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Thyroid Disease in Pregnancy

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ABSTRACT

Thyroid disease is the second most common endocrine disorder affecting women of reproductive age, and when untreated during pregnancy, is associated with an increased risk of miscarriage, placental abruption, hypertensive disorders and growth restriction. Current guidelines recommend targeted screening of women at high risk, including those with a history of thyroid disease, type 1 diabetes mellitus or other autoimmune disease; current or past use of thyroid therapy or a family history of autoimmune thyroid disease. Appropriate management results in improved outcomes, demonstrating the importance of proper diagnosis and treatment. In women with hypothyroidism, levothyroxine is titrated to achieve a goal serum thyroid-stimulating hormone level <2.5 mIU/L. The preferred treatment for hyperthyroidism is antithyroid medications, with a goal of maintaining a serum free thyroxine level in the upper one-third of the normal range. Postpartum thyroiditis is the most common form of postpartum thyroid dysfunction and may present as hyper- or hypothyroidism. Symptomatic treatment is recommended for the former; levothyroxine is indicated for the latter in women who are symptomatic, breastfeeding or who wish to become pregnant. Thyroid disease is second only to diabetes mellitus as the most common endocrinopathy that occurs in women during their reproductive years. Symptoms of thyroid disease often mimic common symptoms of pregnancy, making it challenging to identify. Poorly controlled thyroid disease is associated with adverse outcomes during pregnancy, and treatment is an essential part of prenatal care to ensure maternal and fetal well-being.

Keywords: Hyperthyroidism, hypothyroidism, postpartum thyroiditis, levothyroxine

The thyroid gland is important during pregnancy as it regulates the production of hormones triiodothyronine (T3) and thyroxine (T4), each of which plays a critical role in the development of the baby's brain and nervous system.

During the first trimester, the fetus depends on the mother's supply of thyroid hormone, which is delivered through the placenta. In order to meet this need, the mother's thyroid production will typically go into overdrive, resulting in an enlargement of the gland itself.

Diseases of thyroid hormone (hyperthyroidism and hypothyroidism) are quite commonly seen in pregnancy (2-3%) and 1 in 10 women of childbearing age group will have some indication of reduction of functional reserve of thyroid function.

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THYROID GLAND AND ITS ADAPTION DURING NORMAL PREGNANCY

Thyroid gland is a butterfly-shaped endocrine gland located in front of the neck and releases hormones that regulate the metabolism, heart, nervous system, weight, body temperature and many other processes in the body.

For diagnosing thyroid disease in pregnancy, we need to understand the changes in thyroid physiology and changes in the values of thyroid function tests that occur during pregnancy.

Pregnancy poses various metabolic changes in the body and to meet the increased metabolic needs, thyroid physiology and thyroid function change (Reflected as altered thyroid tests).

There is an increase in serum thyroxine-binding globulin (TBG) and stimulation of thyrotropin (TSH) receptors by hCG (human chorionic gonadotropin) in pregnancy. The serum TBG levels rise almost double because of estrogen (increased TBG production and TBG sialylation). This causes slowing and decrease in TBG clearance.

In response, the total T4 and T3 increase in first half of pregnancy up to 20 weeks, plateauing at 20 weeks of gestation.

The production of thyroid hormones T3 and T4 returns to pre-pregnancy levels at approximately 20 weeks. hCG β-subunit is similar to thyroid-stimulating hormone. Hence, hCG has a weak thyroid-stimulating activity.

1 micro U of hCG = 0.0013 micro U of TSH.

THYROID FUNCTION TESTS IN PREGNANCY

Several population studies have demonstrated that it is normal for TSH in pregnancy to be below the classic lower limit of normal. Therefore, use of non-pregnant reference ranges result in the overdiagnosis of hyperthyroid states and under-recognition of hypothyroid states. Laboratories should provide trimester-specific reference ranges but if these are not available, the trimester-specific TSH ranges indicated in Table 1 are recommended.

Because normal thyroid function is different during pregnancy, TSH values will change as the mother progresses from the first to third trimester. Under normal circumstances, the normal TSH value would range from 0.2 to 4.0 mIU/L.

The lower reference range of TSH can be reduced by approximately 0.4 mIU/L, in first trimester and upper reference range is reduced by approximately 0.5 mIU/L. This corresponds to a TSH upper reference limit of 4.0 mIU/L. This should be applied beginning with the late first trimester, Weeks 7-12, with a gradual return towards the nonpregnant range in the second and third trimesters. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake and negative thyroid-peroxidase antibody (TPOAb) status.

There is an increase in total T4 concentration from 7 to 16 weeks of gestation, ultimately reaching 50% above the pre-pregnancy level. This level is then sustained through pregnancy. Upper range determination can be calculated by shifting the nonpregnant limit 50% higher.

Table 1. Recommended Trimester-specific Reference Ranges for TSH

Trimester	TSH range
First	0.1-2.5 mIU/L
Second	0.2-3.0 mIU/L
Third	0.3-3.0 mIU/L

This can only be used after 16 weeks of pregnancy. If a T4 measurement is required before that time (i.e., 7-16 weeks of pregnancy), a calculation can be made for the upper reference range based on increasing the nonpregnant upper reference limit by 5% per week, beginning with 7 weeks. Accurate estimation of the free T4 (FT4) concentrations can also be done by calculating a FT4 index. Table 2 summarizes thyroid evaluation.

TSH and FT4 are useful for diagnosis of and monitoring thyroid dysfunction in pregnancy. T3 levels are only ordered if a suspicion of T3 predominant thyrotoxicosis is there.

THYROID DISEASES

- Hypothyroidism (Overt and Subclinical)
- Hyperthyroidism (Overt and Subclinical)
- Postpartum thyroiditis
- Thyroid nodule/Goiter

Hashimoto's disease, also known as Hashimoto's thyroiditis, is an autoimmune disease which attacks and gradually destroys the thyroid gland. Hypothyroidism is a common outcome of the disorder and is treated in the same manner using hormone replacement therapy. Typically speaking, a woman with Hashimoto's should maintain her TSH under 3.0 mIU/L.

The provisions for treatment during pregnancy are the same as for other forms of hypothyroidism, although additional attention should be made to keeping the TSH under 2.5 mIU/L as higher levels are associated with a two-fold increase in the risk of miscarriage.

Hypothyroidism

Hypothyroidism in pregnancy is usually due to Hashimoto's disease (3 to 5 out of 1,000 pregnancy). Hashimoto's disease is chronic inflammation of thyroid

Table 2. Basic Thyroid Evaluation

	TSH		
	Low	**Normal**	**High**
FT4			
High	Primary hyperthyroid	Nonthyroid illness-(NTI) or Patients on levothyroxine	Secondary hyperthyroid
Normal	Subclinical hyperthyroid	Euthyroid	Subclinical hypothyroid
Low	Secondary hyperthyroid	NTI	Primary hypothyroid

gland (Hashimoto's thyroiditis is an autoimmune disorder). Euthyroid patients who are antithyroid Ab positive, post-hemithyroidectomy or treated with radioactive iodine have an increased propensity for the development of hypothyroidism in gestation and should be monitored regularly.

Overt hypothyroidism is when there is an elevated TSH and low FT4. This is clearly associated with adverse pregnancy outcomes (Lower IQ) and miscarriages, prematurity, low birth weight and stillbirths. Frequently, elevated maternal TSH is detected when FT4 concentrations are normal. Conversely, low FT4 concentrations can be detected despite normal TSH concentrations, called as isolated hypothyroxinemia.

Symptoms

- Extreme tiredness
- Weight gain
- Constipation
- Difficulty in concentration
- Memory problems
- Sensitivity to cold temperature
- Muscle cramps

Adverse outcomes with overt maternal hypothyroidism include increased risks of premature birth, risk of gestational hypertension, low birth weight, pregnancy loss and lower offspring IQ.

Overt hypothyroidism should be urgently treated by L-thyroxine (LT4) replacement. In severe cases, a loading dose for 3-4 days of 150-200 μg should be given, followed by titration with TSH levels.

In patients with pre-existing hypothyroidism already on replacement therapy, the dose needs to be increased by about 30% (Increase 2 additional doses per week or 7-9 doses per week) on suspicion or confirmation of pregnancy.

T4 and TSH should be checked every 4 weeks in first half of pregnancy and at least once in between 26 and 32 weeks. The aim is to keep TSH within trimester-specific ranges (Table 1).

After delivery, the dose can be reduced to pre-pregnant levels and should be monitored with a serum TSH measurement approximately every 4 weeks until mid-gestation and at least once near 30 weeks of gestation. Adjustment of LT4 dosage when affected women become pregnant and also for the timing of follow-up interval for TSH in treated patients is suggested. Increased requirement for thyroxine (or exogenous LT4) occurs as early as 4-6 weeks of pregnancy. Requirements gradually increase up till 16-20 weeks of pregnancy and plateau thereafter until the time of delivery. Following delivery, maternal LT4 dosing should be reduced to pre-pregnancy levels, and a serum TSH assessed 6 weeks thereafter. However, a study demonstrated that more than 50% of women with Hashimoto's thyroiditis required an increase in the pregestational thyroid hormone dose in the postpartum period, presumably due to an exacerbation of autoimmune thyroid dysfunction postpartum. In women started on LT4 during pregnancy for thyroid autoimmunity in the absence of TSH elevation, the LT4 can be stopped at delivery, with serum TSH assessment at 6 weeks postpartum. A maternal serum TSH concentration <2.5 mIU/L is a reasonable goal. Even lower preconception TSH values (<1.5 mIU/L) could reduce the risk of TSH elevation during the first trimester, but a lower treatment target may not improve outcomes because the LT4 dose can be immediately increased upon a positive pregnancy test. Achieving a TSH concentration at the lower end of the reference range could induce subnormal TSH concentrations in some patients.

Though generally safe for any developing fetus, potential effects upon conception and/or successful implantation are unknown.

If TSH is well-controlled in pregnancy and treatment is adequate, neonatal thyroid function screening is not necessary.

Subclinical hypothyroidism (SCH) is also associated with some adverse outcomes like miscarriage but not proven to cause fetal impaired cognitive functions.

Any pregnant woman with an elevated TSH concentration must also be evaluated for TPOAb status. A dose of only 50 μg/day is typically required for effective treatment of subclinically hypothyroid women.

- LT4 therapy is recommended for:
  - TPOAb-positive women with a TSH greater than the pregnancy-specific reference range
  - TPOAb-negative women with a TSH >10.0 mU/L.
- LT4 therapy may be considered for:
  - TPOAb-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range
  - TPOAb-negative women and TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L.

- LT4 therapy is not recommended for:
  - TPOAb-negative women with a normal TSH <4.0 mU/L.

A clear association has been demonstrated between thyroid antibodies and spontaneous pregnancy loss; however, it does not prove causality and the underlying mechanisms are not known. All women with overt and subclinical hypothyroidism should be treated irrespective of TPOAb positivity with LT4 during pregnancy to maintain serum TSH in the trimester-specific goal range. It has been recommended to check serum TSH every 4 weeks during pregnancy so that appropriate dose adjustments can be made, but our routine practice is to check every 6 weeks. The recommended therapy is with oral LT4, which should be taken on an empty stomach (45 minutes before consumption of food, beverages or other medications). In addition, calcium, iron and prenatal vitamin supplements should be avoided within 4 hours of ingestion of LT4, as these can decrease the absorption of thyroxine.

Immediately after delivery, the requirement of thyroxine drops and women who were taking thyroxine prior to pregnancy will shift to their pre-pregnancy dose, and those who started their thyroxine in pregnancy will require half the dose they were taking just before delivery. In women who had started their thyroxine in pregnancy for subclinical hypothyroidism, the medication can be stopped after delivery and thyroid balance re-assessed again after 6 weeks and decision taken regarding continuation of treatment.

Monitoring of euthyroid women who are thyroid antibody (Ab)-positive during pregnancy

TPOAb are able to cross the placenta. At the time of delivery, cord blood TPOAb levels strongly correlate with third-trimester maternal TPOAb concentrations.

However, maternal passage of either TPOAb or thyroglobulin (Tg)Ab is not associated with fetal thyroid dysfunction.

Euthyroid pregnant women who are TPOAb or TgAb positive should have measurement of serum TSH concentration performed at time of pregnancy confirmation and every 4 weeks through mid-pregnancy. LT4 administration in low dosage (25-50 μg/d) is safe. Therefore, its use among patients with recurrent pregnancy loss may be reasonably considered in the setting of early gestation, especially when no other known cause of prior pregnancy loss has been identified.

Two randomized clinical trials are currently ongoing. One of them is the Thyroid Antibodies and LevoThyroxine study (TABLET) trial in the United Kingdom. There is a greater risk for adverse events in women who are TPOAb-positive versus TPOAb-negative, even when thyroid function is identical.

The recommended treatment of maternal hypothyroidism is oral LT4. Other thyroid preparations, such as T3 or desiccated thyroid, should not be used in pregnancy.

Hyperthyroidism

Pregnancy hyperthyroidism is often due to Grave's disease (GD). It has an incidence of about 1 in 500 pregnancies (0.4%). Hyperthyroidism in pregnancy is also termed gestational thyrotoxicosis.

Pregnant women with GD should be monitored monthly. 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.

Rarely severe vomiting (Hyperemesis gravidarum) can cause dehydration and weight loss; this may be triggered by high levels of hCG and causes temporary hypothyroidism that settles in second trimester.

Symptoms

- Irregular heart beat
- Nervousness
- Severe nausea or vomiting
- Slight tremor
- Trouble sleeping
- Weight loss or low weight gain
- Eye problems (irritation, bulging and puffiness)

Uncontrolled hyperthyroidism in pregnancy can lead to:

- Congestive heart failure
- Pre-eclampsia
- Thyroid storm
- Miscarriage
- Premature birth
- Low birth weight.

Hyperthyroid in newborns can cause:

- Rapid heart rate
- Heart failure
- Early closure of soft spot of skull

- Poor weight gain
- Irritability
- Enlarged gland, causing problem in breathing.

Diagnosis is made on testing for thyroid if there is a suspicion on account of the symptoms. Tests include:

- TSH/Ultra TSH
- T3 and T4
- Thyroid-stimulating immunoglobulin (TSI).

TSH receptor antibody (TRAb) and maternal TT3 may prove helpful in clarifying the etiology of thyrotoxicosis. Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.

Mild hyperthyroidism in which TSH is low but T4 is normal does not need any treatment. Treatment of choice is PTU (propylthiouracil). If patient is on carbimazole (CM), then it is advisable to change to PTU (CM can cause rare embryopathy). If liver function is compromised, then PTU should be stopped and carbimazole should be started. Titration of treatment should be guided by TSH and free T4 levels.

Moderate doses of antithyroid drugs (ATDs) (carbimazole 25-30 mg or PTU <300 mg/day) are recommended during breastfeeding.

Thyroid function should be monitored in mothers on high doses during the postpartum period. Gestational or hCG triggered thyrotoxicosis usually does not require antithyroid treatments; this is self-limiting. Sometimes symptomatic treatment may be needed in these cases.

If the patient opts for radioactive iodine ablative therapy prior to pregnancy, the following recommendations should be provided:

First, TRAb levels tend to increase following ^{131}I therapy and may remain elevated formany months following ^{131}I therapy. Therefore, patients with high TRAb levels or severe hyperthyroidism may favor consideration of other therapeutic options, such as surgery.

Second, a subset of young patients with severe GD may not become stably euthyroid within the first year after ^{131}I therapy.

Third, if ^{131}I therapy is planned, a pregnancy test should be performed 48 hours before ^{131}I ablation to confirm absence of unexpected pregnancy.

Fourth, conception should be delayed for 6 months and until a stable euthyroid state is reached after ablation and initiation of LT4 replacement therapy.

If the patient chooses ATD therapy, the following recommendations should be given:

First, the increased risk of birth defects associated with both PTU and methimazole (MMI) use during early pregnancy should be reviewed. ATDs should be avoided in the first trimester of pregnancy, but when necessary, PTU is generally favored. PTU after the first trimester should be switched to MMI to decrease the risk of liver failure in the mother.

In thyrotoxic patients, the possibility of future pregnancy should be discussed. Women with GD seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation and birth defects with ATD use. In preconception counseling, the risks and benefits of all treatment options and the patient's desired timeline to conception should be discussed.

Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy. Treatment options are associated with risks and benefits. These include ^{131}I ablation, surgical thyroidectomy or ATD therapy.

Management of patients with Graves' hyperthyroidism during pregnancy

In some cases, a woman may experience an overactive rather than underactive thyroid. This is known as hyperthyroidism, commonly referred to as GD.

Obstetric and medical complications are directly related to control of maternal hyperthyroidism, and the duration of the euthyroid state throughout pregnancy.

Poor control of thyrotoxicosis is associated with pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm and maternal congestive heart failure. Moreover, some studies suggest fetal exposure to excessive levels of maternal thyroid hormone may program the offspring to develop diseases such as seizure disorders and neurobehavioral disorders in later life.

During pregnancy, GD is typically treated with an antithyroid medication such as PTU during the first trimester and another called MMI for the remainder.

Thionamide ATDs (MMI, CM and PTU) are the mainstays of treatment for hyperthyroidism during pregnancy. They reduce iodine organification and coupling of monoiodotyrosine and diiodotyrosine, therefore inhibiting thyroid hormone synthesis. The thyroid function tests return to normal gradually over weeks.

Initial doses of ATDs during pregnancy are: MMI, 5-30 mg/day (typical dose in average patient 10-20 mg); CM, 0-40 mg/day and PTU, 100-600 mg/day (typical PTU dose in average patient 200-400 mg/d). The equivalent potency of MMI to PTU is 1:20. PTU dosing should be split into 2-3 daily doses. MMI can be given in one daily dose.

Postpartum Thyroiditis

About 1 in 20 women may get postpartum thyroiditis (PPT).

- 48% are hypothyroidism.
- 22% biphasic where there is hyperthyroidism followed by hypothyroid.
- 30% have isolated hyperthyroidism.

During the thyrotoxic phase of PPT, symptomatic women may be treated with β-blockers. These are safe for lactating women, such as propranolol or metoprolol, at the lowest possible dose to alleviate symptoms; it is the treatment of choice. Therapy is typically required for a few weeks.

ATDs are not recommended for the treatment of the thyrotoxic phase of PPT.

Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4-8 weeks (or if new symptoms develop) to screen for the hypothyroid phase.

Treatment is on the basis of the presenting disease and long-term follow-up with annual thyroid function tests is recommended. All patients with depression, including postpartum depression, should be screened for thyroid dysfunction.

Thyroid Nodule and Cancer

If thyroid nodules are seen is prepregnant period, it is advisable to delay pregnancy by 1 year after ablation.

If detected in pregnancy after 20 weeks, then a biopsy (FNAC) can be done. For malignancy, surgery is delayed till second trimester. Special care is needed during labor and delivery due to anesthesia complications.

In postnatal period, radioactive iodine is contraindicated if patient is breastfeeding.

UNIVERSAL SCREENING

It is still controversial whether to do universal screening of all pregnant women or apply case finding approach.

Table 3. High Risk Attributes for Thyroid Dysfunction

- A history of thyroid dysfunction or surgery
- Family history of thyroid disease
- Goiter
- Antithyroid antibodies present
- Symptoms or signs of hypothyroidism
- Women with type 1 diabetes
- History of miscarriage or preterm delivery
- Autoimmune disorder
- Infertility
- Prior head or neck irradiation
- Morbid obesity
- Age 30 years or older
- Treatment with amiodarone
- Treatment with lithium
- Recent exposure to iodinated contrast

American Thyroid Association guidelines do not support universal screening but recommend ordering a TSH test at first antenatal visit for women with high risk attributes (Table 3).

KEY POINTS

- Pregnancy-specific reference ranges should be used to guide diagnosis and monitoring of thyroid conditions in pregnancy.
- The World Health Organization (WHO) recommends a daily intake of iodine 250 μg during pregnancy and lactation.
- Hypothyroid states should be treated with thyroxine aiming for TSH <2.5 prior to conception and in the first trimester and TSH <3.0 for the second and third trimesters.
- Thyroxine should be increased by two additional doses per week (or 30%) on suspicion or confirmation of pregnancy in women already taking thyroxine.
- It is important to separate thyroxine intake from preparations that may reduce absorption.
- Women with high risk attributes for thyroid dysfunction are appropriate for antenatal screening with TSH.
- Gestational thyrotoxicosis needs to be differentiated from Graves' disease and rarely requires thioamide treatment.
- It is important to maintain a high index of suspicion for postpartum thyroiditis, especially in those with known thyroid antibodies or autoimmune conditions.

Pearls of Practice – Thyroid Dysfunction

Hypothyroidism

- T4 essential for early fetal development
- Little T4 crosses placenta after first trimester
- Adequate treatment - good outcome

Postpartum Thyroiditis

- Occurs 3-4 months postpartum
- Autoimmune disorder
- Phases of hyper- and hyporecovery
- Annual thyroid function tests

Hyperthyroidism

- Careful D/D at early weeks
- Untreated poor pregnancy outcome
- Drug cross placenta: lowest optimal dosage
- Cord blood - thyroid function

Thyroid Nodule and Cancer

- Defer pregnancy for 1 year after treatment with radioactive iodine
- Nodule identified beyond 20 weeks - biopsy after delivery
- Large goiter - anesthetic complications

FIGO RECOMMENDS THE FOLLOWING

- Screening for thyroid function is recommended in the first trimester particularly in countries with a deficient iodine diet and in symptomatic patients.
  - TSH is the superior method for screening. FT4 and TPOAb testing are not recommended for screening. The best reliable tests for TSH are by chemiluminescence immunoassay (CIA) or third-generation radioimmunoassay (RIA). Notably, normal thyroid test values change in pregnancy.
- Treatment for hypothyroidism is recommended when TSH levels are >2.5 and >3.0 mIU/L during the first and second/third trimesters, respectively. The only replacement therapy is LT4. Treating subclinical hypothyroidism, in the presence of negative thyroid autoantibodies, is still debatable. Importantly, women on LT4 before pregnancy should increase their dosage by 30-50% when they first recognize the pregnant state.
- Treatment of hyperthyroidism due to GD is by ATDs (PTU/CM/MMI). It is not recommended to change drugs during pregnancy. Symptomatic treatment with β-blockers for short-term may be needed.
- Primary prevention of hypothyroidism is by a healthy diet and iodized fortified salt (especially in iodine deficient areas).
- If the patient has a thyroid nodule, she should be evaluated and treated during pregnancy. The first steps are performance of a thyroid ultrasonogram and a fine needle aspiration (FNA), as needed. Surgery should be preferably deferred to the postpartum period.
- Follow-up and postpartum TSH evaluation and reduction of LT4 dose to pre-pregnant levels in patients with hypothyroidism.

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