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Thyroid Disorders During Pregnancy

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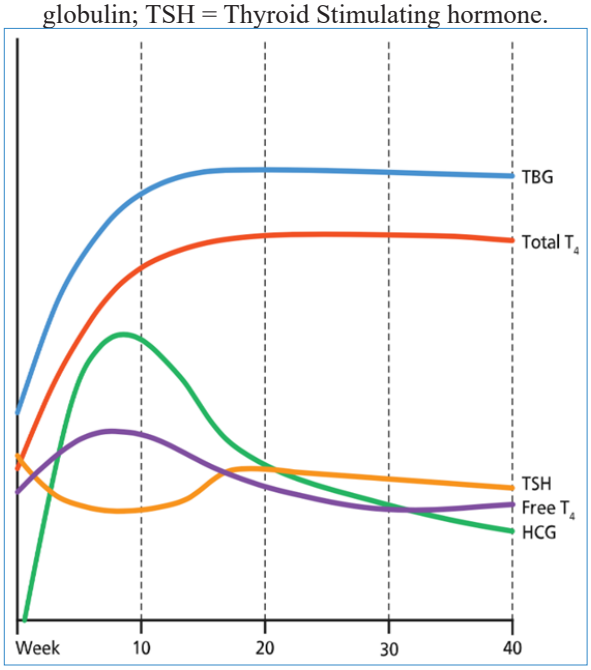
Changes in thyroid hormones during pregnancy. Differentiation of Gestational hyperthyroidism versus Graves' disease[1,2,3,4,5]

- Human Chorion Gonadotropin(hCG) shares a common alpha-subunit with Thyroid-stimulating hormone(TSH) and cross-reacts with the TSH receptor. TSH declines 1st trimester – nl = 0.03-2.0 mU/l. Estrogens increase Thyroid binding globulin (TBG), and Total Thyroxine and total triiodothyronine (TT4/TT3) increase with stable FT3/FT4.
- A radioactive iodine (RAI) scan is contraindicated during pregnancy
- DX of GD first during pregnancy - 0.1-0.4% - Presence of TSH receptor Antibodies, Graves ophthalmopathy, thyroid acropachy, or pretibial myxedema or hyper vascular on Doppler goiter, and continuation of symptoms beyond the first trimester of pregnancy differentiates GD during pregnancy from Gestational hyperthyroidism.
- Gestational hyperthyroidism - usually in the first 12-16 weeks of pregnancy, especially if the woman has hyperemesis gravidarum or molar pregnancy with high hCG. In 1-3% of pregnancies, complications occur. Gestational hyperthyroidism is transient..
- Previously diagnosed Graves' disease before pregnancy usually worsens during the first trimester, with improvement thereafter during pregnancy.

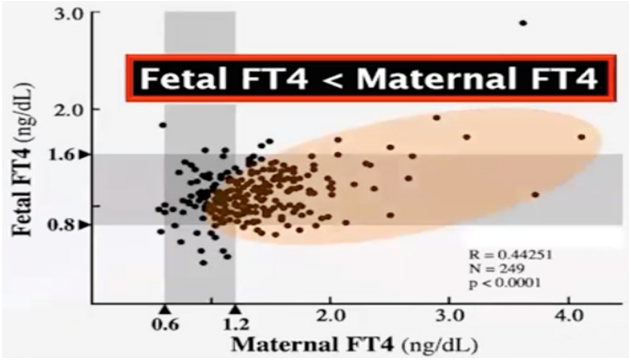
	Gestational thyrotoxicosis	Graves'
Nausea/Emesis	Yes	No
Thyrotoxic symptoms	Variable	Yes
PEx findings of Graves' Goiter, bruit, orbitopathy	No	Yes
TRAb	No	Yes
T3/T4 ratio (ng/mcg/dl)	<20:1	>20:1
Thyroid US POC US by Endo consult team:	Normal size Normal echogenicity Not vascular Thyroid normal size and echogenicity, not vascular	Enlarged Heterogeneous Vascular

Thyroid function in pregnancy. HCG = Human Chronic Gonadotropin; T_4 = Thyroxine, TBG = Thyroid binding globulin; TSH = Thyroid Stimulating hormone.

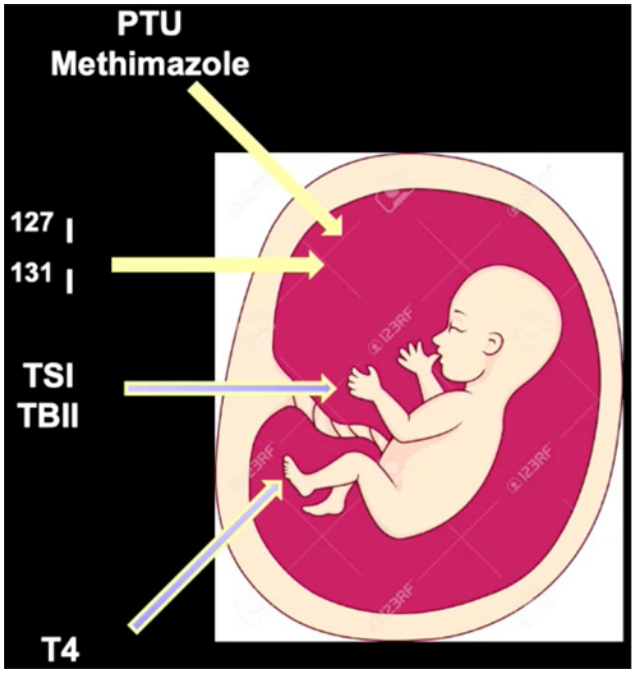


Hyperthyroid Pregnancy

- Infertility
- Spontaneous abortion
- Premature labor
- Small for age infants
- Neonatal mortality
- Maternal CHF
- Goiter
- Pulse greater than 90
- Weight loss
- Muscle weakness
- Increased frequency of bowel movements



Maternal Fetal Transplacental Passage



Pregnancy Hyperthyroidism

- Radioiodine forbidden!
- Try to avoid surgery unless necessary!

Methimazole Embryopathy

- Choanal atresia
- Esophageal atresia / TEF
- Scalp defect (aplasia cutis)
- Omphalocoele
- Omphalomesenteric duct abnormality
- Congenital heart disease (septal defects)
- Andersen et al

JCEM 2013; 98: 4373

Anti-thyroid Drug Concerns

- Neither MMI nor PTU is completely safe in 1st trimester
- PTU may be safer than MMI
- In some studies MMI + PTU may be worse than PTU alone
- Rare liver disease with PTU.
- Defects likely begin at 4 weeks gestation although most seem to occur at 6 - 10 weeks gestation.
- If high doses of ATD are necessary to control
- hyperthyroidism consider definitive therapy prior to pregnancy

PTU Embryopathy

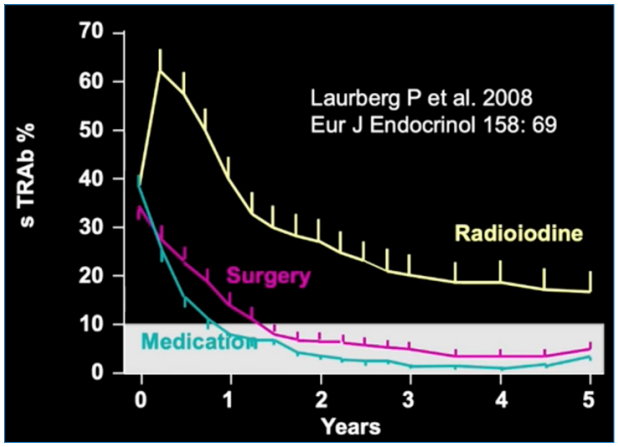
- Face and neck (sinuses and cysts) often requiring surgery
- Hydronephrosis and genital abnormalities (surgery in half)

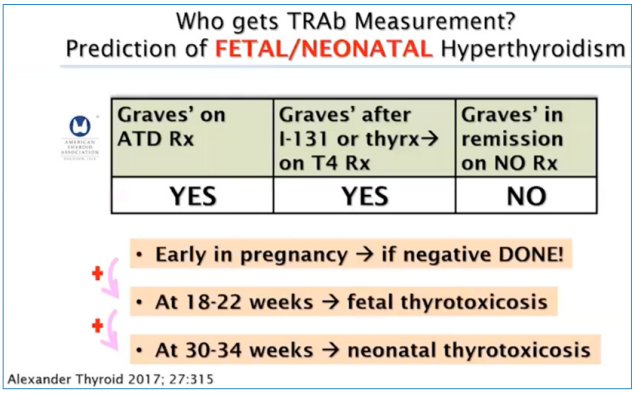
Andersen et al
Thyroid 2014; 24: 1533

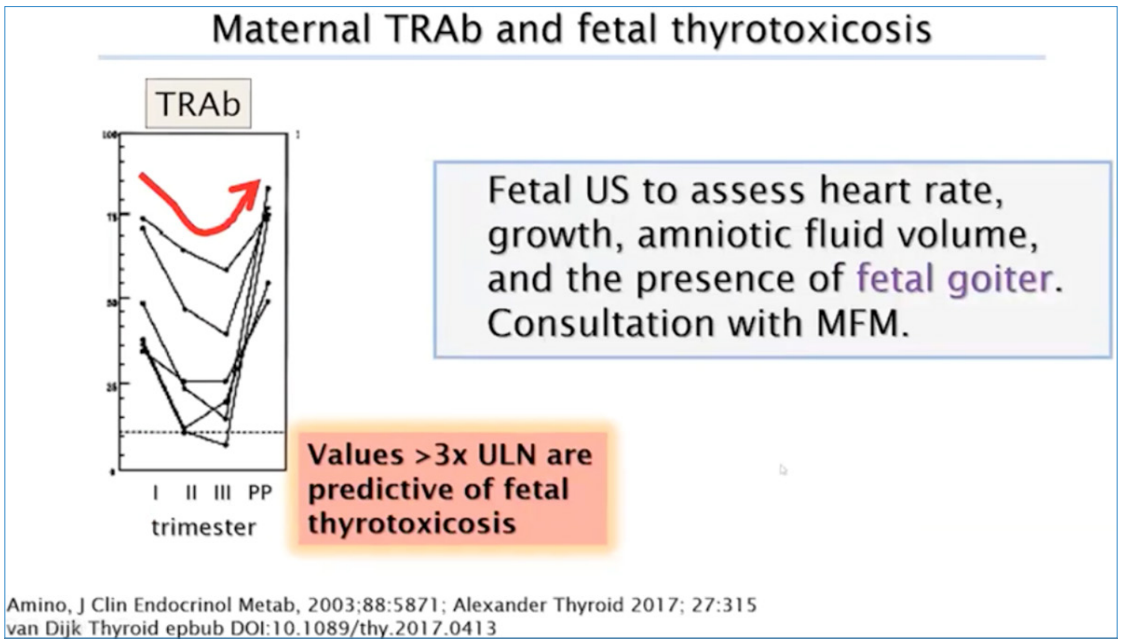
Pregnancy Guidelines for TRAb Measurements

- Euthyroid pregnant woman with prior anti-thyroid drugs for Graves' disease: TRAB measurements not necessary.
- Euthyroid pregnant woman with prior Ral or surgery for Graves' disease: Measure in early pregnancy to assess risk for fetal hyperthyroidism and late for neonatal.
- Pregnant woman on ATD for Graves: Measure TRAB in last trimester to assess for neonatal hyperthyroidism.

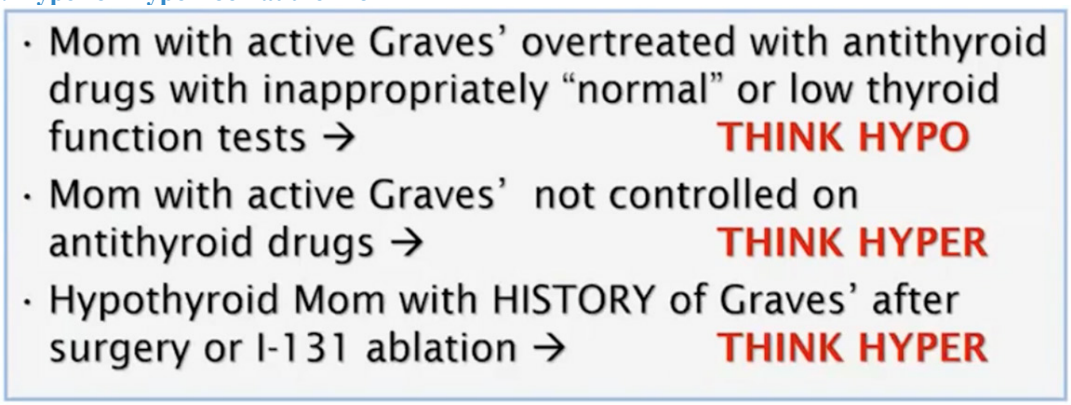
Change in Graves' Autoimmunity







Fetal Goiter : Hyper or Hypo Look at the Mom



What do the ATA 2017 Guidelines Suggest?

- No therapy until 12 weeks (particularly with maintenance
- MMI dosage ≤ 5-10 or PTU ≤ 100-200 mg /day).
- Switch to PTU as early as possible.
- If switch to PTU first trimester consider switch back to MMI second trimester.

ATA 2017 guidelines recommendation 47

Summary

- Gestational thyrotoxicosis-- emesis, ↑ TFTS, T3:T4 <20, no goiter, use ultrasound, TRAB
- Hyperthyroidism--PTU preferred in 1st trimester
- Mild hyperthyroidism→ withdraw Rx if TRAb negative • Use lowest dose of antithyroid drug titrated to FT4 upper normal
- Check TRAB for risk of fetal thyrotoxicosis
  1st trimester TRAB positive → fu TRAB → fetal US

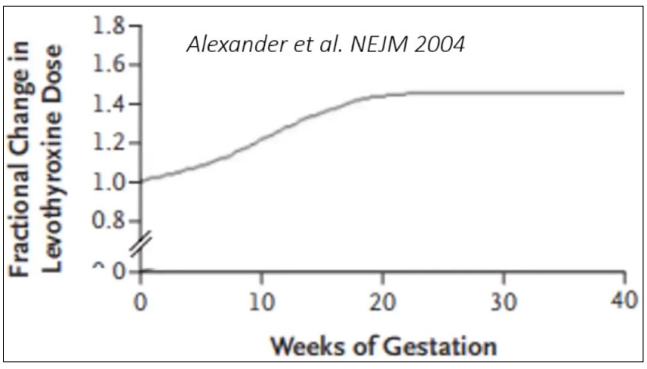
Iodine Requirements and Prenatal Vitamins

- **Iodine deficiency in pregnancy:** intellectual disability, intrauterine growth restriction, goiter

Iodine requirements increase in pregnancy

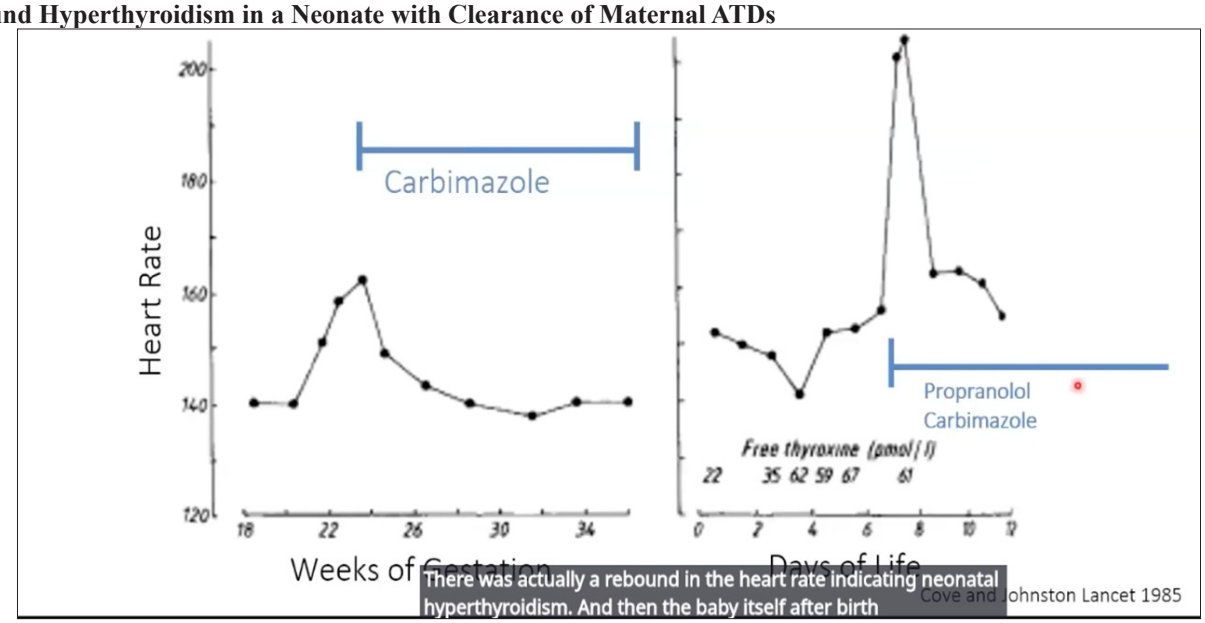
- 150 ug supplementation daily recommended (->220 ug total daily intake)
- 2013 study of urinary iodine: inadequate intake in US pregnant women

Levothyroxine requirements increase 30-50% across gestation



Add 2 pills per week with positive pregnancy test
May require 2 mcg/kg/day (vs 1.6 mcg/kg/day outside pregnancy)
Return to pre-pregnancy dose immediately after delivery

Rebound Hyperthyroidism in a Neonate with Clearance of Maternal ATDs



After delivery, if Thyroid-stimulating Immunoglobulin(TSI) in the mother is positive at 34 weeks, neonatal hyperthyroidism ensues - until 6- months Post partum- We should c/o Methimazole and beta blockers post delivery[6]

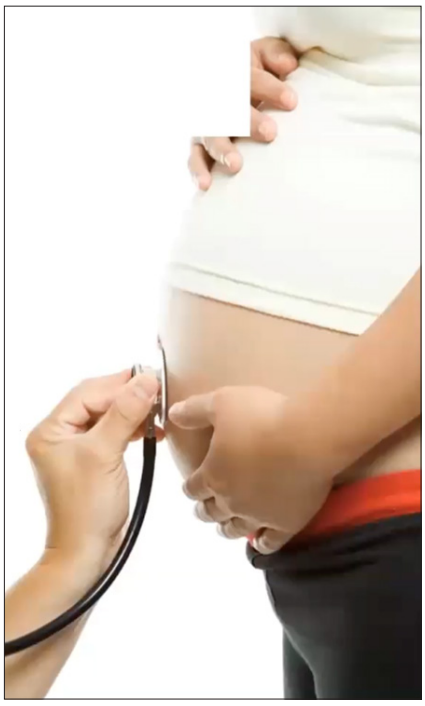
Monitoring for Fatal Thyroid Disease in Pregnants with Graves'

Check Antibodies

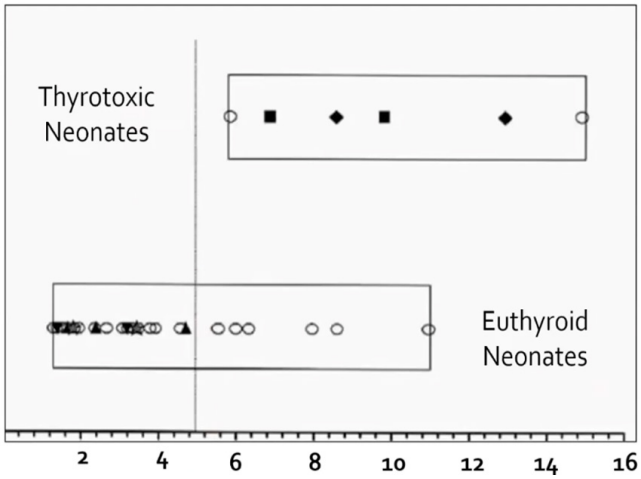
- 18-22 weeks in women s/p RAI or surgery
- 24-28 weeks in active Graves' on ATDs

Monitor (if active or +Abs >3x upper limit)

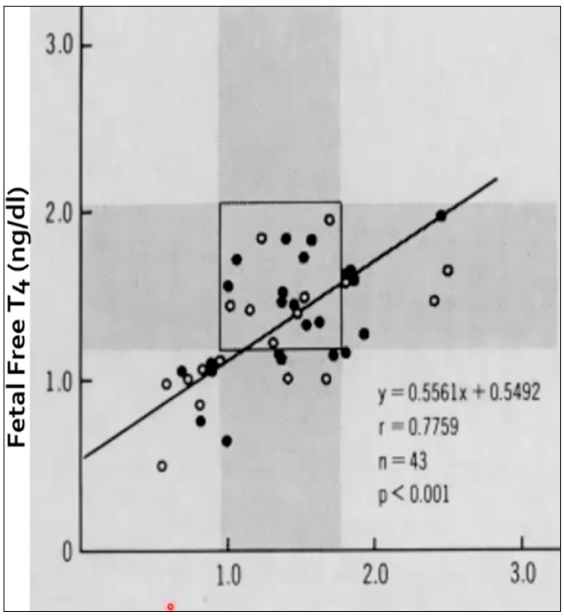
- Fetal heart rate
- Fetal growth
- Fetal thyroid



TSI Predicts Neonatal Thyrotoxicosis



TSI above 3 times nl- predicts fetal/postpartum hyperthyroid in fetus. Usually, TSI decreases with pregnancy but increases postpartum [6,7,8]



Anti Thyroid Drugs and Fetal Thyroid Function:
Maintain maternal free T4 in the upper normal or slightly high range.

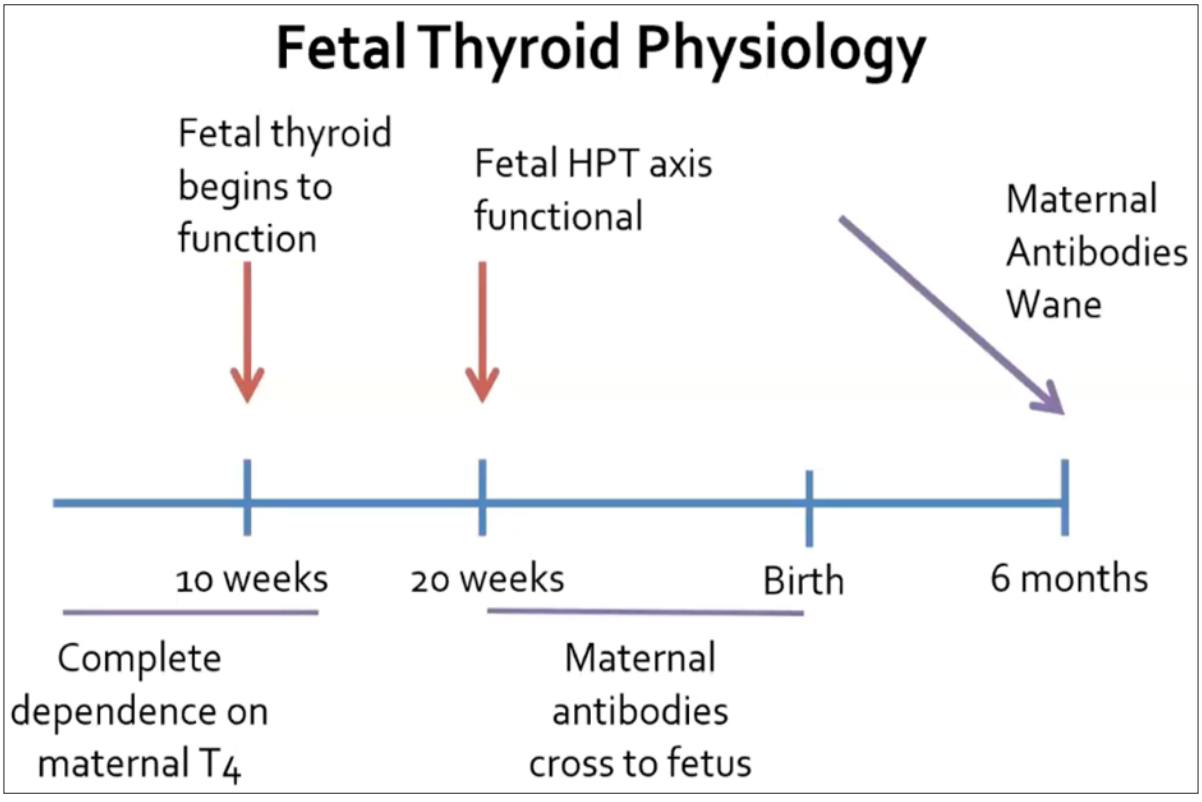
Signs/Symptoms of Fetal Thyroid Disease

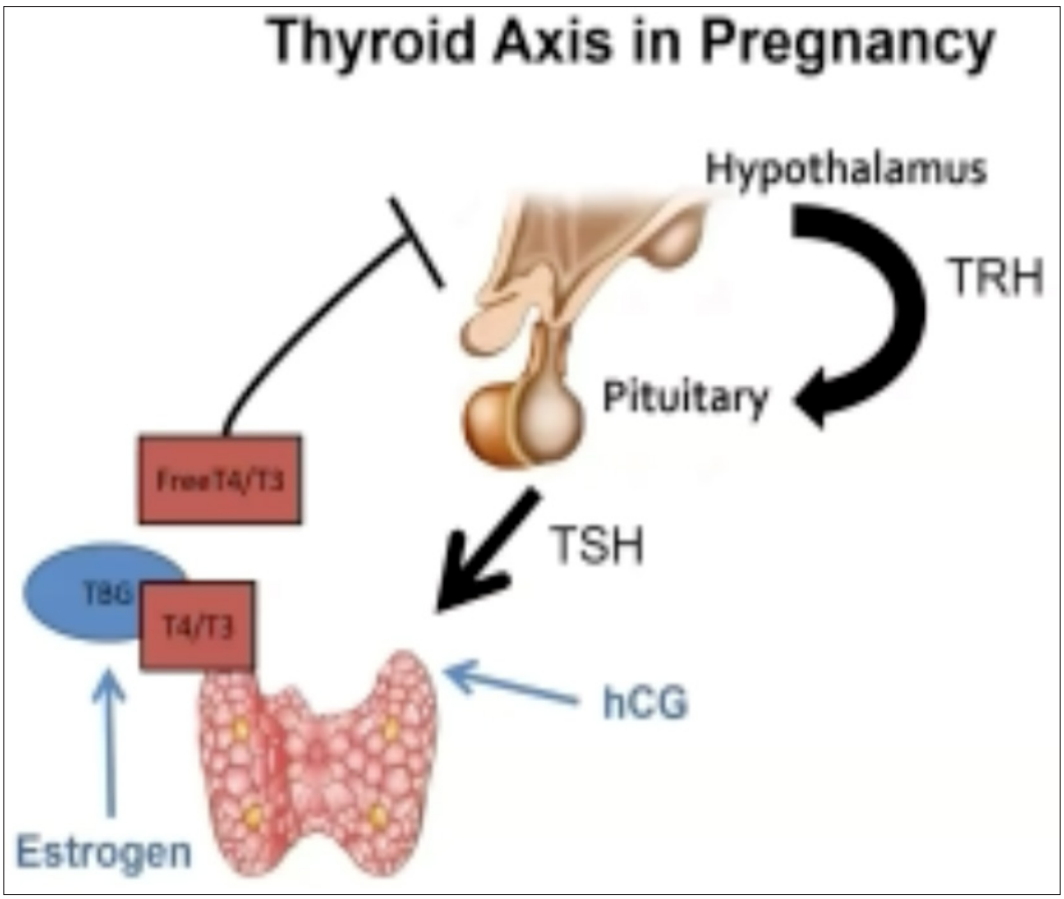
Hyperthyroidism

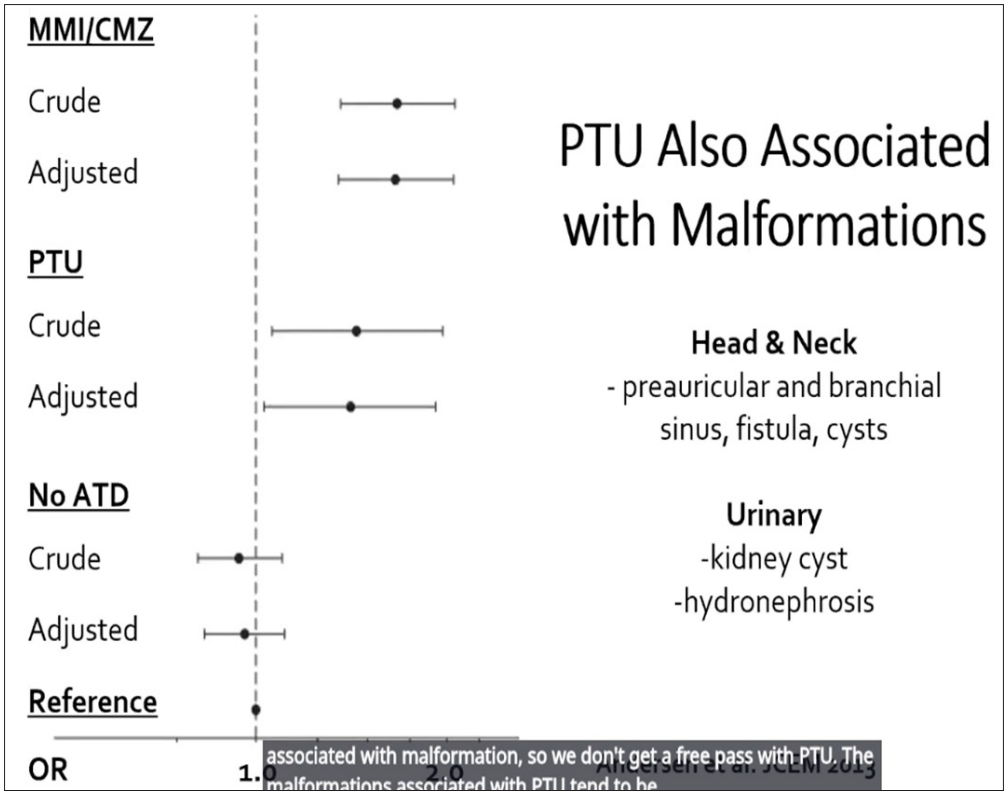
- Goiter
- Fetal Tachycardia
- Growth Restriction
- Hydrops
- Advanced Bone Age

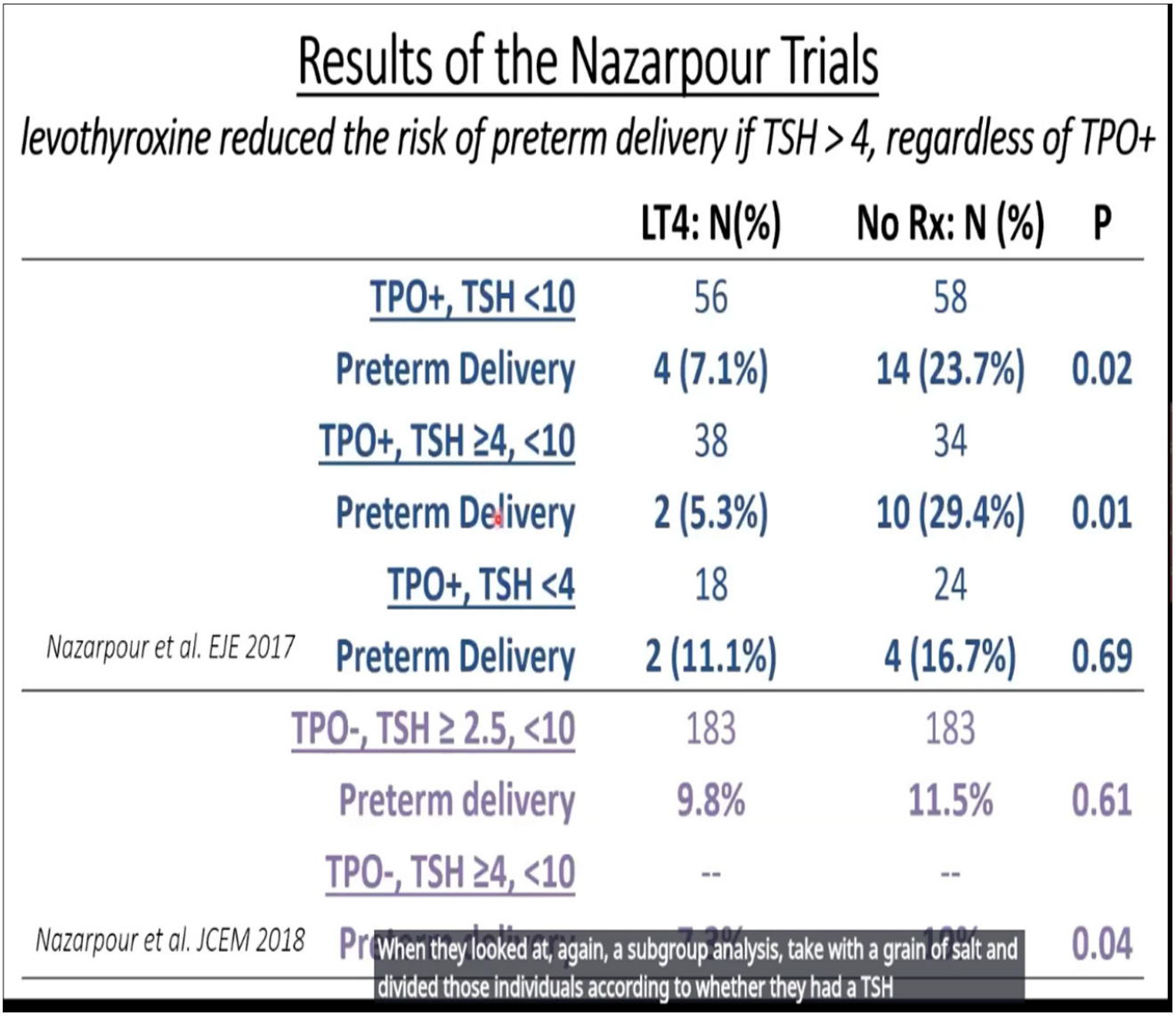
Hypothyroidism

- Goiter
- Delayed bone age
- Impaired neurologic development




Thyroid Axis in Pregnancy
Hypothalamus
TRH
Pituitary
FreeT4/T3
TSH
TBG
T4/T3
hCG
Estrogen


MMI/CMZ
Crude
Adjusted
PTU
Crude
Adjusted
No ATD
Crude
Adjusted
Reference
OR
1.0
PTU Also Associated with Malformations
Head & Neck
- preauricular and branchial sinus, fistula, cysts
Urinary
-kidney cyst
-hydronephrosis
associated with malformation, so we don't get a free pass with PTU. The
malformations associated with PTU tend to be

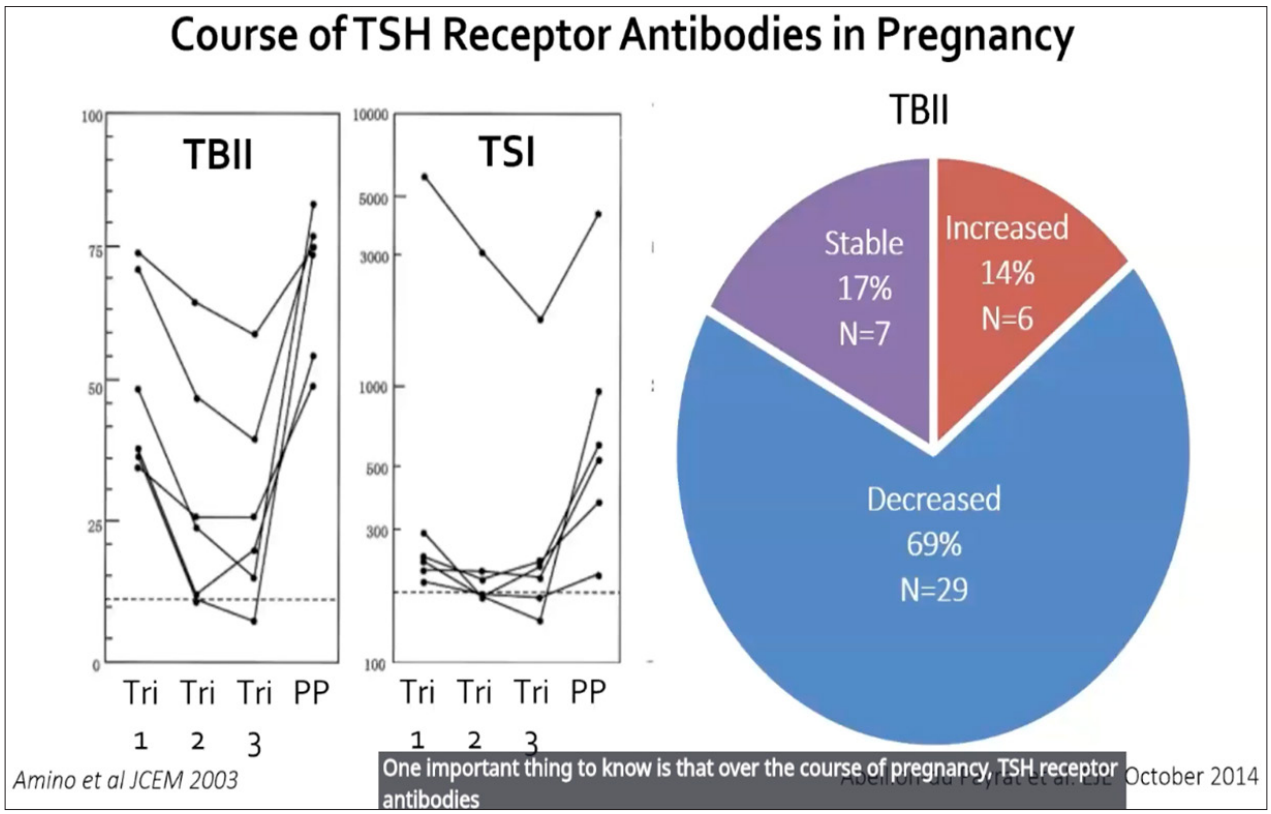


Also, the Intelligence quotient(IQ) if TSH above 10 lower of the fetus compared to no TSH[9]

Indications for TSH Receptor Antibody Assessment in Pregnancy

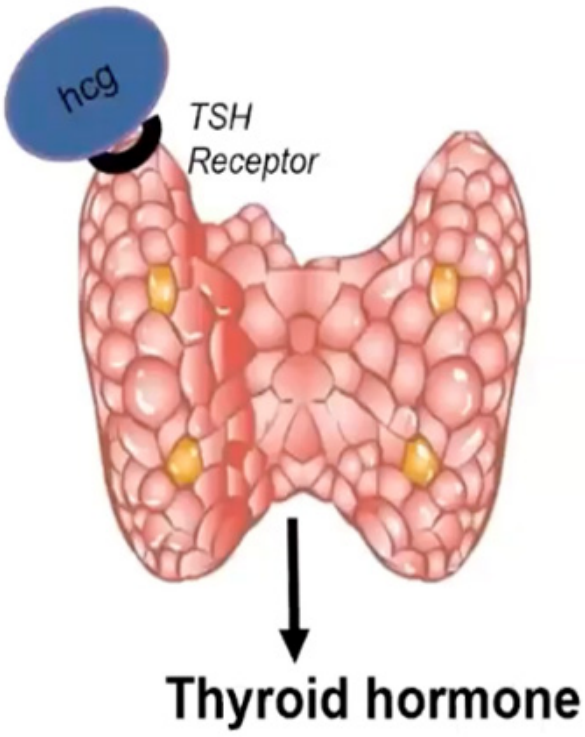
1. To determine cause of hyperthyroidism at diagnosis
2. In early pregnancy (1st trimester, repeat 18-22 wks if ↑`)
3. To determine the risk of fetal hyperthyroidism in definitively treated maternal Graves' (s/p RAI or Surgery) With an intact gland, maternal thyroid function is the best indicator
4. To assess for Graves' remission when considering cessation of anti-thyroid drugs Opportunity to avoid risks of teratogenesis and fetal hypothyroidism!
5. In late pregnancy (30-34 weeks)

To assess risk of neonatal hyperthyroidism in maternal Graves' treated with anti-thyroid drugs Unlikely to increase if low in early pregnancy. And finally, in late pregnancy, we may test these antibodies to assess the risk apte
Lof neonatal hyper

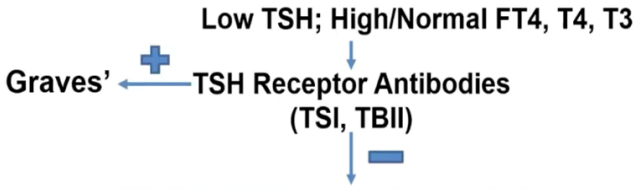


hCG-mediated hyperthyroidism

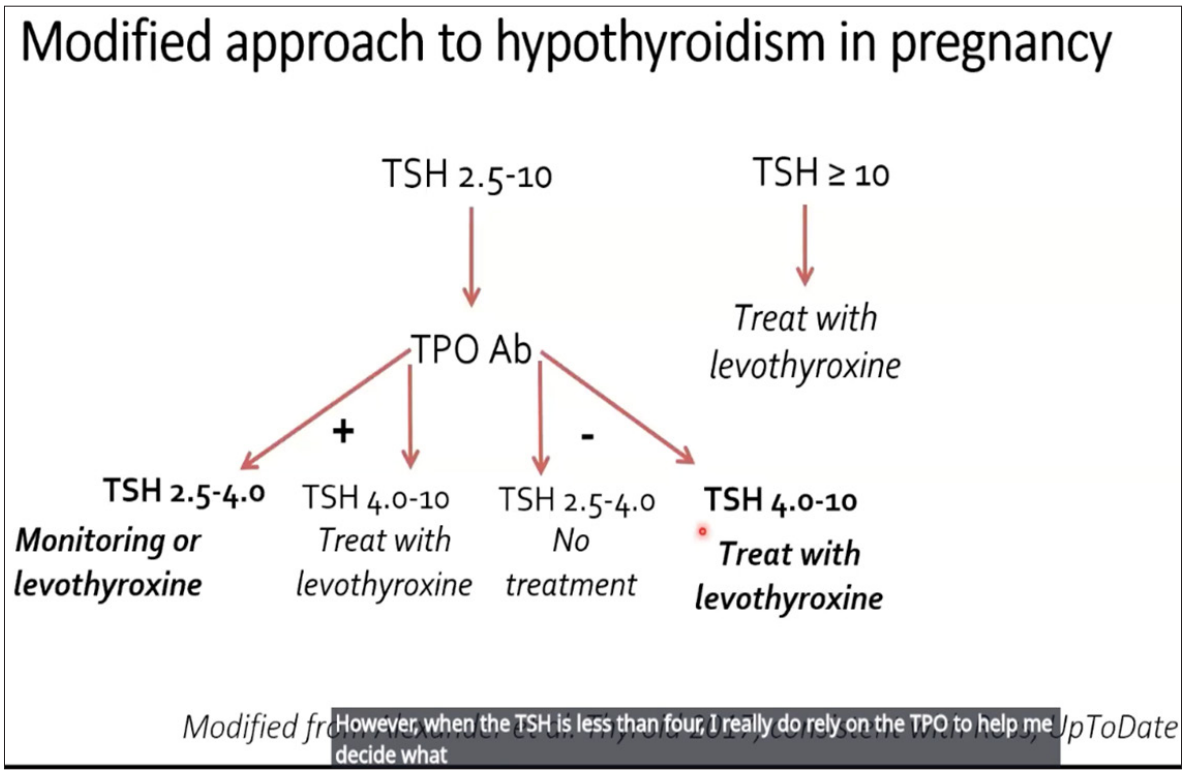
- Syndromes Described:
- Transient Gestational Hyperthyroidism
- Hyperemesis Gravidarum
- Trophoblastic Hyperthyroidism



Evaluation of Hyperthyrodism in Pregnancy



Differential Diagnosis / Use of Ultrasound	
hCG-mediated	No well-defined characteristics on u/s
Toxic nodule(s)	Rare in pregnancy, nodule(s) on u/s
Thyroiditis	Rare in pregnancy, common postpartum, decreased vascularity on u/s
Antibody-negative Graves'	Minimal fetal risk, but postpartum implications

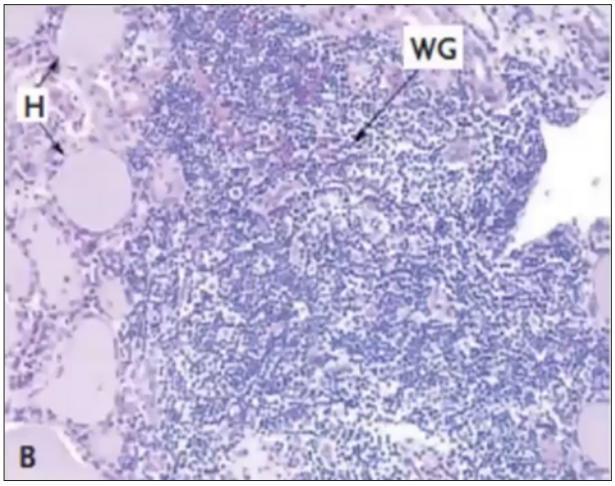


Most Experts Recommend if TPO Antibody is Positive and TSH is Above or Equal To 2.5, To Treat with Levothyroxine During or Before The Pregnancy

Anti Thyroid Peroxidase (TPO) Antibodies

Associated with

- pregnancy loss
- preterm birth
- childhood neurocognitive outcomes
- (IQ, ADHD)
- postpartum thyroiditis

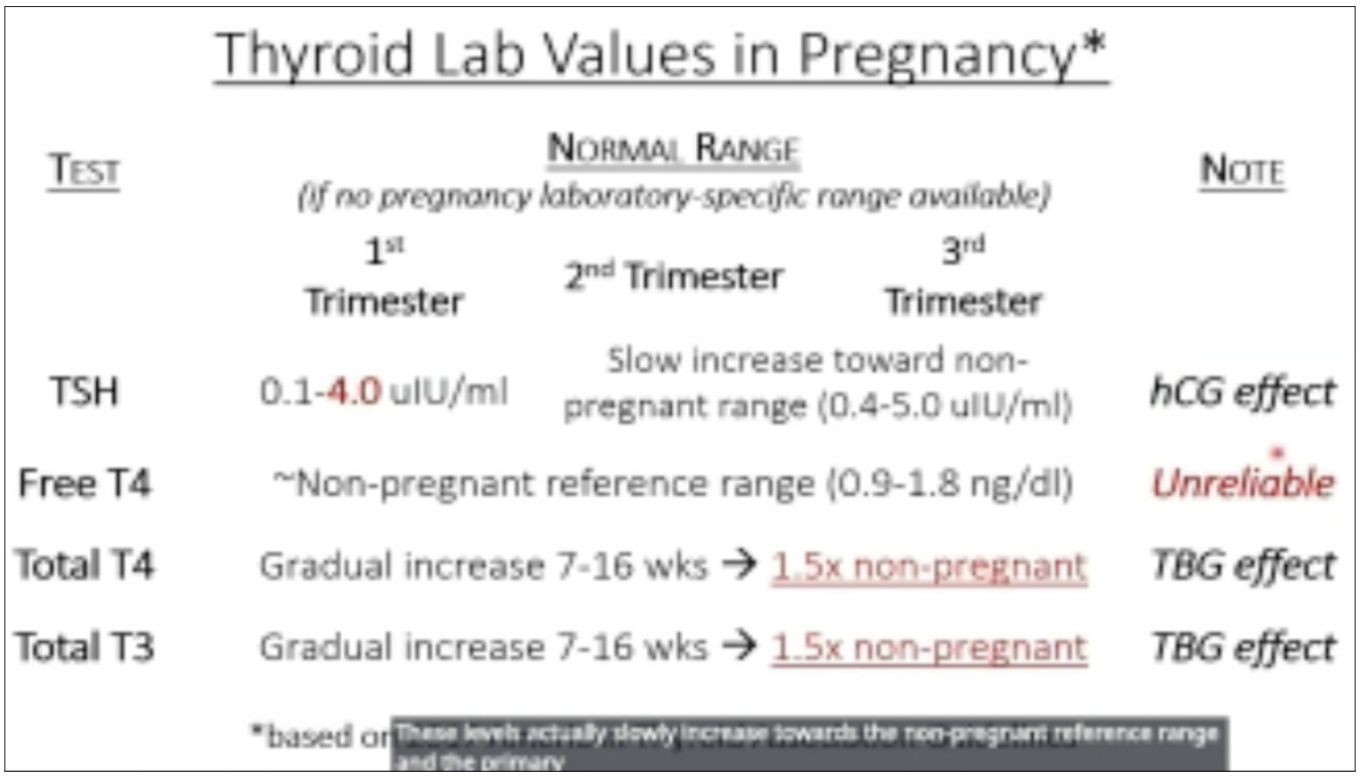


Subclinical Maternal Hypothyroidism

- Pregnancy Loss?
- Preterm Birth?
- Low Birth Weight?
- Hypertensive Disorders of Pregnancy?
- Childhood Neurocognitive Outcomes (e.g. IQ)?

Overt Maternal Hypothyroidism

- Pregnancy Loss
- Preterm Birth
- Low Birth Weight
- Hypertensive Disorders of Pregnancy
- Childhood Neurocognitive Outcomes (e.g. IQ)



Key Points: Thyroid Disease and Pregnancy

- In normal pregnancy, thyroid hormone requirements increase
- Treat subclinical hypothyroidism with TSH > 4.0 regardless of TPO; consider treating TSH 2.6 to 4.0 with +TPO
- Use TSH receptor antibodies to distinguish Graves' disease from hCG- mediated hyperthyroidism (usually self-limited)
- Both methimazole and PTU (1st trimester exposure) are associated with congenital malformations
- When treating overt hyperthyroidism in pregnancy, maintain mild maternal hyperthyroidism to avoid fetal hypothyroidism
- Monitor for fetal/neonatal Graves' when maternal TSH receptor antibodies are >3x the upper limit of normal

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