به نام

خداوند

جان و خرد

Thyroid And pregnancy

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OUTLINE

- Thyroid Autoimmunity &Pregnancy
- Normal changes during pregnancy
- Hypothyroidy &Pregnancy
- Hyperthyroidy&Pregnancy
- Post partum & lactation

IODINE STATUS AND NUTRITION

- **What is the recommended daily iodine intake in women planning pregnancy, women who are pregnant, and women who are breastfeeding?**

250 µg/d in pregnancy & lactation

A daily oral supplement *150 lg of iodine*

3months before pregnancy.

No need to iodine supplementation :

1) In pregnant women who are being treated for hyperthyroidism
2) who are taking LT4

Sustained iodine intake exceeding 500 lg daily should be avoided during

(potential for fetal thyroid dysfunction)

- A 25 year old woman is seeking lab tests for prepregnancy evaluation.
- Do you screen her for thyroid dysfunction?

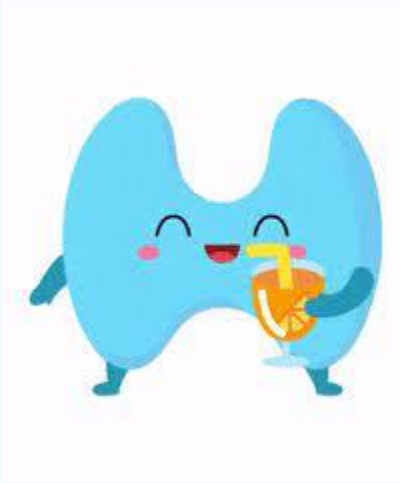
Screening for Thyroid Dysfunction Before or During Pregnancy

- There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy.

Testing for serum TSH is recommended:

1. A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
2. Known thyroid antibody positivity or presence of a goiter
3. History of head or neck radiation or prior thyroid surgery
4. Age >30 years
5. Type 1 diabetes or other autoimmune disorders

Screening for Thyroid Dysfunction Before or During Pregnancy



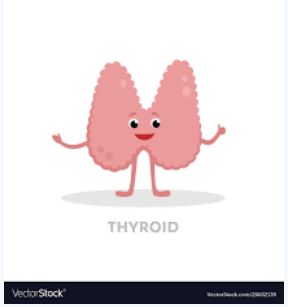
6. History of pregnancy loss, preterm delivery, or infertility
7. Multiple prior pregnancies (> 2)
8. Family history of autoimmune thyroid disease or thyroid dysfunction
9. Morbid obesity (BMI > 40 kg/m2)
10. Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
11. Residing in an area of known moderate to severe iodine insufficiency

- A 38-year-old woman with a history of 2 first trimester miscarriages presents for prepregnancy counseling. She has no notable medical history. Laboratory test results:

  TSH = 2.4 mIU/L (0.4-4.0 mIU/L)

  Free T4 = 1.1 ng/dL (0.8-1.8 ng/d)

  TPO antibodies = 320 IU/mL



- **Which of the following should be advised?**

  A. Start levothyroxine, 1.6 mcg/kg daily

  B. Start levothyroxine, 25 to 50 mcg daily

  C. Reassure the patient and recommend routine antenatalcare

  D. Repeat thyroid function tests in the first trimester of pregnancy

  E. Recommend glucocorticoid treatment in the first trimester of pregnancy

THYROID AUTO-ANTIBODIES AND PREGNANCY COMPLICATIONS

Anti-TPO or anti-Tg thyroid autoantibodies in

2% to 17% of pregnant women

Associated with increased risk for preterm delivery

Euthyroid pregnant with positive TPOAb or TgAb

measurement of TSH at time of pregnancy

every 4 weeks through midpregnancy

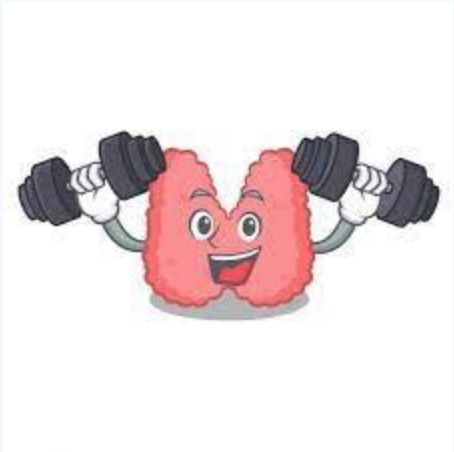
at list repeated one more time in 26-32 weeks of pregnancy.

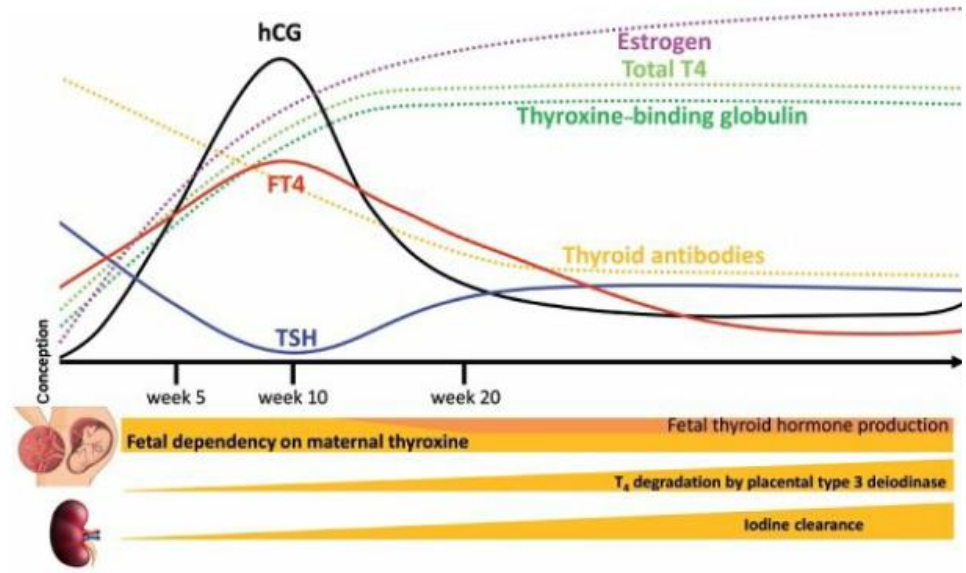
- Does treatment with LT4 or intravenous immunoglobulin therapy or selenium decrease the risk for pregnancy loss in euthyroid women with thyroid autoimmunity?

Is not Recommended

THYROID FUNCTION TESTING AND PREGNANCY

- How do thyroid function tests change during pregnancy?
- What is the normal reference range for serum TSH concentrations in each trimester of pregnancy?





NORMAL CHANGES IN PREGNANCY

PHYSIOLOGICAL CHANGE	IMPACT
Iodine clearance (renal & transplacental)	Relative iodine deficiency state Risk of fetal & maternal hypothyroidism
Placental deiodination of T4	T4 ⟶ Reverse T3
TBG ↑	TT3 & TT4 levels ↑ FT4 same
1st trimester HCG ↑ (Weak TSH effect)	FT4 ↑ & TSH ↓ Fetal & placental devp
3rd trimester - placenta enlarge, preparation for delivery	FT4 ↓ & TSH ↑ Mild hypothyroidism
TSHR Ab reduced	Grave's disease improvement
Postpartum increase in thyroid Ab	Postpartum thyroiditis Grave's disease exacerbation

HYPOTHYROIDISM AND PREGNANCY

- HYPOTHYROIDISM

- 1-3 per 1000 pregnancies
- Types:

  OVERT HYPOTHYRODISM

  SUBCLINICAL HYPOTHYRODISM

  ISOLATED HYPOTHYROXINEMIA

• SUBCLINICAL HYPOTHYROIDISM

- Elevated TSH & Normal FT4 & FT3
- 2-5% in pregnancy
- 31% positive for TPO Ab
- Associated with Gest HTN, preterm deliveries, stillbirths, abruption.
- Fetal psychomotor development may be impaired.

ISOLATED HYPOTHYROXINEMIA

- Normal TSH, FT4 ↓
- 1-2% pregnancies
- No adverse effects in pregnancy(may be cognitive developmen impairment,Prematurity low birth weight)
- No benefit of levothyroxine therapy

Isolated hypothyroxinemia should not be routinely treated in pregnancy

EFFECTS OF HYPOTHYROIDISM

- *ON PREGNANCY*
  - Prolonged infertility t/t
  - Recurrent abortions
  - Preeclampsia 5-10%
  - Placental abruption 1%
  - Preterm delivery 10-15%
  - Anemia
  - Myxedema coma
  - LBW
  - Stillbirth

ON FETUS

- Neurodevelopmental delay
- Deafness
- Stunted growth
- Peripartum hypoxia
- Neonatal mortality

- A 32-year-old woman presents for her first antenatal appointment at 8 weeks' gestation. She has had 3 first-trimester miscarriages. Laboratory test results: TSH = 4.2 mIU/L (0.4-4.0 mIU/L) Free T4 = 0.9 ng/dL (0.8-1.8 ng/dL) TPO antibodies = 350 IU/mL
- **Which of the following should be advised?**

A. Reassure patient and discharge to routine antenatal care

B. Repeat thyroid function tests after 4 weeks

C. Repeat thyroid function tests at 20 weeks' gestation

D. Start levothyroxine, 1.6 mcg/kg daily

E. Start levothyroxine, 25 to 50 mcg daily

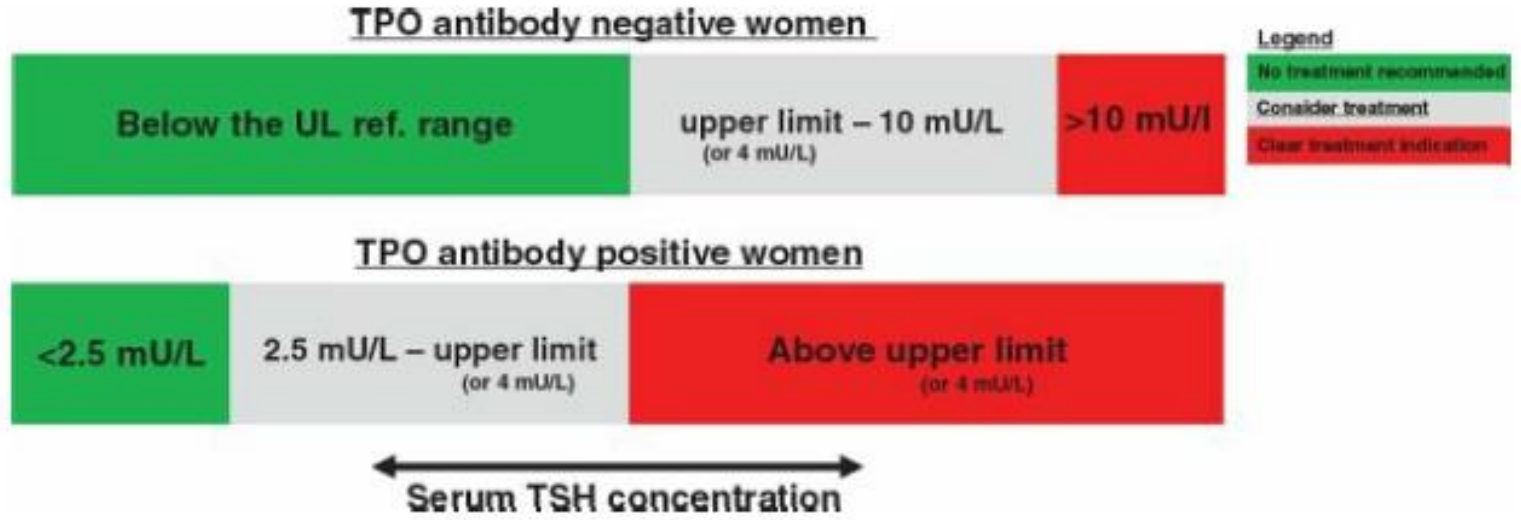
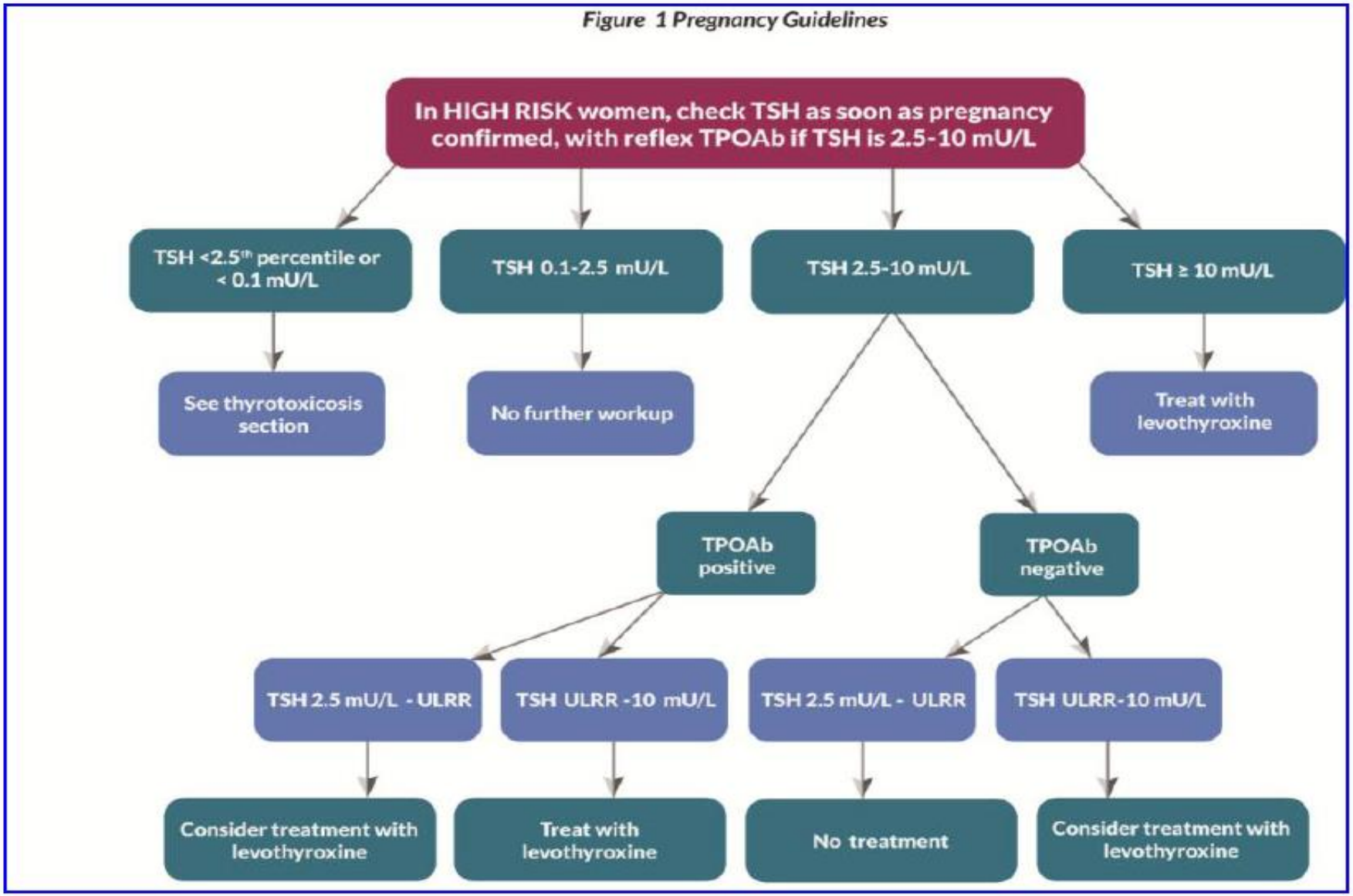

TPO antibody negative women
Below the UL ref. range
upper limit – 10 mU/L
(or 4 mU/L)
>10 mU/l
Legend
No treatment recommended
Consider treatment
Clear treatment indication
TPO antibody positive women
<2.5 mU/L
2.5 mU/L – upper limit
(or 4 mU/L)
Above upper limit
(or 4 mU/L)
Serum TSH concentration

Figure 1 Pregnancy Guidelines



- A 26-year-old lady, who is a known hypothyroid for 5 years, on levothyroxine 50 µg per day presented at 12 weeks of gestation with a TSH of 13 mIU/ml. How to optimize the therapy?

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

- In hypothyroid women treated with levothyroxine who are planning pregnancy, serum TSH should be evaluated preconception, and levothyroxine dose adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.

- Between 50% and 85% of LT4-treated hypothyroid women need to increase exogenous LT4 dosing during pregnancy.

- The incremental increase largely depends on the underlying etiology of the hypothyroidism.

- There is a greater likelihood that dose increases will be required in those patients without functional thyroid tissue (e.g., due to radioablation or surgery) in comparison with patients with Hashimoto's thyroiditis.

- The LT4 adjustment should be made as soon as possible after pregnancy is confirmed to reduce the probability of hypothyroidism.

HOW SHOULD PRECONCEPTION LEVOTHYROXINE BE ADJUSTED IN TREATED HYPOTHYROID WOMEN PLANNING PREGNANCY?

- levothyroxine dose should be adjusted to achieve a **TSH <2.5 (<1)**
- with a suspected or confirmed pregnancy (e.g. positive home pregnancy test) should independently **increase their dose of LT4 by ~20-30%**
- One means of accomplishing this is to

  administer 2 additional tablets weekly of the patient'scurrent daily levothyroxine dosage.

WHAT IS THE BIOCHEMICAL GOAL WHEN TREATING HYPOTHYROIDISM IN PREGNANT WOMEN?

- TSH< 2.5 mU/L (first trimester)
- TSH< 3mU/L (second trimester)
- TSH< 3mU/L (third trimester)

HOW SHOULD LT4 BE ADJUSTED POSTPARTUM?

Following delivery, LT4 should be reduced to the patient's preconception dose

- **women with Hashimoto's thyroiditis may required an increase in the pregestational dose in the postpartum period**

(presumably due to an exacerbation of autoimmune thyroid dysfunction postpartum)

- **Additional thyroid function testing should be performed at approximately 6 weeks postpartum**

- **women in whom LT4 is initiated during pregnancy may not require LT4 postpartum especially when the LT4 dose is ≤50 mcg daily**

- **If LT4 is discontinued, serum TSH should be evaluated in ~ 6 weeks.**

ARE EUTHYROID WOMEN AT RISK FOR HYPOTHYROIDISM ONCE PREGNANT?

- anti-thyroid Ab positive(TPOAb- or TgAb)
- posthemithyroidectomy

serum TSH every 4 weeks until mid-gestation
and
at least once near 30 weeks gestation

- treated with radioactive iodine

- should be monitored regularly in pregnancy

SHOULD ADDITIONAL MATERNAL OR FETAL TESTING RECOMMEND IN TREATED, HYPOTHYROID WOMEN DURING PREGNANCY?

- no other maternal or fetal testing (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) is recommended beyond measurement of maternal thyroid function unless needed due to other circumstances of pregnancy.

An exception!!

- women with Graves' disease effectively treated with 131I ablation(6 years) or surgical resection(1year), require TRAb monitoring

THYROTOXICOSIS IN PREGNANCY

- **What are the causes of thyrotoxicosis in pregnancy?**
- The most common cause of hyperthyroidism in women of childbearing age is:

autoimmune GRAVES DESEASE

occurring before pregnancy in 0.4%–1.0 % of women and in approximately 0.2% during pregnancy.

- Less common non-autoimmune causes include:

  toxic multinodular goiter and toxic adenoma.

  Subacute painful or painless thyroiditis

  TSH-secreting pituitary adenoma

  factitious

“Gestational transient thyrotoxicosis”

- limited to the first half of pregnancy.
- 1%–3% of pregnancies.
- Secondary to elevated hCG levels.
- Often it is associated with **hyperemesis gravidarum**, defined as severe nausea, vomiting , more than 5% weight loss, dehydration, and ketonuria.

- Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation, hydatidiform mole, and choriocarcinoma

What is the appropriate initial evaluation of a suppressed serum TSH concentration during the first trimester of pregnancy?

- Serum TSH may decrease in the first trimester of normal pregnancy as a physiological response to the stimulating effect of hCG upon the TSH receptor.
- A peak hCG level typically occurs between 7 and 11 weeks gestation.
- In particular, a serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in approximately 5% of women by week 11 of pregnancy .
- The biochemical diagnosis of overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or T3.

How can gestational transient thyrotoxicosis be differentiated from Graves' hyperthyroidism in pregnancy?

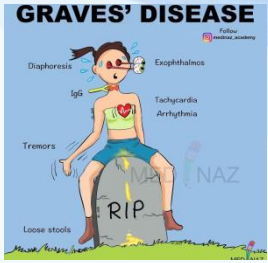
- In both situations, common clinical manifestations include palpitations, anxiety, tremor, and heat intolerance.
- A careful history and physical examination is of utmost importance in establishing the etiology.
- The findings of no prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), a self-limited mild disorder, and symptoms of emesis favor the diagnosis of gestational transient thyrotoxicosis.
- If other causes for thyrotoxicosis are suspected, measurement of TRAb is indicated.
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.

What is the appropriate management of gestational transient thyrotoxicosis?

- Antithyroid drugs (ATDs) are not indicated because the serum T4 returns to normal by 14–18 weeks gestation and ATD use in early pregnancy increases risk of birth defects.
- The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed.

- ATDs are not recommended, though b-blockers may be considered.

How should women with GD seeking future pregnancy be counseled?



- Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy.
- Treatment options:

  131I ablation

  Surgical thyroidectomy

  ATD therapy.
- TRAb levels tend to increase following 131I therapy and may remain elevated for many months following 131I therapy.
- Patients with high TRAb levels or severe hyperthyroidism may favor consideration of other therapeutic options such as surgery.

- In a newly pregnant woman with GD, who is euthyroid on a low dose of MMI (<=5–10 mg/d) or PTU (<=100– 200 mg/d), the physician should consider discontinuing all antithyroid medication given potential teratogenic effects.

Following cessation of antithyroid medication:

1) Thyroid function testing (TSH, and FT4 or TT4)
2)Clinical examination should be performed every 1–2 weeks

If remains clinically and biochemicall yeuthyroid:

Test intervals may be extended to 2–4 weeks during the second and third trimester.

- Factors predicting high clinical risk include being currently hyperthyroid, or requirement of >5–10 mg/d MMI or >100–200 mg/d PTU to maintain a euthyroid state.

- (a) PTU is recommended for the treatment of maternal hyperthyroidism through 16 weeks of pregnancy.

- (b) Pregnant women receiving MMI who are in need of continuing therapy during pregnancy should be switched to PTU as early as possible.

- (c) When shifting from MMI to PTU, a dose ratio of approximately 1:10 should be used (e.g., MMI 5 mg/ d = PTU 50 mg twice daily).

- (d) If ATD therapy is required after 16 weeks gestation, it remains unclear whether PTU should be continued or therapy changed to MMI.

What are the principles of thyroid testing and ATD administration when treating Graves' hyperthyroidism during pregnancy?

- Importantly, all ATDs tend to be more potent in the fetus than in the mother.

  Thus, when the mother is made euthyroid, the fetus is often overtreated(fetal goiter and or fetal hypothyroidism.

The smallest dose of ATDs to maintain maternal TT4/FT4 just above the pregnancy-specific upper limit of normal

Maternal TT4/FT4 and TSH (and in cases of severe hyperthyroidism, also serum T3) :

every 2–4 weeks following initiation of therapy

every 4– 6 weeks after achieving the target value.

A TT4 measurement with reference value 1.5 times the nonpregnancy range may be used insecond and third trimest

- In the first trimester of pregnancy some women with GD experience an exacerbation of symptoms, which is parallel to the moderate increase in incidence of GD in early pregnancy.

- By the third trimester the incidence of GD becomes very low corresponding to the general decrease in thyroid autoimmunity with a decrease in TRAb.

- Discontinuation of all ATD therapy is feasible in 20%– 30% of patients in the last trimester of gestation.
- Maternal serum TSH well within the reference range is a sign that the ATD dose has to be reduced to avoid fetal overtreatment.

What are the indications and timing for thyroidectomy in the management of GD during pregnancy?

1)Allergies/contraindications to both ATD
2) Not compliant with drug therapy
3) euthyroidism cannot be achieved even on large doses of ATDs

- If surgery is indicated, the second trimester is the optimal time.

- Thyroidectomy is often followed by a gradual, but not immediate disappearance of TRAb, and withdrawal of ATD in the mother after thyroidectomy may lead to isolated fetal hyperthyroidism.

- High serum TRAb values before surgery indicate a risk for isolated fetal hyperthyroidism, and after maternal ATD withdrawal a program of careful fetal monitoring and possible therapy should be planned.

What is the value of TRAb measurement in the evaluation of a pregnant woman with Graves' hyperthyroidism?

- Fetal risks in women with previous or current Graves' hyperthyroidism include:

  (a) fetal hyperthyroidism,

  (b) neonatal hyperthyroidism

  (c) fetal hypothyroidism

  (d) neonatal hypothyroidism

  (e) central hypothyroidism

- TRAb is measurable in around 95% of patients with active Graves' hyperthyroidism, and levels may remain high following ablation therapy, even more so after radioiodine treatment than surgical removal.

Indications for ordering a TRAb test in pregnant women with GD include:

- Indications for ordering a TRAb test in pregnant women with GD include:

(a) Mothers with untreated or ATD-treated hyperthyroidism in pregnancy

(b) A previous history of GD with past treatment with radioiodine or total thyroidectomy

(c) A previous history of delivering an infant with hyperthyroidism

(d) A known history of thyroidectomy for the treatment of hyperthyroidism in pregnancy

- A determination of serum TRAb in late pregnancy in a mother who is still in need of ATD therapy to remain euthyroid, is helpful for detecting risk for neonatal hyperthyroidism.

- If TRAb becomes undetectable in a pregnant woman taking ATD, it may be feasible to reduce or withdraw the ATD to protect the fetus against hypothyroidism and goiter.

- In women who are in remission and euthyroid after a previous course of ATD therapy for GD, measurement of TRAb in pregnancy is not required.

How should hyperthyroidism caused by autonomous thyroid nodules be handled in pregnancy?

Quite rare under the age of 40 years
more insidiously and be less severe than in GD

no TRAb is produced by the mother ➡ the fetal thyroid is not stimulated as it is in GD.

If the mother become euthyroid
the risk of hypothyroidism and goiter in the fetus would significantly increase

A low dose of ATD should be administered :
goal of maternal FT4 or TT4 concentration

upper limit or moderately above

Carefull monitoring for :
goiter and signs of hypothyroidism during the second half of pregnancy.

Maternal surgical therapy with removal of autonomous nodule(s)

considered if signs of fetal hypothyroidism develop.

Generally, if possible, ablative therapy should be considered before conception for hyperthyroidism caused by thyroid autonomy in women seeking future pregnancy.

What are the etiologies of thyrotoxicosis in the postpartum period?

The most common :postpartum thyroiditis (PPT)

- Mild and of short duration
spontaneously revert to euthyroidism and the majority return to normal in one year post partum

severe cases in need of a short course of b-blockers are seen in patients with high levels of TPOAb, and they are often followed by aperiod of hypothyroidism.

❖The postpartum increase in thyroid autoimmunity is also associated with a 3- to 4-fold increase in the incidence of new GD,in addition to the increase in the risk of relapse of GD in remission after previous ATD therapy.

Thyroid Disease and Lactation

- As maternal hypothyroidism can adversely impact lactation, women experiencing poor lactation without other identified causes should have TSH measured to assess for thyroid dysfunction.
- Given its adverse impact upon milk production and letdown, subclinical and overt hypothyroidism should be treated in lactating women seeking to breastfeed.
- The impact of maternal hyperthyroidism upon lactation is not well understood. Therefore, no recommendation to treat maternal hyperthyroidism on the grounds of improving lactation can be made at this time.

ARE ANTITHYROID MEDICATIONS (PTU, MMI) TRANSFERRED INTO BREAST MILK, AND WHAT ARE THE CLINICAL CONSEQUENCES TO THE BREASTFED INFANT?

- Together, these data have led experts to confirm the safety of low to moderate doses of both PTU and MMI/CM in breastfeeding infants. However, given the relatively small size of the studied population, maximal daily doses of 20 mg MMI or 450 mg PTU are advised.

Take Home Message

- There is no need to initiate iodine supplementation :
  1) In pregnant women who are being treated for hyperthyroidism
  2) who are taking LT4
- Euthyroid pregnant women who are TPOAb or TgAb positive :

  Just follow with TSH measurement at time of pregnancy and during pregnancy
- TSH goal in prepregnancy and first trimester is 2.5 ,in 2th and 3th trimester is 3.
- All pregnant women with TSH>4 should be concidered for LT4 therapy .
- All anti TPO positive pregnant women with TSH>2.5 should be concidered for LT4 therapy .
- The dosage of LT4 with a suspected or confirmed pregnancy should increase ~20-30% or administer 2 additional tablets weekly.
- Following delivery, LT4 should be reduced to the patient's preconception dose.

Additional thyroid function testing should be performed at approximately 6 weeks postpartum.

- Serum TSH may decrease in the first trimester of normal pregnancy as a physiological response to the stimulating effect of hCG upon the TSH receptor. A peak hCG level typically occurs between 7 and 11 weeks gestation.
- In particular, a serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in approximately 5% of women by week 11 of pregnancy .
- Antithyroid drugs (ATDs) are not indicated because the serum T4 returns to normal by 14–18 weeks gestation and ATD use in early pregnancy increases risk of birth defects.
- In order to avoid a deleterious fetal impact, the aim of treatment is to maintain maternal TT4/
- FT4 values at, or just above the pregnancy-specific upper limit of normal.
- As a general rule, the smallest possible dose of ATDs should be used whenever possible.
- TT4/FT4 and TSH (and in cases of severe hyperthyroidism, also serum T3) should be measured approximately every 2–4 weeks following initiation of therapy, and every 4– 6 weeks after achieving the target value.
- TT4 measurement with reference value 1.5 times the nonpregnancy range may be used in second and third trimesters.
- The most common cause of thyrotoxicosis in the postpartum period is postpartum thyroiditis (PPT), with a thyrotoxicosis prevalence of 4%.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