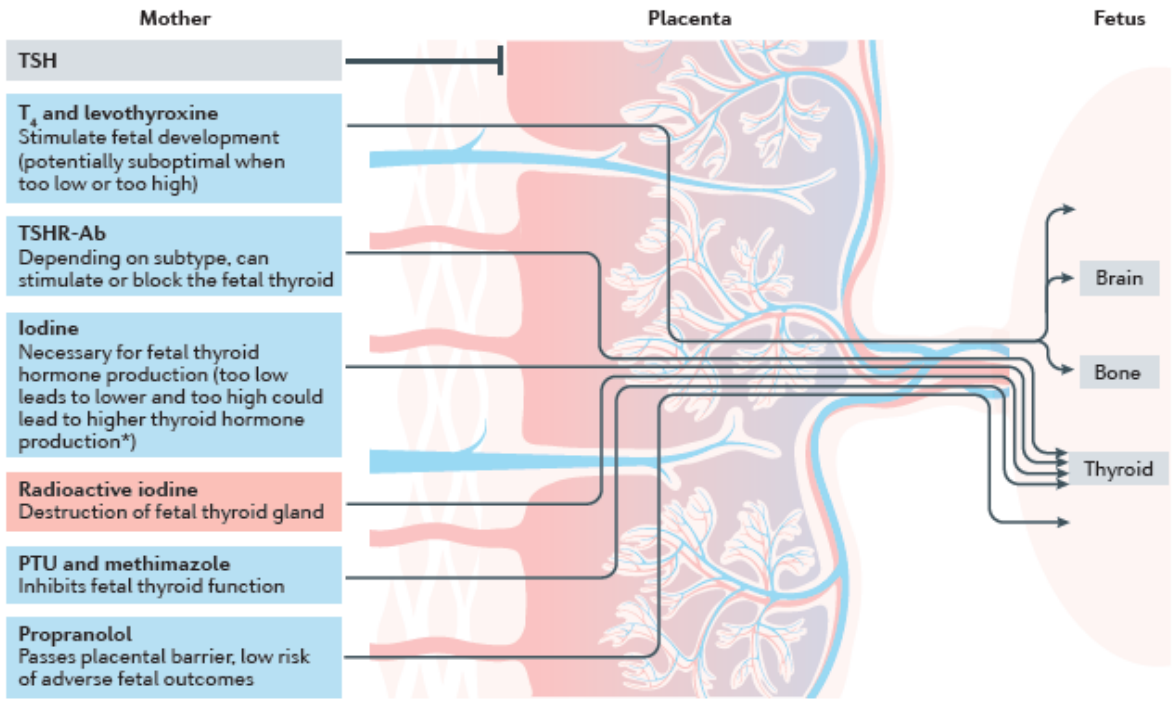
- Symptoms of hyperthyroidism
  - Usually PRESENT
- Labs
  - Not completely suppressed TSH
  - FT4 not higher than 1.5 ULN
  - T3 not elevated (T3:T4<20:1)
  - TSI/TBII negative
- Associated with multiple gestation pregnancies and hyperemesis
- Thyroid eye disease and goiter not seen
- Treatment
  - Spontaneous resolution after 12-15 weeks
  - No thionamides
  - Supportive measures

Graves' disease

- Symptoms of hyperthyroidism
  - Usually ABSENT
- Labs
  - Suppressed TSH
  - FT4 higher than 1.5 ULN
  - T3 elevated (T3:T4 >20:1)
  - TSI/TBII positive
- Thyroid eye disease can be present
- Goiter can be present
- Treatment
  - No spontaneous resolution
  - Thionamides indicated if FT4 high

Graves' disease in pregnancy

- Radioactive iodine contraindicated
- Surgery can be considered in the second trimester
- Thionamides
  - Methimazole preferred over PTU in non-pregnant → fulminant hepatic failure
  - Both Methimazole and PTU are teratogenic
  - Should be avoided if possible in the first trimester
  - If treatment can not be avoided, we prefer
    - PTU in the first trimester
    - Switch to Methimazole in the second trimester
  - Block-and-replace NOT recommended
  - Graves' might improve starting on the second trimester → maternal immune tolerance

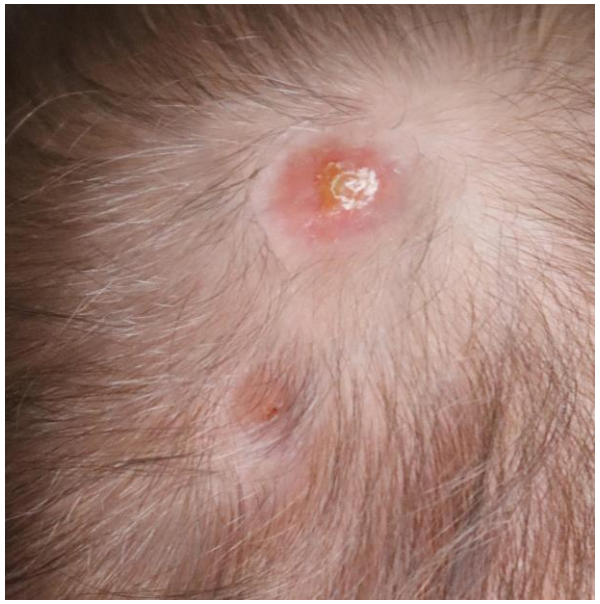


Korevaar TI et al. Nat Rev Endo 2017;13: 610.

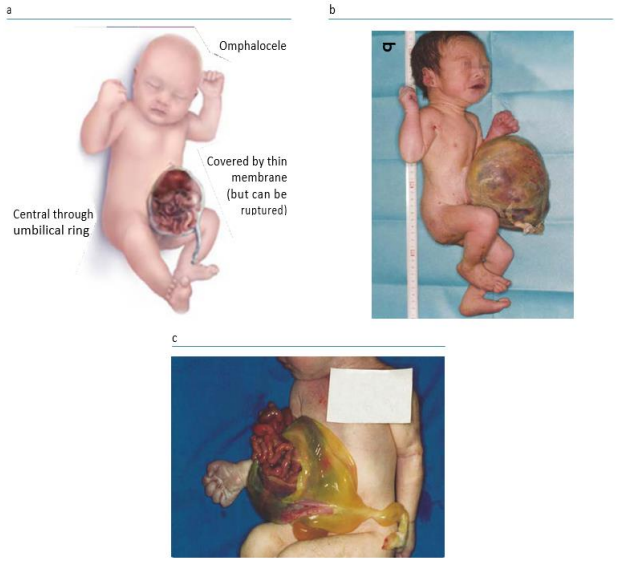
Teratogenicity of thionamides

- Facial dysmorphism: Short, upslanting palpebral fissures, broad nasal bridge, small nose, and broad forehead
- Congenital heart disease: Ventricular septal defect
- Esophageal atresia
- Choanal atresia
- Omphalocele
- Renal system malformations
- Aplasia cutis

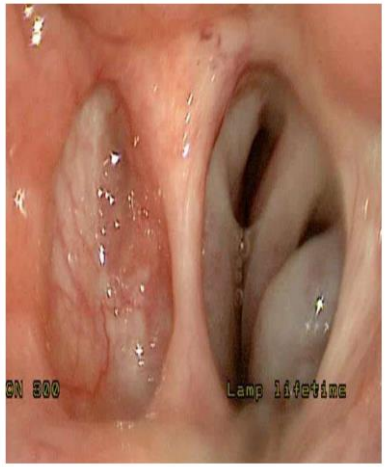
Aplasia cutis



Omphalocele



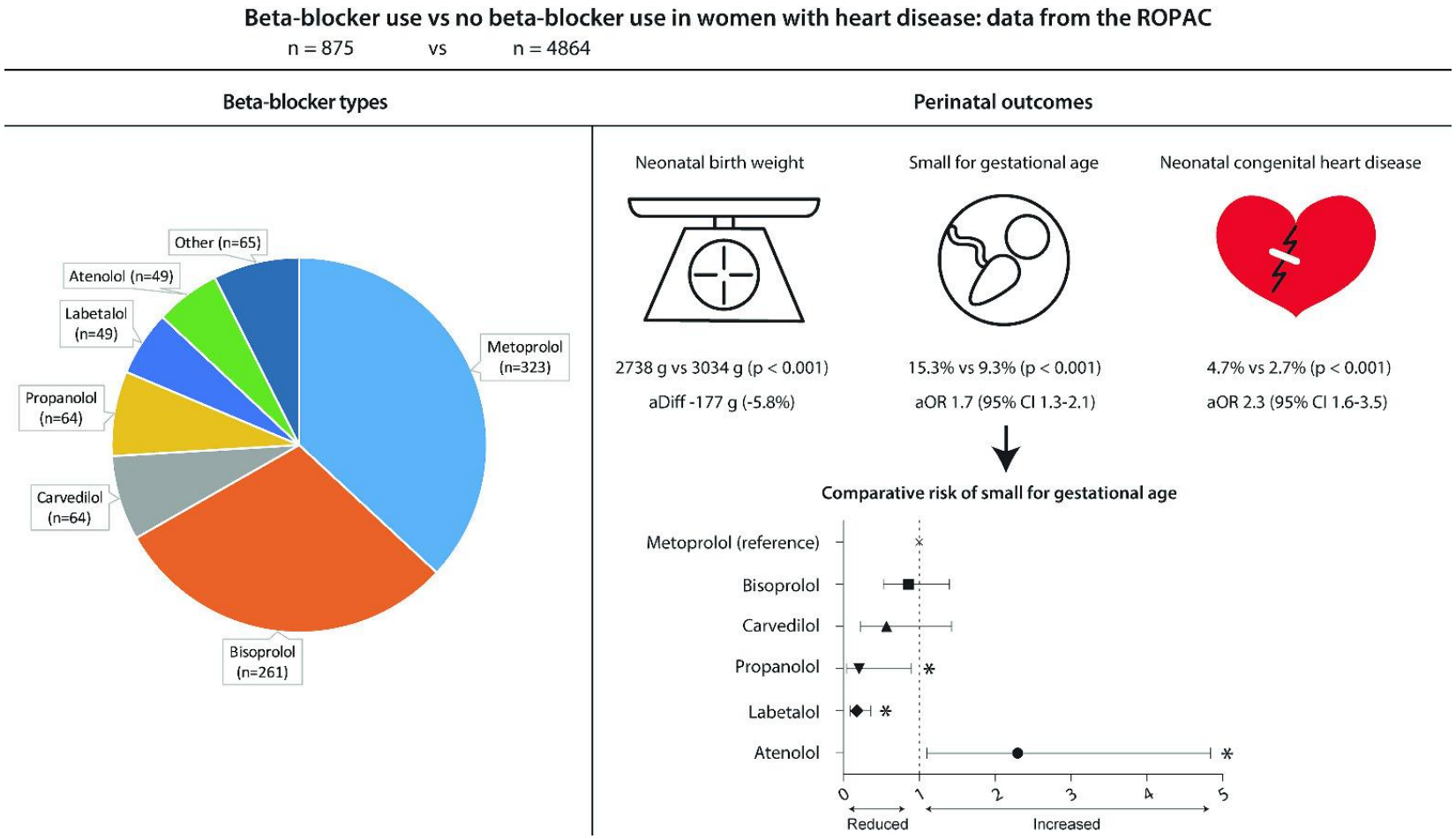
Choanal atresia



Beta-blockers in pregnancy

- Beta-blockers can be used in pregnancy to treat tachycardia and tremor
- Metoprolol and Propranolol are preferred
- Long-term treatment (longer then 3-6 weeks) with bb should be avoided
- Concern for fetal growth retardation and hypoglycemia
- Higher concern for Atenolol, that should be avoided

Beta-blockers in pregnancy



Beta-blocker use is independently associated with small for gestational age infants.

•Labetalol has the lowest risk of small for gestational age and atenolol the highest.

•Fetal growth scans are recommended in women using beta-blockers.

•Women should be counselled about the benefits and risks of medication use.

Ramlakhan KP et al. Int J Cardiol. 2024; 410:132234.

Case #3 (continued)

- Patient starts on PTU 50 mg TID. She does feel better with less anxiety, palpitations.
- She returns for labs after 3 weeks, now on week 16 of gestation
- Serum thyroid-stimulating hormone level is 0.1 mU/L, FT4 is 1.9 ng/dl (normal 0.9-1.7), TT3 215 ng/dl (normal 90-150).

Case #3 (continued)

- Which of the following is the best next step in management?
  A. Increase PTU to 100 mg TID
  B. Switch to Methimazole 30 mg daily
  C. No changes in dosing and recheck TSH, FT4, T3 in 4 weeks
  D. Refer for total thyroidectomy

Case #3 (answer)

❖ Which of the following is the best next step in management?

A. Increase PTU to 100 mg TID

B. Switch to Methimazole 30 mg daily

C. <u>No changes in dosing and recheck TSH, FT4, T3 in 4 weeks</u>

D. Refer for total thyroidectomy

Case #3 (answer- explanation)

❖ Which of the following is the best next step in management?

A. Increase PTU to 100 mg TID

Maintain FT4 in the ULN, or TT4-TT3 levels at 1.5x ULN. Ok to keep TSH low

B. Switch to Methimazole 30 mg daily

Methimazole is 20-30x more potent than PTU. 30 mg MMI is approx. 600 mg PTU

C. <u>No changes in dosing and recheck TSH, FT4, T3 in 4 weeks</u>

<u>Keep following labs, might improve over time and PTU stopped (immune tolerance</u>

D. Refer for total thyroidectomy

That should be considered if patient is intolerant to thionamides, has agranulocytosis/liver injury

Case #4

- A 34-year-old female presents to the Endocrine clinic after a referral from her OB team. Currently at 22 weeks of gestation. This is her first pregnancy. She reports some nausea, but no vomiting. A nodule was palpated on the initial OB visit and patient was referred to Thyroid Clinic.

- Medications include a prenatal multivitamin

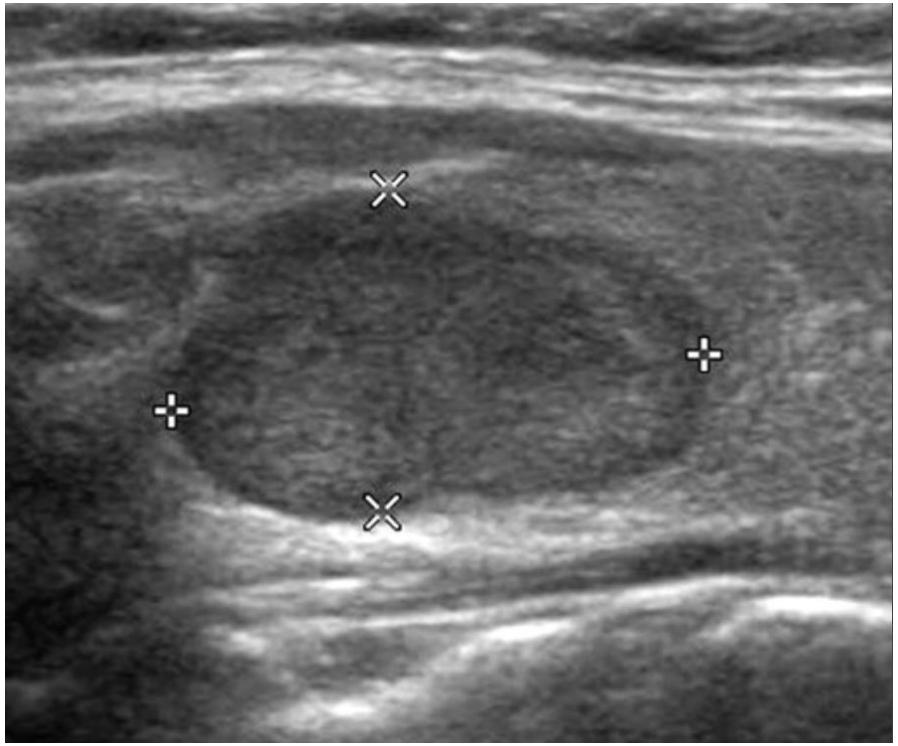
- On physical examination, vital signs are normal. The patient's thyroid gland is nontender, nonenlarged and a 2cm nodule is palpated on the right thyroid gland.

- Serum thyroid-stimulating hormone level is 1.3 mU/L.

- A thyroid US is performed

Case #4

- A thyroid US is performed
- No abnormal lymphadenoapthy



Case #4

- Which of the following is the best next step in management?

A. Proceed with I-123 thyroid uptake and scan

B. Start PTU 50 mg BID

C. Proceed with fine needle aspiration

D. Check FT4 and TSHr antibodies

Case #4 (answer)

❖ Which of the following is the best next step in management?

A. Proceed with I-123 thyroid uptake and scan

B. Start PTU 50 mg BID

C. <u>Proceed with fine needle aspiration</u>

D. Check FT4 and TSHr antibodies

Case #4 (answer- explanation)

❖ Which of the following is the best next step in management?

A. Proceed with I-123 thyroid uptake and scan

   Contraindicated in pregnancy. Also, patient is not hyperthyroid

B. Start PTU 50 mg BID

   Patient is not hyperthyroid. No reason to start on PTU

C. <u>Proceed with fine needle aspiration</u>

D. Proceed with right thyroid lobectomy

   Thyroidectomy can be considered in pregnancy. However, this is premature since there is no information if this is a malignancy

Management of thyroid nodules in pregnancy

- FNA is safe to perform during pregnancy
- If there is no evidence of rapid growth or aggressive features (extrathyroidal extension, abnormal lymphadenopathy), it is reasonable to wait until after delivery
- Management dependent on cytology

Bethesda II (benign)
follow clinically and only repeat thyroid US if significant growth/symptoms

Bethesda III/IV (indeterminate)
depending on the level of suspicion, this can be monitored or repeat FNA with molecular studies can be pursued. Shared decision making is important

Bethesda V/VI (suspicious for malignancy or malignant) →
depending on timing

- Thyroidectomy can be performed safely in the second trimester
- If discovered late, safe to follow and perform thyroidectomy in the postpartum period in the vast majority of cases

Progression of thyroid cancer during pregnancy

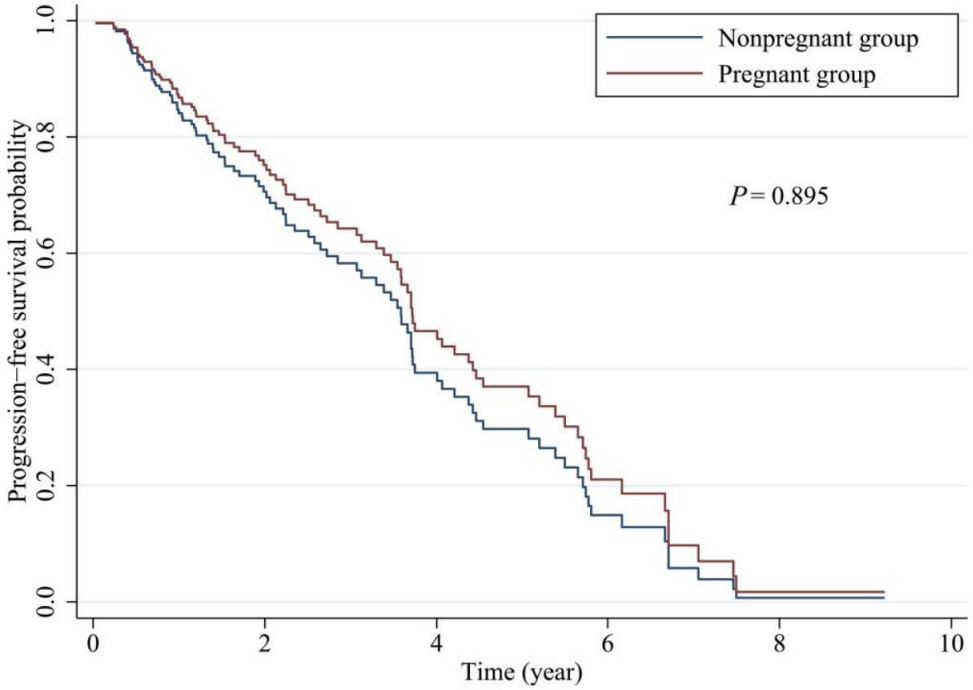


Figure 2. Adjusted Kaplan–Meier survival curves for DTC progression. Note: Adjusted for age, tumor size at baseline, type of thyroid cancer, the median TSH level, and Hashimoto's thyroiditis status.

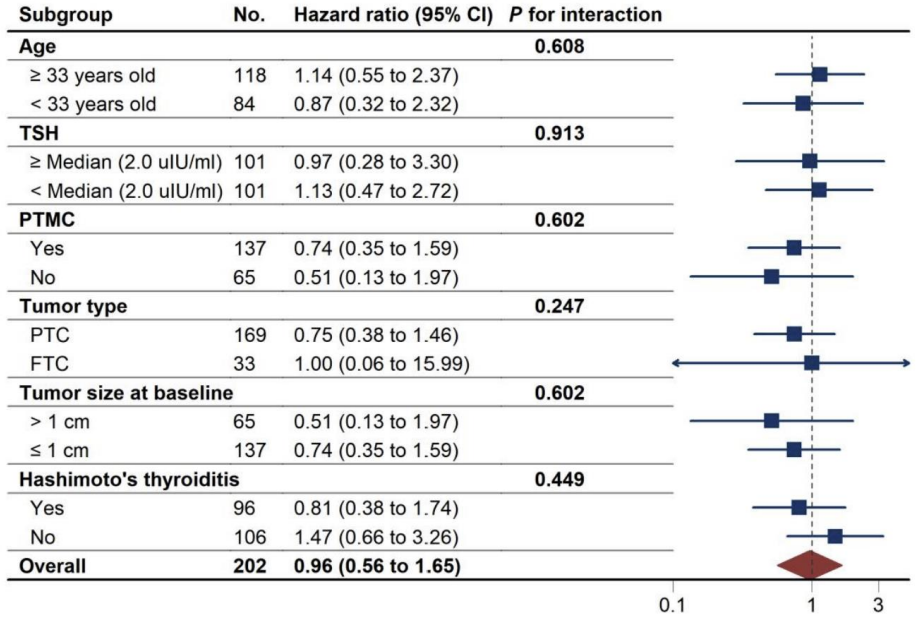


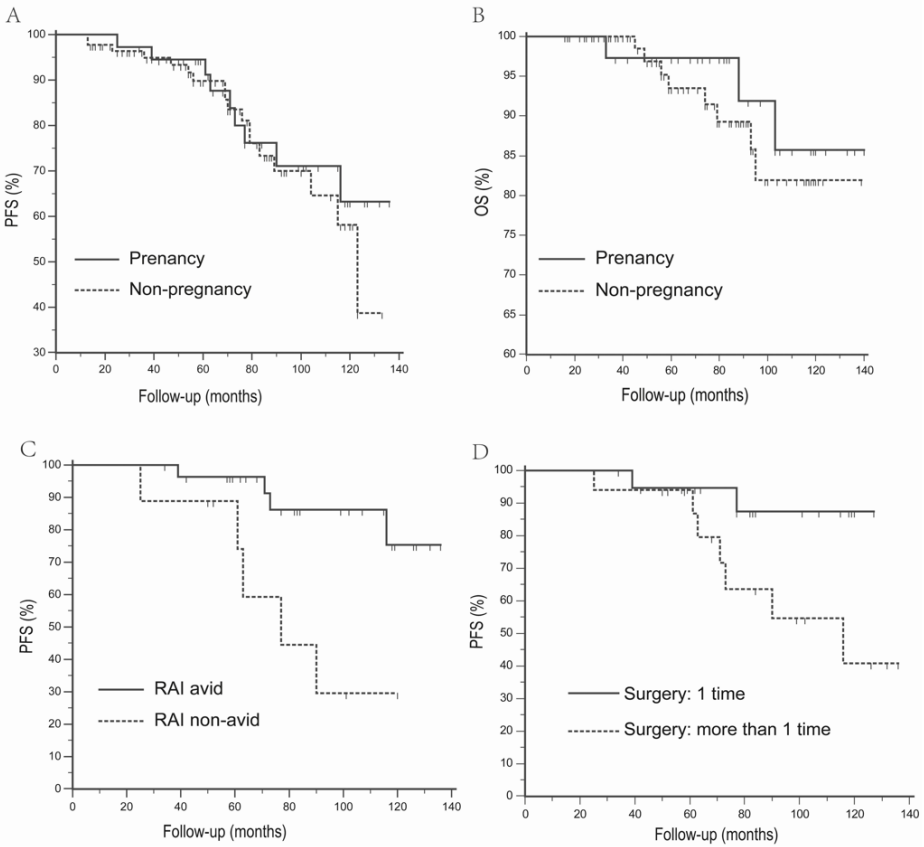
Figure 3. Subgroup analysis of the association of pregnancy with progression-free survival.

Table 2. Association of pregnancy with the progression-free survival in the stratified Cox proportional risk models[a]

Outcomes	HR[a]	95% CI	*P*
Main analyses			
DTC progression	0.96	0.56, 1.65	.895
Tumor enlargement	0.99	0.56, 1.76	.969
LNM	0.67	0.21, 2.13	.498
Sensitivity analyses[b]			
DTC Progression	0.84	0.45, 1.58	.594
Tumor enlargement	0.86	0.43, 1.69	.655
LNM	0.63	0.17, 2.39	.499

Xiao WC et al. JCEM 2024;109: 837.

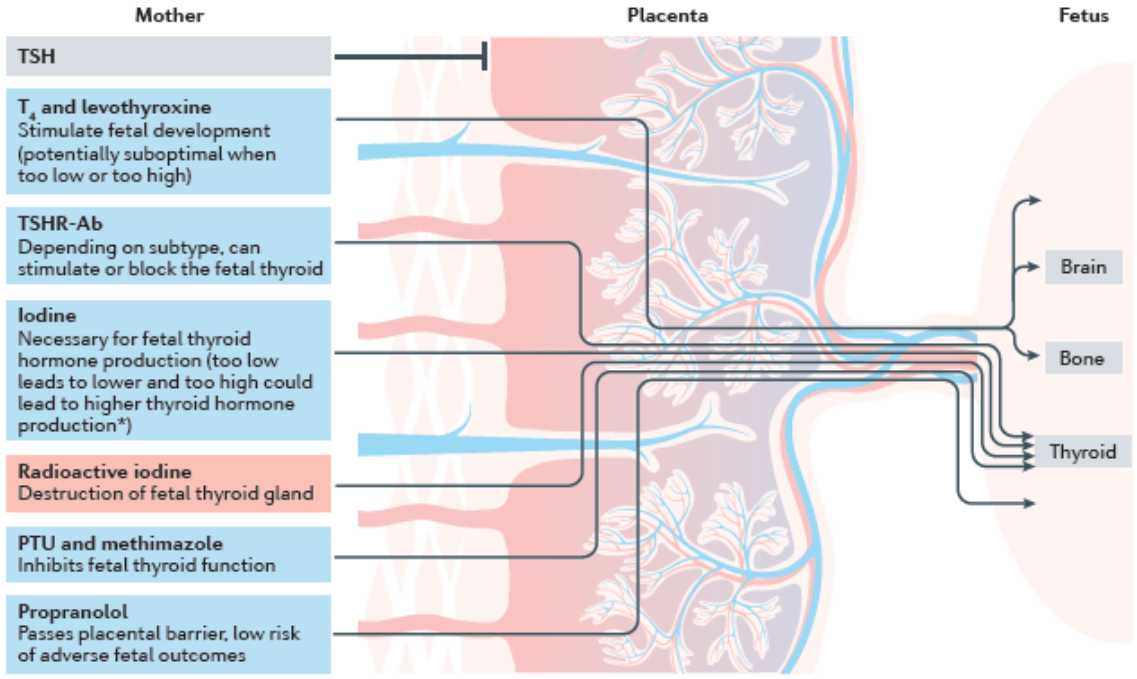
Progression of metastatic thyroid cancer during pregnancy



Xi C et al. JCEM 2021 106(8):e3185-e3197.

I-131 in pregnancy and postpartum period

- I-131 is contraindicated during pregnancy
- If indicated, it should be delayed after delivery
- If breastfeeding, they should be counseled to **stop breastfeeding at least 6 weeks to 3 months prior to I131 radioactive iodine** treatment in order to prevent potential adverse effects of radiation on breast tissues and breastfed infants



Case #5

- A 34-year-old female presents to the Endocrine clinic. She is 8 weeks postpartum. She reports fatigue, anxiety, palpitations, diarrhea. She was able to breastfeed for 4 weeks.

- Past medical history is significant for Hashimoto's thyroiditis. Medications include a prenatal multivitamin.

- On physical examination, she is tachycardic to 104 bpm. The patient's thyroid gland is slightly tender, nonenlarged and no nodules are palpated. + fine tremor of outstretched hands

- Serum thyroid-stimulating hormone level is 0.02 mU/L, FT4 is 2.8 ng/dl (normal 0.9-1.7), TT3 190 ng/dl (normal 90-150), TSI and TBII are sent and pending at this time.

Case #5

- Which is the most likely etiology of her presentation?
  A. Graves' disease
  B. Toxic adenoma
  C. Postpartum thyroiditis
  D. Biotin interference

Case #5 (answer)

❖ Which is the most likely etiology of her presentation?

A. Graves' disease

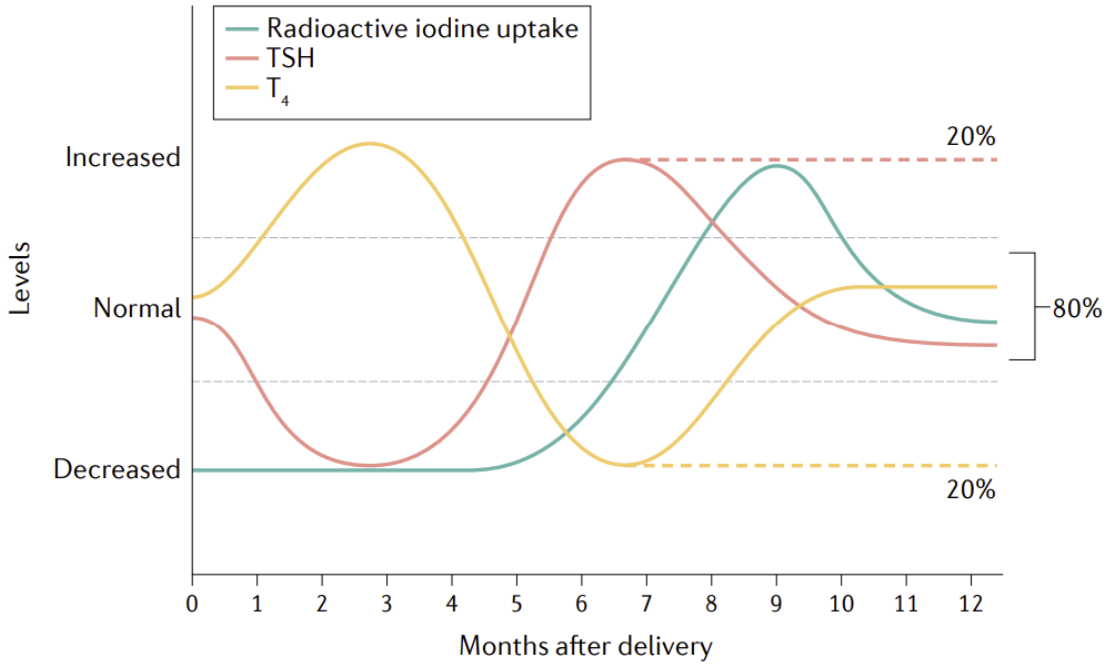
B. Toxic adenoma

C. <u>Postpartum thyroiditis</u>

D. Biotin interference

Post-partum thyroiditis

- Destructive thyroiditis → 5–8% of women within the first 12 months after delivery
- Rebound of underlying thyroid autoimmunity occurring after the immune tolerance induced by pregnancy has ended
- More common with TPO antibodies
- Course varies
  - ~25% of women only have a thyrotoxic phase
  - 50% of women only have a hypothyroid phase.
  - Majority return to euthyroidism
  - Up to 50% will develop persistent hypothyroidism even after initial recovery



Lee SY, Pearce EN. Nat Rev Endo 2022;18: 159.

Summary

- Thyroid diseases are prevalent in pregnancy
- Overt hypothyroidism and hyperthyroidism should be treated
- Subclinical hyperthyroidism is well tolerated, and should be monitored
- Individualized approach on subclinical hypothyroidism
- It is safe to perform FNA during pregnancy
- DTC does not tend to progress during pregnancy (aggressive cancers can be removed in the second trimester)

References

1. Lee, S. Y., & Pearce, E. N. (2022). Assessment and treatment of thyroid disorders in pregnancy and the postpartum period. Nature Reviews Endocrinology, 18(3), 158–171. https://doi.org/10.1038/s41574-021-00604-z

2. Korevaar, T. I. M., Medici, M., Visser, T. J., & Peeters, R. P. (2017). Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews. Endocrinology, 13(10), 610–622. https://doi.org/10.1038/nrendo.2017.93

3. Cooper, David S, Prof, & Laurberg, Peter, Prof. (2013). Hyperthyroidism in pregnancy. The Lancet. Diabetes & Endocrinology, 1(3), 238–249. https://doi.org/10.1016/S2213-8587(13)70086-X

4. Alexander, E. K., Pearce, E. N., Brent, G. A., Brown, R. S., Chen, H., Dosiou, C., Grobman, W. A., Laurberg, P., Lazarus, J. H., Mandel, S. J., Peeters, R. P., & Sullivan, S. (2017). 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid, 27(3), 315–389. https://doi.org/10.1089/thy.2016.0457

5. Bryan R. Haugen, Erik K. Alexander, Keith C. Bible, Gerard M. Doherty, Susan J. Mandel, Yuri E. Nikiforov, Furio Pacini, Gregory W. Randolph, Anna M. Sawka, Martin Schlumberger, Kathryn G. Schuff, Steven I. Sherman, Julie Ann Sosa, David L. Steward, R. Michael Tuttle, & Leonard Wartofsky. (2016). 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 26(1), 1–133. https://doi.org/10.1089/thy.2015.0020

Thank you!

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