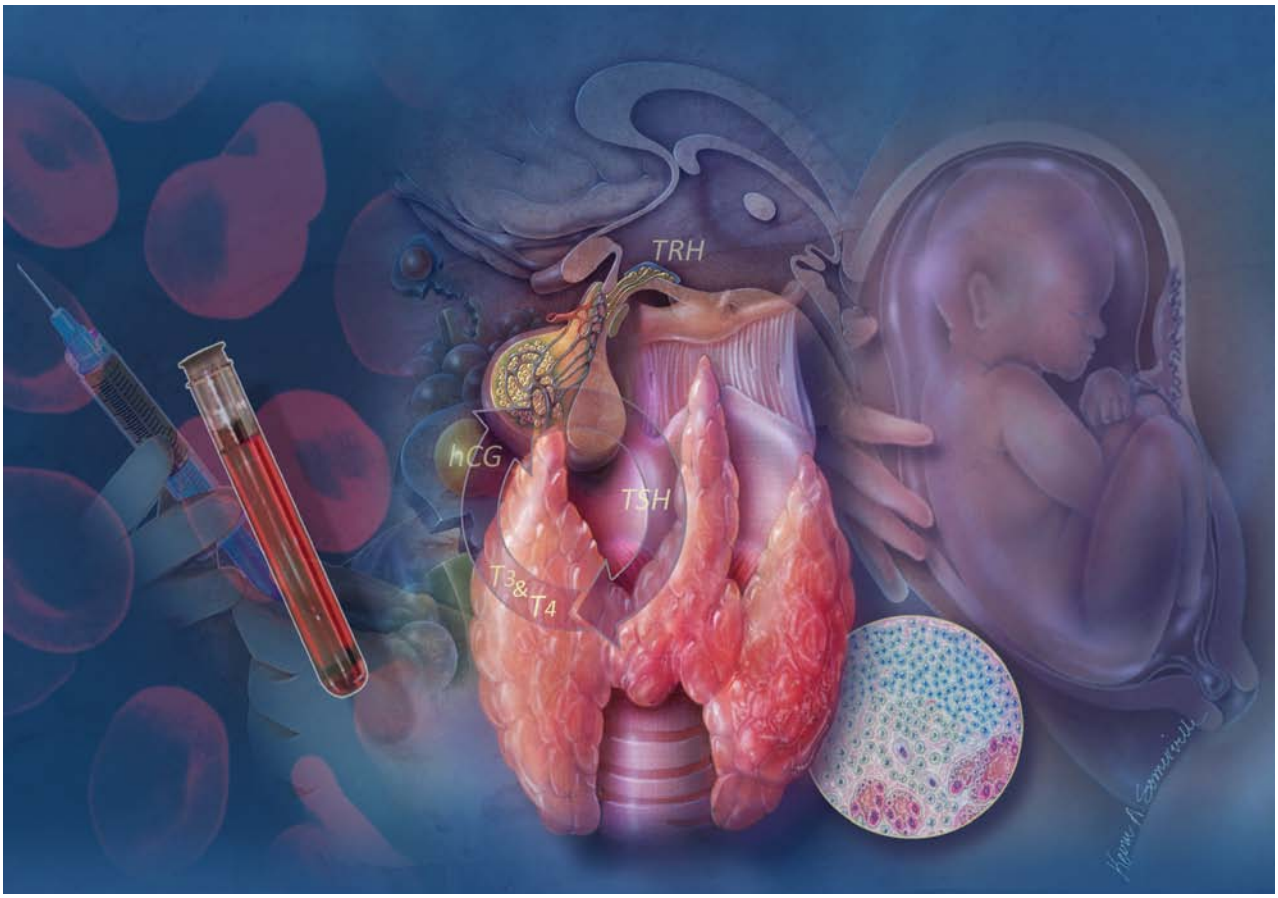

THYROID DISEASE DURING PREGNANCY

PART 1:

Thyroid Function Testing and Hypothyroidism

David E. Abel, MD

This article is the first of a 2-part series highlighting thyroid disease during pregnancy. The focus of this article is thyroid physiology and thyroid function testing during pregnancy, as well as the diagnosis and management of hypothyroidism. Subclinical hypothyroidism and postpartum thyroiditis are also discussed.

Thyroid disease is one of the most common conditions the clinician may encounter in a pregnant patient.

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THYROID PHYSIOLOGY DURING PREGNANCY

The thyroid gland is under the influence of the hypothalamic-pituitary axis. Thyrotropin-releasing hormone, produced by the hypothalamus, induces secretion of thyroid-stimulating hormone (TSH) from the pituitary gland. The production of the 2 main thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), is induced when TSH binds to its receptors on the thyroid gland. T_3 and T_4 are mostly protein bound by thyroid-binding globulin (TBG), as only 0.04% of total T_4 (TT_4) and 0.5% of total T_3 (TT_3) are available in their free form (FT_4 and FT_3) in serum. The free hormone negatively feeds back on the pituitary gland to down-regulate TSH production.

TT_4 and TT_3 increase early in pregnancy due to greater production and decreased degradation of TBG. The high levels of estrogen associated with pregnancy stimulate the liver to produce TBG and extend its half-life as well, resulting in a significant increase in TBG levels (~200%). The high TBG levels plateau at 20 weeks' gestation and remain unchanged until delivery. With increased TBG levels, one would expect the levels of free thyroid hormones to decrease, as more would be protein bound. However, human chorionic gonadotropin (hCG) acts as a weak thyroid stimulator on the TSH receptor.

This TSH-like effect by hCG leads to enhanced production of T_4 and TSH suppression. In fact, low TSH levels may be seen in 15% of normal pregnant women in the first trimester.[1] The hCG effect may be more pronounced in multiple gestations. Thus, a suppressed TSH in the face of a normal FT_4 level is consistent with normal pregnancy, and treatment is not warranted.

After the first trimester, as peak levels of hCG are reached, TSH suppression by hCG decreases and the TSH often normalizes. Currently, data support 2.5 mU/L as an upper limit of normal serum TSH in the first trimester. Of note, the thyrotropic properties of hCG (increased T_4 production and TSH suppression) can make the diagnosis of hypothyroidism in early pregnancy difficult.

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TABLE 1. The Effect of Pregnancy on Thyroid Function Tests

TSH	No change, decreased in 15%
Total T_4	Increased
Total T_3	Increased
Free T_4	No change
Free T_3	No change
FTI	No change
RT_3U	Decreased

Abbreviations: FTI, free thyroxine index ; RT_3U, resin triiodothyronine uptake; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

The free thyroxine index (FT_4I) is not altered during pregnancy and may be used to estimate the FT_4 if direct determination is not available. Due to inconsistencies among the various laboratories, it has been suggested that the FT_4I may be a more reliable method if indirectly assessing the FT_4 level.

Another test, the resin T_3 uptake test (RT_3U), is an alternate way of indirectly determining FT_4 levels by measuring unoccupied binding sites in the TBG molecule. The RT_3U value is then multiplied by the TT_4 (or TT_3) concentration to obtain the FT_4I (or FT_3I). Table 1 summarizes the alterations in thyroid function testing seen during pregnancy.

FOCUSPOINT
A low TSH level may be seen in 15% of normal pregnancies.

THYROID FUNCTION TESTING

The hypermetabolic state of pregnancy may mimic the symptomatology seen in hyperthyroidism. Thus, laboratory testing is the best diagnostic tool when considering hyperthyroidism. Periodic laboratory testing is also necessary when treatment with antithyroid medication has been initiated.

In a pregnant patient with suspected hyperthyroidism or hypothyroidism, both TSH and FT_4 should be measured. Of note, a recent study questioned the diagnostic accuracy of FT_4 immunoassays during pregnancy.[2] FT_3 is not measured routinely. However, FT_3 assessment should be considered in patients with signs of thyrotoxicosis, a suppressed TSH and a normal FT_4. An elevated FT_3 indicates T_3 thyrotoxicosis,

TABLE 2. Indications for Thyroid Antibody Testing During Pregnancy

- High maternal FT_4 (free thyroxine) levels
- History of fetal/neonatal thyroid dysfunction in previous pregnancy
- History of infant with congenital hypothyroidism
- Status/post–radioablation treatment due to Graves disease
- Fetal goiter noted on ultrasound

which may occur before increased production of FT_4.[3]

The clinical utility of evaluating thyroid-stimulating immunoglobulin (TSI) levels during pregnancy is controversial. These autoantibodies are immunoglobulin G antibodies that can cross the placenta and stimulate the fetal thyroid gland. Fetal effects are not correlated with maternal disease, but high levels of TSI (≥200%-500%) increase the risk of fetal and neonatal hyperthyroidism.[4] The risk for neonatal Graves disease due to transplacental passage of TSI is 1% to 5%.[3]

Currently, ACOG does not endorse routine evaluation of TSI levels.[5] However, in pregnant women with a history of Graves disease, TSI activity may decrease, leading to chemical remission.[6,7] Recommendations for when to consider TSI measurements during pregnancy are listed in Table 2.

Gestational transient thyrotoxicosis is a biochemical hyperthyroidism specific to pregnancy that is associated with high hCG levels. It is commonly associated with hyperemesis gravidarum (HEG), although it can be seen in gestational trophoblastic disease. The high hCG levels lead to temporary hyperthyroidism due to TSH receptor stimulation. These patients are rarely symptomatic, and antithyroid treatment is not warranted. As pregnancy progresses past the first trimester, FT_4 levels normalize, although TSH levels may remain suppressed for several weeks. In patients with HEG, routine assessment of thyroid function is not indicated unless clinical signs of hyperthyroidism are apparent.[5] Table 3 lists the various clinical scenarios with corresponding laboratory results.

TABLE 3. Clinical Scenarios With Corresponding Laboratory Results

Condition	TSH	Free T_4
Pregnancy	Decreased	Normal
Hypothyroidism	Increased	Normal
Subclinical hypothyroidism	Increased	Normal
Hypothyroxinemia	Normal	Decreased
Hyperthyroidism	Decreased	Increased
Subclinical hyperthyroidism	Decreased	Normal

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

HYPOTHYROIDISM

The incidence of hypothyroidism in the general population is 1%, and 1 to 3 in 1,000 in pregnancy. It is seen with a greater frequency with concurrent autoimmune disease, such as type 1 diabetes mellitus (5%-8%).

In developed countries, the most common cause of hypothyroidism during pregnancy is Hashimoto thyroiditis, also known as chronic autoimmune thyroiditis. This condition is characterized by the presence of antithyroid antibodies, including antimicrosomal and antithyroglobulin antibodies. Rarely, these antibodies can cause neonatal hypothyroidism, which is transient.

Other causes of primary hypothyroidism include subacute viral thyroiditis, radioactive iodine treatment, thyroidectomy, and iodine deficiency. The latter is the most common cause of hypothyroidism worldwide. Hashimoto disease and iodine deficiency are associated with goiter. Certain medications, including lithium, iodine, and amiodarone, are uncommon causes of hypothyroidism.

Signs and Symptoms of Hypothyroidism

Due to TSH suppression by hCG in early pregnancy and symptoms that mimic those commonly seen during pregnancy, the di-

FOCUSPOINT
ACOG does not endorse routine screening for subclinical hypothyroidism during pregnancy.

agnosis of clinical hypothyroidism can be difficult. The classic symptoms of hypothyroidism include cold intolerance, dry skin, fatigue, constipation, hair loss, and muscle cramps. These may progress to weight gain, hair loss, insomnia, voice changes, carpal tunnel syndrome, and intellectual slowness. Hypothyroidism can lead to myxedema and coma if left untreated. It is unusual for uncontrolled hypothyroidism to present during pregnancy.

Maternal and Fetal Risks of Hypothyroidism

Well-controlled hypothyroidism has minimal impact upon pregnancy. Poorly or partially controlled thyroid disease may be associated with adverse pregnancy outcomes including preeclampsia, placental abruption, preterm birth, low birth weight, and fetal death.

Uncontrolled thyroid disease can also place the fetus at risk for neuropsychologic deficits. The fetus does not produce thyroid hormone until approximately 12 weeks' gestation, depending on maternal FT_4 for brain development in the first trimester. Therefore, treatment should be initiated during pregnancy as early as possible.

Management of Hypothyroidism

At least 50% of patients diagnosed with hypothyroidism prior to pregnancy will need an increase in the thyroxine replacement dose during pregnancy. TSH and FT_4 should be checked at the first prenatal visit. The goal of levothyroxine replace-

Coding for Thyroid Disease During Pregnancy: Part 1

Philip N. Eskew Jr, MD

This is a clinical condition that requires the use of different ICD-9 codes from 2 different sections of the book. The first is the section regarding the pregnant state:

648 Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium
Use additional code(s) to identify the condition
Requires fifth digit

First, you must code the clinical condition in pregnancy and then the appropriate fifth digit:

648.1 Thyroid dysfunction
[0-4]
- **0** unspecified as to episode of care or not applicable
- **1** delivered, with or without mention of antepartum condition
- **2** delivered, with mention of postpartum complication
- **3** antepartum condition or complication
- **4** postpartum condition or complication

Second, you should code the specific symptom or disease state:

245.2 Chronic lymphocytic thyroiditis, Hashimoto disease, chronic autoimmune thyroiditis
245.1 Subacute thyroiditis, viral
244.1 Other postablative hypothyroidism, following therapy, such as irradiation
244.0 Postsurgical hypothyroidism

There are several symptoms that can also be coded as further documentation and support for the need of extra prenatal visits:

780.99 Cold intolerance
701.1 Dry skin syndrome
780.79 Other malaise and fatigue, tiredness
564.00 Constipation, unspecified
704.00 Alopecia, unspecified, loss of hair
729.82 Other musculoskeletal symptoms referable to limbs, cramp
783.1 Abnormal weight gain
780.52 Insomnia, unspecified
784.49 Other voice and resonance disorders, change in voice
354.0 Carpal tunnel syndrome

For postpartum thyroiditis, you would code it as follows:

648.14 Thyroid dysfunction, postpartum condition or complication

And use either

245.2 Thyroiditis, autoimmune
245.9 Thyroiditis, unspecified

There are 2 V codes that could also be used for further documentation:

V12.2 Personal history of endocrine, metabolic, and immunity disorders
V18.19 Family history of other endocrine and metabolic diseases

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ment is a TSH of 0.5 to 2 mU/L and FT_4 in the normal range.

As it takes approximately 4 to 6 weeks for the TSH to reequilibrate to the new thyroid replacement dose, thyroid functions should be checked 4 weeks after any dose adjustment is made and every 4 weeks thereafter, until a stable TSH level is reached. Increasing the dose in 25- to 50-mcg increments is a reasonable approach. An elevated TSH warrants an increase in the levothyroxine dose, and labs should be rechecked in 4 weeks. Once a stable TSH is reached, thyroid functions should be checked at least every trimester.

For women diagnosed with hypothyroidism during pregnancy, the starting dose of levothyroxine ranges from 1 to 2 mcg/kg/day, or approximately 100 mcg/day. In the unlikely event levothyroxine is unavailable, desiccated thyroid preparation such as Armour Thyroid can be used. The initial dose is 30 mg/day, increased incrementally by 15 mg every 2 to 3 weeks, until a maintenance dose of 60 to 120 mg/day is reached. In stable patients, checking TSH/FT_4 levels every trimester is prudent. Any dose adjustments warrant a recheck of thyroid functions in 4 weeks. Of note, certain medications can interfere with levothyroxine absorption (eg, ferrous sulfate, cholestyramine, aluminum hydroxide antacids) or metabolism (eg, phenytoin, carbamazepine, and rifampin).

Antepartum management includes serial ultrasounds to assess fetal growth. If the fetus is growing appropriately and the disease is well controlled, nonstress tests are not necessary. In poorly controlled disease, antepartum testing starting at 32 to 34 weeks should be considered.

SUBCLINICAL HYPOTHYROIDISM

The topic of subclinical hypothyroidism (elevated TSH and normal FT_4) has received considerable attention over the past few years. Based on observational data, 2 studies suggested a link between subclinical hypothyroidism and impaired neurocognitive development.[8,9] The studies, both retrospective and noninterventional, showed a lower IQ in children born to mothers with an elevated TSH in mid-gestation.

TABLE 4. Screening for Hypothyroidism During Pregnancy

- Personal history of thyroid disease
- Symptoms of thyroid disease
- Previous treatment for hyperthyroidism
- Family history of thyroid disease
- History of high-dose neck irradiation
- Type 1 diabetes mellitus
- Goiter or palpable thyroid nodule
- Hyperlipidemia
- Medications (iodine, rifampin, amiodarone, lithium, phenytoin)

These results led several national endocrine authorities, including the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society, to recommend routine screening and treatment for subclinical hypothyroidism during pregnancy.[10] Specifically, they recommend screening TSH preconceptionally, or as soon as pregnancy is established, with a follow-up FT_4 if the TSH is abnormal. However, the results must be interpreted with caution. There was no difference when the untreated hypothyroid patients were compared with treated hypothyroid patients, as the comparison group was normal controls.

FT_4 is necessary for fetal brain development and maturation, independent of the TSH level.[8,11,12] Therefore, it is unclear how a normal thyroxine level, as noted in subclinical hypothyroidism, impacts fetal brain development. In fact, isolated hypothyroxinemia (normal TSH and low FT_4) may be more of a concern.[13,14] A large, multicentered, randomized clinical trial (clinicaltrials.gov identifier: NCT00388297) is in progress to help determine if screening and treatment of subclinical hypothyroidism and hypothyroxinemia will have a long-term effect on pediatric neurodevelopment.[14]

To date, there have been no interventional studies to determine whether

screening and treating pregnant patients for subclinical hypothyroidism will improve the neuropsychologic performance of their offspring. In contrast to the national endocrine authorities, ACOG does *not* recommend routine screening and treatment of subclinical hypothyroidism during pregnancy.[5] However, it is reasonable to have a low threshold to screen patients if risk factors are present (Table 4).

POSTPARTUM THYROIDITIS

All patients with thyroid disease requiring treatment during pregnancy should have follow-up thyroid function testing in the postpartum period. Postpartum thyroiditis represents an autoimmune inflammation of the thyroid gland that occurs within 1 year postpartum. It is seen in 5% of women who do not have a history of thyroid disease and can occur after pregnancy loss. The recurrence risk is 70%. The diagnosis is made by confirmation of new-onset abnormal levels of TSH, FT_4, or both.

Clinically, 3 presentations are possible that can include hyperthyroidism or hypothyroidism. Symptoms are vague and nonspecific, including carelessness, memory impairment, and depression. If the diagnosis is in doubt, measurement of antimicrosomal or thyroid peroxidase antibodies can be useful. Treatment of postpartum thyroiditis is controversial, usually reserved for those with symptoms. Although often transient, a portion of women will develop permanent hypothyroidism.

Part 2 of "Thyroid Disease During Pregnancy" will focus on the diagnosis and management of hyperthyroidism.

The author reports no actual or potential conflict of interest in relation to this article.

REFERENCES

1. Hershman JM. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. *Best Pract Res Clin Endocrinol Metab.* 2004;18(2):249-265.
2. Lee RH, Spencer CA, Mestman JH, et al. Free T_4 immunoassays are flawed during pregnancy. *Am J Obstet Gynecol.* 2009;200(3):260.e1-e6.
3. Weetman AP. Graves' disease. *N Engl J Med.* 2000; 343(17):1236-1248.
4. Peleg D, Cada S, Peleg A, Ben-Ami N. The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. *Obstet Gynecol.* 2002;99(6):1040-1043.
5. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 37, August 2002. (Replaces Practice Bulletin Number 32, November 2001). Thyroid disease in pregnancy. *Obstet Gynecol.* 2002;100(2):387-396.
6. Kung AW, Jones BM. A change from stimulatory to blocking antibody activity in Graves' disease during pregnancy. *J Clin Endocrinol Metab.* 1998;83(2):514-518.
7. Casey BM, Leveno KJ. Thyroid disease in pregnancy. *Obstet Gynecol.* 2006;108(5):1283-1292.
8. Pop VJ, Kuijpens JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf).* 1999;50(2):149-155.
9. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999;341(8):549-555.
10. Gharib H, Tuttle RM, Baskin HJ, et al. Consensus Statement #1. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *Thyroid.* 2005;15(1):24-28.
11. Morreale de Escobar G, Obregon MJ, Escobar del Ray F. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab.* 2000;85(11): 3975-3987.
12. Spong CY. Subclinical hypothyroidism: should all pregnant women be screened? *Obstet Gynecol.* 2005;105(2):235-236.
13. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow up study. *Clin Endocrinol (Oxf).* 2003;59(3):282-288.
14. Gyamfi C, Wapner RJ, D'Alton ME. Thyroid dysfunction in pregnancy: the basic science and clinical evidence surrounding the controversy in management. *Obstet Gynecol.* 2009;113(3):702-707.