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Thyroid Disease in Pregnancy

BACKGROUND

Thyroid disorders are common in young women and may first come to attention when the patient presents for pregnancy care. Various physiologic changes during pregnancy make evaluation of thyroid function during gestation different from that in non-gravid women (see Figure 1 and Table 1.)

-thyroid gland enlargement
-increased thyroid binding globulins (TBG)
-decreased thyroid stimulating hormone (TSH) (changes each trimester)
-variable changes in free thyroxine (fT4) (changes each trimester)
-increased total thyroxine (tT4)
(no change during pregnancy at 7.5-18.0 mcg/dL)

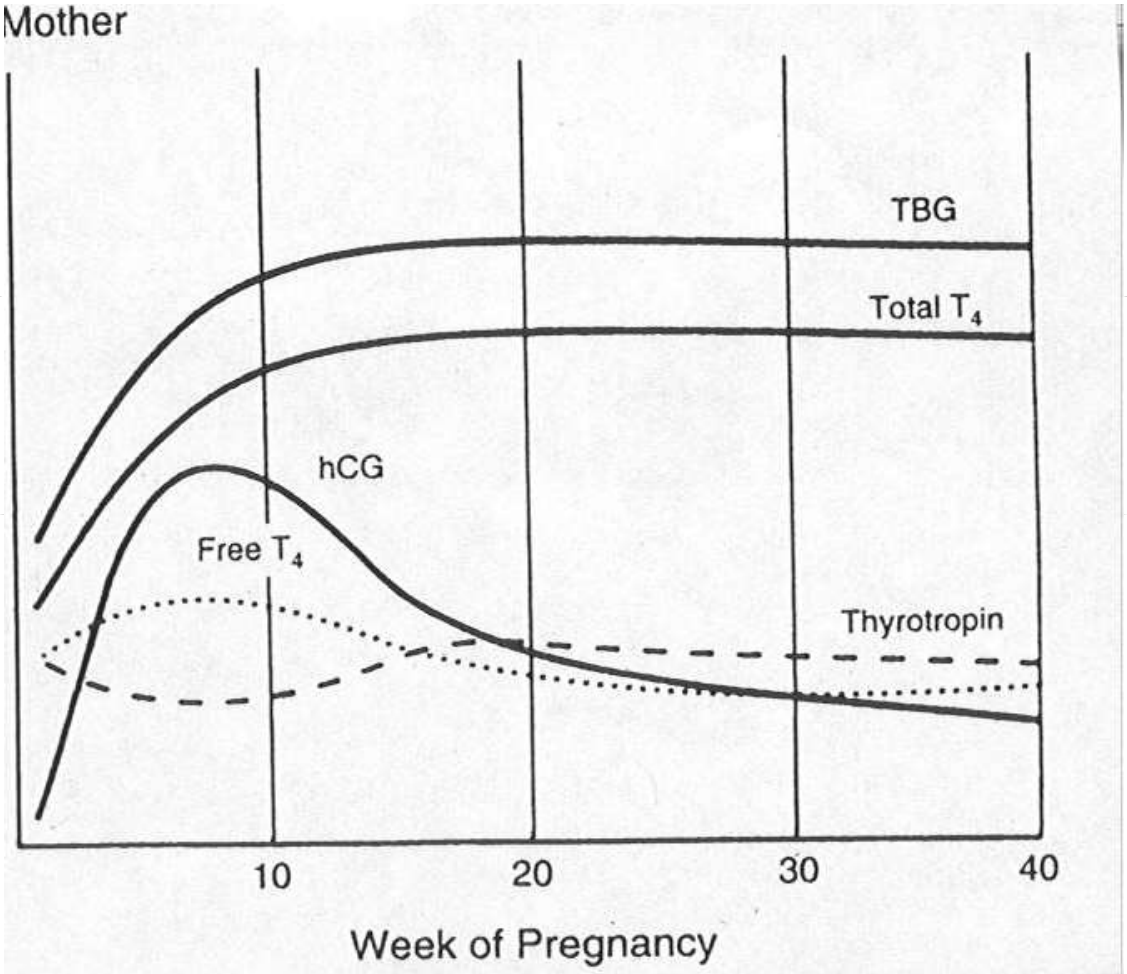

Figure 1

TBG = thyroid binding globulin
Total T4 = total thyroxine
Free T4 = free thyroxine
Thyrotropin (TSH) = thyroid stimulating hormone
hCG = human chorionic gonadotropin

* this guideline assumes use of standard ANMC normal lab values

Table 1. Changes in Thyroid Function Test Results in Normal Pregnancy and in Thyroid Disease ⇦

Maternal Status	TSH	Free T_4
Pregnancy	Varies by trimester*	No change
Overt hyperthyroidism	Decrease	Increase
Subclinical hyperthyroidism	Decrease	No change
Overt hypothyroidism	Increase	Decrease
Subclinical hypothyroidism	Increase	No change

Abbreviations: T_4, thyroxine; TSH, thyroid-stimulating hormone.

*The level of TSH decreases in early pregnancy because of weak TSH receptor stimulation due to substantial quantities of human chorionic gonadotropin during the first 12 weeks of gestation. After the first trimester, TSH levels return to baseline values.

Table 2
Signs / Symptoms of Thyroid Disease

Hypothyroidism	**Hyperthyroidism**
Cold intolerance	Heat intolerance
Constipation	Diarrhea
Weight gain	Weight loss
Dry skin	Warm moist skin
Poor appetite	Increased appetite
Somnolence	Insomnia
Fatigue / lassitude	Irritability / Nervousness
Periorbital puffiness	Exophthalmia
Decreased libido	Diaphoresis
Hoarseness	Goiter
Depression	Palpitations
Hair loss	Tachycardia at rest
	Hyperdynamic precordium
	Hyperreflexia
	Fine resting tremor

HYPERTHYROIDISM

The classic *symptoms* of Graves' disease are common in pregnant women without thyroid disease and include: palpitations, heat intolerance, weight loss, insomnia, and irritability. (See Table 2)

The *clinical signs* of Graves' disease are usually not present in euthyroid pregnant women however. They are usually readily apparent and enable the diagnosis. They include: goiter, exophthalmos, tachycardia at rest, a hyperdynamic precordium, hyperreflexia, and fine tremor.

The *complications* of untreated severe maternal hyperthyroidism are significant and include: preterm birth, fetal growth restriction, severe preeclampsia, pulmonary edema ("thyroid storm"), and rarely (1-2%) fetal hyperthyroidism.

Diagnosis

The *diagnosis* can be made by finding:
-elevated free T4 and decreased TSH
-in combination with the clinical picture (Table 2)

As noted above, TSH may normally be low in pregnancy, and the free thyroxine (fT4) may vary.

An occasional patient may be seen with symptoms of hyperthyroidism and a low TSH, but a normal thyroxine (T4). This may be a spuriously low TSH, but some of these women may have *"T3-toxicosis"*, where only the free triiodothyronine (fT3) will be elevated.

Over 90 percent of women with Graves' disease, an autoimmune disorder, will have *thyroid stimulating immunoglobulins (TSI)*, also known as thyrotropin receptor blocking antibodies (TBII). Documenting their presence or absence will often help make the diagnosis clear (see below about transient thyrotoxicosis and thyroiditis).

Treatment

The *treatment* of hyperthyroidism in pregnancy is usually with thioamides: propylthiouracil (PTU") or methimazole. These drugs readily cross the placenta, and can cause fetal hypothyroidism, with resultant neurodevelopment impairment. (See Table 3) As the fetus is totally dependent on maternal thyroxine until 12-13 weeks gestation, it is better to defer treatment early in pregnancy unless the maternal disease is severe.

Use of thioamides has been associated with agranulocytosis and severe drug-induced hepatitis in young adults. Methimazole is now the recommended first choice drug for hyperthyroidism after the first trimester of pregnancy.

The 2015 ACOG Practice Bulletin points out that methimazole has been associated with fetal esophageal or choana atesia as well as aplasia cutis. The FDA and two major endocrine societies recommend that methimazole only be used after the first trimester.

If the patient has documented severe Graves' disease early in pregnancy, she may be started on PTU and then switched to methimazole after 12 weeks.

Due to the possible fetal effects, these two medications should be used at the lowest dose, keeping the free T4 at the upper limit of normal. Suggested starting doses are:
First trimester only

-propylthiouracil 50 to 150 mg p.o. t.i.d.

Second trimester onward

-methimazole 10 to 40 mg p.o. b.i.d. or t.i.d.

Maternal cardiac or neurologic symptoms may be treated with beta-blockers, such as:

-propranolol 10 to 25 mg p.o. t.i.d.
or
-metoprolol 25 to 50 mg p.o. b.i.d.

Free T4, fetal growth and maternal heart rate should be measured every 4 weeks in women with documented hyperthyroidism. If no complications develop, they do not necessarily need to be delivered early.

After any change in dose, please obtain a free T4 one month later to evaluate the medication changes effect.

Postpartum, women with hyperthyroidism should receive a TSH and free T4 at 6 weeks postpartum. They should be referred to Endocrinology for follow up and consideration for definitive treatment with radioiodine thyroid ablation.

THYROID STORM

Thyroid storm is a medical emergency that occurs in 1% to 2% of pregnancies complicated by hyperthyroidism. Patients with severe and life-threatening thyrotoxicosis typically have an exaggeration of the usual symptoms of hyperthyroidism.

Cardiovascular symptoms include tachycardia to rates that can exceed 140 beats/min, along with congestive heart failure in many patients. Hyperpyrexia to 104 to 106ºF is common. Agitation, delirium, psychosis, stupor, or coma are common and are considered by many to be essential to the diagnosis. Severe nausea, vomiting, or diarrhea, and hepatic failure with jaundice can also occur.

Although thyroid storm can develop in patients with long-standing untreated hyperthyroidism, precipitating factors include infection, preeclampsia, labor and delivery, trauma, and nonthyroidal surgery.

See Appendix 1: Treatment of Thyroid Storm in Pregnant Women

HYPEREMESIS GRAVIDARUM AND GESTATIONAL TRANSIENT THYROTOXICOSIS

While vomiting is not a common symptom of hyperthyroidism, the accompanying weight loss and tachycardia seen with severe nausea and vomiting of early pregnancy may

suggest Graves' disease. hCG, which is a weak thyroid stimulator, may cause transient subclinical hyperthyroidism.

Likewise, up to two thirds of women diagnosed with hyperemesis have laboratory evidence of mild hyperthyroidism, most commonly with
-a very low TSH and
-borderline high free T4

Their physical exam however will usually have no findings to suggest Graves' disease, and borderline high free T4. They will *not* be found to have thyroid stimulating immunoglobulins (TSI) detected.

Since the fetus is completely dependent on maternal thyroid hormones up until 12-13 weeks gestation, treating this "pseudo-hyperthyroidism" with thioamides can result in adverse fetal consequences, and is to be avoided. ACOG recommends *against* testing for thyroid function in women with hyperemesis. If doubt exists, repeat a free T4 at 18-20 weeks.

HYPOTHYROIDISM

The symptoms of normal pregnancy, lassitude, weight gain, and constipation, may suggest thyroid deficiency. Physical exam will usually be normal in women with hypothyroidism. (See Table 2)

Diagnosis

Finding a high TSH and a low free T4 will confirms the diagnosis. Untreated maternal hypothyroidism has been well documented to result in neurodevelopmental problems in their children.

Treatment

In women with known preexisting hypothyroidism, thyroxine requirements usually go up in pregnancy. As soon as possible, their usual dose should be increased by 50 mcg to meet fetal needs, e.g., if a woman was on 100 mcg of levothyroxine prior to pregnancy, her dose may be empirically increased to 150 mcg when pregnancy is diagnosed. TSH should be checked each trimester. Changes in dose take at least 4-6 weeks to be reflected in laboratory results. (See Table 3)

Subclinical hypothyroidism

ACOG does not currently recommend universal TSH screening in pregnant women in order to diagnosis *subclinical hypothyroidism*, although this subject remains controversial. ACOG also does not recommend treatment. (See Table 3)

THYROIDITIS

The majority of new cases of hypothyroidism diagnosed during pregnancy are a result of *Hashimoto's disease* (chronic autoimmune thyroiditis). Physical findings are usually normal. Subacute lymphocytic thyroiditis is more common postpartum, and an enlarged

tender gland is usually found. In Hashimoto's disease, there may be an initial transient hyperthyroid phase, which can cause diagnostic confusion with Graves' disease.

Diagnosis
The *diagnosis* of Hashimoto's disease is fairly straightforward, as over 90% of cases will have elevated levels of *anti-thyroid peroxidase antibodies* (also known as antimicrosomal antibodies). Even if in they are in the hyperthyroid phase, unlike Graves' disease patients, they will not have thyroid stimulating immunoglobulins present. Testing for thyroid antibodies is usually not necessary, but may be very helpful where clinical doubt about the diagnosis exists.

Treatment
See hypothyroid therapy above. As soon as possible, their usual dose should be increased by 50 mcg to meet fetal needs. TSH should be checked each trimester. Changes in dose take at least 4-6 weeks to be reflected in laboratory results.

THYROID NODULES

-Young women represent a significant proportion of cases of thyroid cancer.
-Solitary thyroid nodules are often first discovered during pregnancy, and may be malignant in up to 40% of cases.
-Pregnancy is not thought to impact the outcome of this type of cancer.

Diagnosis
Palpable nodules should be further investigated with ultrasound. This may characterize nodules as solid, cystic, or mixed, but cannot differentiate benign from malignant nodules. Ultrasound guided fine needle aspiration is indicated, but excision may be necessary to establish a definitive diagnosis.

Treatment
Current evidence does not demonstrate that thyroxine suppressive therapy of benign nodules or cysts is effective. Definitive therapy is postponed till the postpartum period.

Clinical Pearls

Use TSH to monitor hypothyroidism

Use free T4 to monitor hyperthyroidism

Do not order 'Thyroid function studies' in routine hyperemesis

Check appropriate lab tests 4 weeks after making any medication changes
(free T4 for hyperthyroidism and TSH for hypothyroidism)

No need to treat subclinical hypothyroidism

Table 3: Management of Thyroid Disease In Pregnancy

↑ TSH	↑ TSH	↓ TSH
↓	↓	↓
check freeT4	check free T4	check free T4
↓	↓	↓
↓ free T 4	nl free T4	↑ free T4 (or ↑ free T3)
↓	↓	↓
Hypothyroidism	Subclinical Hypothyroidism	Hyperthyroidism
↓	↓	↓
Levothyroxine 50 to 100 mcg/day (1-2 mcg/kg/day)	Levothyroxine 25 to 50 mcg/day (ONLY if Sx)	PTU 50-150 mg tid (1^{st} trim. onward) or Methimazole 15-40 mg/day (2nd Trim onward)
↓	↓	↓
check TSH q 4 week	check TSH q 4 weeks	check free T4 q 4 weeks
↓	↓	↓
adjust dose Levothyroxine until TSH WNL (by 25 to 50 mcg/day)	adjust dose Levothyroxine until TSH WNL (by 25 to 50 mcg/day)	adjust dose until free T4 is upper limits of NL
↓	↓	↓

Check TSH 4 week after dose adjustment	**Check TSH 4 week after dose adjustment**	**Incrementally decrease dose following free T4 levels q 4 week**

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Appendix 1:

Thyroid Storm During Pregnancy

I. General

Thyroid storm is a severe and life-threatening thyrotoxicosis characterized by exaggerated symptoms of hyperthyroidism

The most common underlying cause of thyrotoxicosis in cases of thyroid storm is Grave's Disease. Other causes include solitary toxic adenoma, toxic multinodular goiter and in rare cases hypersecretory thyroid carcinoma, thyrotropin-secreting pituitary adenoma, struma ovarii/teratoma and hCG-secreting hydatidiform mole to name a few.

Usually precipitated by surgery, infection, trauma or labor and delivery

Rare- occurs in only 1% of pregnant patients with hyperthyroidism

20-30% of all cases are fatal

II. Diagnosis

Thyroid Storm is a clinical diagnosis. It is important to recognize the signs and symptoms and to treat immediately. The consequences if left untreated can be shock, stupor, coma or death. (see Diagnostic Criteria below)

Signs and Symptoms include: hyperthermia, tachycardia, dehydration, nausea, vomiting, diarrhea, abdominal pain, diaphoresis, cardiac arrhythmias and change in mental status.

Diagnostic Criteria Scoring System: point system developed to assess patients with severe thyrotoxicosis to determine their likelihood of having or developing thyroid storm (located at the end of this guideline).

Labs: Elevated FT4 and FT3 with a depressed TSH

Other possible lab findings: hyperglycemia, hypercalcemia, elevated alkaline phosphatase, leukocytosis and elevated liver enzymes

REMEMBER: if you suspect thyroid storm, treatment should begin IMMEDIATELY, do not hold treatment waiting for thyroid lab results to return.

III. Management

1. Aggressive reversal of thyroidotoxins with antithyroid drugs (ATDs)

a. **Propylthiouracil (PTU)** 600-800 mg orally STAT followed by 150-200 mg by mouth every 4-6 hours; can be administered by NG tube or as rectal suppository if patient unable to take by mouth

b. Starting 1-2 hours after PTU administration:

Saturated solution of potassium iodide (SSKI) 2-5 drops every 8 hours or
Sodium iodide 0.5-1g IV every 8 hours or
Lugol's solution 8 drops every 6 hours or
Lithium carbonate 300 mg orally every 6 hours

c. **Dexamethasone** 2 mg IV or IM every 6 hours X 4 doses

d. **Propanolol** 20-80 mg orally every 4-6 hours or

Propanolol 1-2 mg IV every 5 minutes for a total of 6 mg, then 1-10 mg IV every 4 hours

**If patient has h/o severe bronchospasm:

Resperpine 1-5 mg IM q 4-6 hours, Guanethidine 1 mg/kg PO q 12 hours, Diltiazem 60mg PO q 6-8 hours

e. **Phenobarbital** 30-60 mg PO every 6-8 hours PRN for extreme restlessness

2. Supportive management of signs and symptoms:

a. Fluids (D5 or D10 1/2 NS)

b. Nutritional support

c. Oxygen

d. Antipyretics – acetaminophen (do not use salicylates)

e. Correction of electrolyte imbalance

3. Continuous cardiac monitoring and frequent monitoring of vital signs (ICU setting may be indicated)

4. Careful monitoring of the fetus (U/S, BPP or NST)

5. Avoid delivery unless fetal indications for delivery outweigh the risks to the women

Thyroid Storm References:

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Diagnostic Criteria for Thyroid Storm

Diagnostic parameters	Scoring points
Thermoregulatory dysfunction	
Temperature F (C)	
99–99.9 (37.2-37.7)	5
100–100.9 (37.8-38.2)	10
101–101.9 (38.3-38.8)	15
102–102.9 (38.9-39.4)	20
103–103.9 (39.5-39.9)	25
≥104.0 (40)	30
Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy	20
Severe (seizures, coma)	30
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular dysfunction	
Tachycardia (beats/minute)	
90–109	5
110–119	10
120–129	15
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitating event	
Absent	0
Present	10

Scoring system:

A score of 45 or greater is highly suggestive of thyroid storm

A score of 25–44 is suggestive of impending storm

A score below 25 is unlikely to represent thyroid storm.

Adapted from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22(2):263–77.