Thyroid Diseases in Pregnant Women; Review Article

Manal Mohamed El Behery, Hoda Sibai AbdAlsalam,

Amany Aly Abdelhaleem Mohamed*, Ahmed Metwally El katawy

Abstract

Background: Pregnancy is a physiological state in which significant changes in thyroid function occur. Several factors contribute to these changes. Indeed, since the beginning of pregnancy, the HCG (human chorionic gonadotrophin) secreted by the placenta, given its homology of structure with TSH (thyroid stimulating hormone), exerts a stimulatory effect on thyroid gland leading to an increase in the secretion of thyroid hormones (T3 and T4) and a decrease in TSH, especially during the first trimester. In addition, pregnancy induces increase in metabolic function and requires a higher production of thyroid hormone. Demand for iodine intake increases especially as there is a greater urinary excretion of iodine and a transfer of iodine to the fetus when his thyroid becomes functional. Early diagnosis and treatment of thyroid diseases before and during pregnancy is important for maintaining the health of the mother and the baby. **Objective:** The early diagnosis of thyroid dysfunction for better health care of pregnancy. **Conclusion:** The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroidstimulating hormone typically is evaluated every 4–6 weeks while adjusting medications.

KeyWords: Thyroid, Pregnant Women.

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Introduction

Thyroid disease in pregnancy is common. At least 2–3% of women are affected by thyroid dysfunction and around 10% suffer from autoimmune thyroid disease despite euthyroidism (1).

Pregnancy may modify the course of thyroid disease, and pregnancy outcomes can depend on optimal management of thyroid disorders. Consequently, obstetric providers must be familiar with thyroid physiology and management of thyroid diseases in pregnancy (2).

Correspondingauthor: Amany Aly Abdelhaleem Mohamed **Email:** amany.ali90200@gmail.com

Mobile:+201067583125

Affiliations: Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt

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❖ Thyroid Function during Pregnancy:

A number of physiological changes during pregnancy influence thyroid hormone production, transport, and disposal (Table 1).

Table (1): Physiological changes in pregnancy and their influence on thyroid function tests [3]

Physiologic change	Serum thyroid test change
Increased thyroid gland size (women in areas of insufficient iodine intake)	Increased thyroglobulin
Estrogen-mediated increase in serum levels of TBG	Elevated total T4 and T3 concentrations
Increased plasma volume	Increased T4 and T3 pool
First-trimester elevation in serum hCG	Transient reduction in TSH and probable increase in free T4 concentrations
Increased expression of type 3 deiodinase (D3) in placenta and uterus	Accelerated degradation of T4 and T3
T4, thyroxine; T3, triiodothyronine; hCG, human chorionic gonadotropin; TBG, thyroxine-binding globulin.	

❖ Role of Thyroid Hormones during Pregnancy

Thyroid hormones are crucial for normal development of your baby's brain and nervous system. During the first trimester—the first 3 months of pregnancy—your baby depends on your supply of thyroid hormone, which comes through the placenta. At around 12 weeks, your baby's thyroid starts to work on its own, but it doesn't make enough thyroid hormone until 18 to 20 weeks of pregnancy.

Two pregnancy-related hormones human chorionic gonadotropin (hCG) and estrogen cause higher measured thyroid hormone levels in your blood. The thyroid enlarges slightly in healthy women during pregnancy, but usually not enough for a health care professional to feel during a physical exam.

Thyroid problems can be hard to diagnose in pregnancy due to higher levels of thyroid hormones and other symptoms that occur in both pregnancy and thyroid disorders. Some symptoms of hyperthyroidism or hypothyroidism are easier to spot and may prompt your doctor to test you for these thyroid diseases.

Another type of thyroid disease, postpartum thyroiditis, can occur after your baby is born.

❖ Thyroid Dysfunction during Pregnancy

As a result of the major changes in thyroid physiology that occur during pregnancy, gestational thyroid disease is best defined according to pregnancy-specific reference ranges calculated in a population of pregnant women free of major factors that interfere with thyroid function (4).

According to large epidemiological studies, thyroid disorders in pregnancy are associated with serious maternal, fetal and newborn complications: spontaneous abortions31, preterm birth32, preeclampsia, gestational diabetes, induction, cesarean section, ICU admission, placental abruption and breech presentation (5).

❖ Hypothyroidism during Pregnancy:

The most common thyroid gland dysfunction in pregnancy is hypothyroidism with a prevalence of about 0.3–0.5% for overt hypothyroidism and 2% to 3% for subclinical hypothyroidism of pregnant women (6).

The previously described physiological factors that influence thyroid function during pregnancy — increased iodine clearance, increased serum TBG concentration, increased D3 activity in the placenta and uterus, and increased volume of thyroid hormone distribution in the plasma — are a "stress" on the thyroid gland (3).

Women with normal thyroid glands in iodine-sufficient areas can compensate for these changes, but women in iodine-insufficient areas or those with underlying hypothyroidism may not be able to maintain euthyroxinemia. Although the fetal thyroid gland begins to function at 10–12 weeks of development, maternal thyroid status influences fetal development throughout pregnancy. Up to 40% of the cord blood thyroid hormone concentrations at delivery arise from the mother (7).

❖ Hyperthyroidism during Pregnancy:

-Manifest/Overt Hyperthyroidism:

Overt hyperthyroidism is characterized by a decreased TSH level and an increased free T4 level. Hyperthyroidism occurs in 0.2–0.7% of pregnancies, and Graves disease accounts for 95% of these cases(8).

Table (1): Changes in Thyroid Function Test Results in Thyroid Disease		
Maternal Status	**TSH**	**Free T4**
Overt hyperthyroidism	**Decrease**	**Increase**
Subclinical hyperthyroidism	**Decrease**	**No change**
Overt hypothyroidism	**Increase**	**Decrease**
Subclinical hypothyroidism	**Increase**	**No change**

The signs and symptoms of hyperthyroidism include nervousness, tremors, tachycardia, frequent stools, excessive sweating, heat intolerance, weight loss, goiter, insomnia, palpitations, and hypertension. Distinctive features of Graves disease are ophthalmopathy (signs include lid lag and lid retraction) and dermopathy (signs include localized or pretibial myxedema). Although some symptoms of hyperthyroidism are similar to normal symptoms of pregnancy or some nonthyroid-associated diseases, the results of serum thyroid function tests differentiate thyroid disease from these other possibilities (9).

Inadequately treated maternal thyrotoxicosis is associated with a greater risk of preeclampsia with severe features, maternal heart failure, and thyroid storm than treated, controlled maternal thyrotoxicosis (10).

- ***Fetal and Neonatal Effects***

Pregnancy outcomes generally depend on whether metabolic control is achieved before and during pregnancy (11). Inadequately treated hyperthyroidism is associated with an increase in medically indicated preterm deliveries, low birth weight, miscarriage, and stillbirth (6).

Fetal and neonatal risks associated with Graves disease are related either to the disease itself or to thioamide (propylthiouracil or methimazole) treatment of the disease. Because of the persistence of maternal antibodies, the possibility of fetal thyrotoxicosis should be considered in all women with a history of Graves disease (12).

Fetal thyrotoxicosis typically manifests as fetal tachycardia and poor fetal growth. If fetal thyrotoxicosis is suspected, consultation with a clinician with expertise in such conditions is warranted.

Because a large proportion of thyroid disease in women is mediated by antibodies that cross the placenta, there is a concern about the risk of development of immune-mediated hypothyroidism and hyperthyroidism in the neonate. Pregnant women with Graves disease can have thyroid-stimulating immunoglobulin and TSH binding inhibitory immunoglobulins (also known as thyrotropin-binding inhibitory immunoglobulins) that can stimulate or inhibit the fetal thyroid, respectively.

In some cases, maternal TSH-binding inhibitory immunoglobulins may cause transient hypothyroidism in neonates of women with Graves disease(13). Also, 1–5% of these neonates have hyperthyroidism or neonatal Graves disease caused by the transplacental passage of maternal thyroidstimulating immunoglobulin(14).

In neonates, maternal antibodies are cleared less rapidly than thioamides, which sometimes results in delayed presentation of neonatal Graves disease(14).

Therefore, the pediatrician should be notified of maternal Graves disease at the time of delivery, and the neonate should be followed for potential development of Graves disease(14). The incidence of neonatal Graves disease is unrelated to current maternal thyroid function. The neonates of women with Graves disease who have been treated surgically or with radioactive iodine-131 before pregnancy, and whose mothers required no thioamide treatment, still may have circulating antibodies, and therefore remain at risk of neonatal Graves disease and should be monitored accordingly(8).

- ***Subclinical Hyperthyroidism***

Subclinical hyperthyroidism, reported in 0.8–1.7% of pregnant women, is characterized by an abnormally low serum TSH concentration with free T4 levels within the normal reference range. Importantly, it has not been associated with adverse pregnancy outcomes. According Treatment of pregnant women with subclinical hyperthyroidism is not recommended because there is no demonstrated benefit to the mother or fetus. In addition, there are theoretical risks to the fetus because antithyroid medications cross the placenta and may adversely affect fetal thyroid function (15).

Therefore, the American College of Obstetricians and Gynecologists, the Endocrine Society, and the American Association of Clinical Endocrinologists recommend against universal screening for thyroid disease in pregnancy and recommend testing

during pregnancy only for women who are at increased risk of overt hypothyroidism(16).

The American Thyroid Association currently finds that there are insufficient data to recommend for or against universal thyroid screening(8).

Laboratory diagnose of thyroid disease during pregnancy

Levels of TSH and thyroid hormone are both used to diagnose thyroid disease in pregnancy. If indicated, the first-line screening test to assess thyroid status should be measurement of the TSH level. Assuming normal hypothalamic–pituitary function, an inverse loglinear relationship exists between serum TSH and serum thyroid hormone, such that small alterations in circulating hormone levels will produce large changes in TSH(17).

Furthermore, because the free hormone assays used by most clinical laboratories do not use physical separation techniques, such as equilibrium dialysis, test results depend on individual binding protein levels and represent only estimates of actual circulating free T4 concentrations. Therefore, TSH is the most reliable indicator of thyroid status because it indirectly reflects thyroid hormone levels as sensed by the pituitary gland. When the TSH level is abnormally high or low, a follow-up study to measure the free T4 level should be performed to determine if there is overt thyroid dysfunction. In cases of suspected hyperthyroidism, total T3 also is measured (Fig. 1) (17).

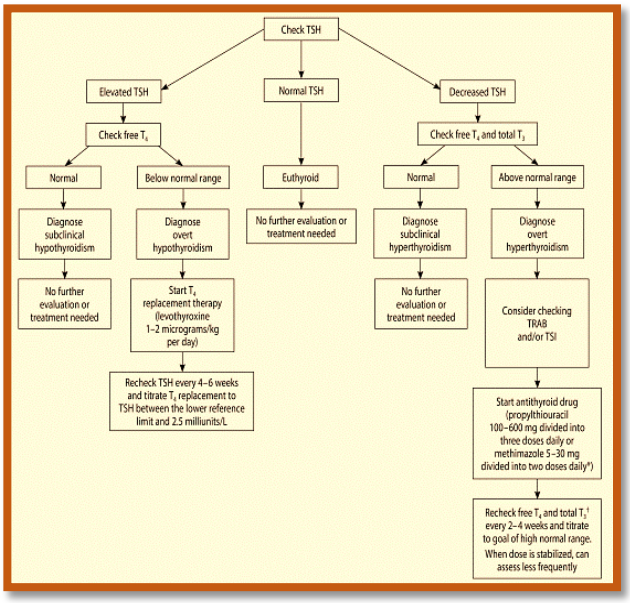

Figure (7): Algorithm for management of thyroid disorders during pregnancy.

- ***Screening or Testing for Thyroid Autoantibodies***

Measurement of antithyroid antibodies in situations of overt and subclinical thyroid dysfunction has been proposed. Autoantibodies to thyroid peroxidase and thyroglobulin have been identified in up to 20% of reproductive-age women (18).

Women with thyroid peroxidase antibodies are at increased risk for progression of thyroid disease and development of postpartum thyroiditis (19). **-**

Management

1) Treatment of Overt hypothyroidism

According to ACOG guidelines released 2020; Pregnant women with overt hypothyroidism should be treated with adequate thyroid hormone replacement to minimize the risk of adverse outcomes. For the treatment of overt hypothyroidism in pregnancy, the American Thyroid Association and the American Association of Clinical Endocrinologists recommend T4 replacement therapy, beginning with levothyroxine in dosages of 1–2 micrograms/kg daily or approximately 100 micrograms daily (20). Pregnant women who have no thyroid function after thyroidectomy or radioiodine therapy may require higher dosages. T3-containing preparations (e.g., desiccated thyroid extract or synthetic T3) of thyroid hormone should be avoided in pregnancy as high levels of T3 compared to T4 in these preparations leads to supraphysiologic levels of maternal T3 and low levels of T4. Maternal T4 is critical for fetal central nervous system development (8).

Unlike in pregnant women with hyperthyroidism, assessment of therapy in pregnant women with hypothyroidism is guided by measurement of TSH levels rather than free T4 levels. The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroid stimulating hormone typically is evaluated every 4–6 weeks while adjusting medications (8).

Pregnancy is associated with an increasing T4 requirement in approximately one third of women receiving thyroid hormone supplementation (21).

This increased demand is believed to be related to increased estrogen production (22). Anticipatory 25% increases in T4 replacement at pregnancy confirmation can be considered for women receiving treatment for known hypothyroidism at the time of presentation to prenatal care.

2) Treatment of Overt hyperthyroidism

According to ACOG guidelines released 2020; pregnant women with overt hyperthyroidism should be treated with antithyroid drugs (thioamides). Either propylthiouracil or methimazole, both thioamides, can be used to treat pregnant women with overt hyperthyroidism. The choice of medication is dependent on trimester of pregnancy, response to prior therapy, and whether the thyrotoxicosis is predominantly T4 or T3. Women should be counseled about the risks and benefits of the two thioamides described below using shared decision making to develop an appropriate treatment plan(17).

Methimazole typically is avoided in the first trimester because it has been associated with a rare embryopathy characterized by esophageal or choanal atresia as well as aplasia cutis, a congenital skin defect(23).

In a 2012 review of 5,967 live births to women with known Graves disease, there was a twofold increased risk of major fetal malformations reported in those who were exposed to methimazole compared with those exposed to propylthiouracil (23). Specifically, seven of nine cases of aplasia cutis, and the only case of esophageal atresia, occurred in methimazole-exposed infants. Therefore, propylthiouracil generally is prescribed for control of hyperthyroidism in the first trimester.

After the first trimester, either methimazole or propylthiouracil can be used for treatment of hyperthyroidism. In rare cases, propylthiouracil results in clinically significant hepatotoxicity (Ross et al(24), which has prompted some health care professionals to transition to methimazole after the first trimester. However, a transition from propylthiouracil to methimazole may result in a period of poor control of hyperthyroidism. Both medications have known adverse effects that must be weighed against each other and discussed with the patient (24) As such, some women are maintained on propylthiouracil throughout the pregnancy. In addition, propylthiouracil decreases T4 to T3 conversion and is used preferentially for T3-predominant thyrotoxicosis (24). Decision making regarding whether and how to transition from one agent to another often occurs in conjunction with endocrinology or maternal– fetal medicine subspecialists. If a switch is deemed appropriate, a dose ratio of 20:1 propylthiouracil to methimazole is recommended.

3) Treatment of hyroid Storm and Thyrotoxic Heart Failure Diagnosed and Treated in Pregnancy

Thyroid storm and thyrotoxic heart failure are rare, acute, and life-threatening conditions in pregnancy. Thyroid storm in pregnancy carries a high risk of maternal heart failure(25). Thyroid storm is a hypermetabolic state caused by an excess of thyroid hormone. It is a clinical diagnosis in the setting of severe thyrotoxicosis accompanied by systemic decompensation (24). Clinical scoring systems such as the Burch-Wartofsky Point Scale can be used to confirm the diagnosis and evaluate the severity of disease. Thyroid storm typically manifests clinically as a combination of the following signs and symptoms: fever, tachycardia, cardiac dysrhythmia, and central nervous system dysfunction (24).

Ultrasonographic characteristics associated with malignancy include hypoechoic pattern, irregular margins, and microcalcifications (26). When all three characteristics are present, these features correlate with a malignancy risk exceeding 70% (8). If ultrasonographic test results are suspicious for malignancy, fine-needle aspiration can be used for histologic examination, including tumor markers and immunostaining to evaluate for malignancy (17). Radioiodine scanning in pregnancy is not recommended because of the theoretic risk associated with fetal irradiation. However, if there has been inadvertent administration of radioiodine before 12 weeks of gestation, the American Thyroid Association has noted that the fetal thyroid gland, which does not become significantly functionally active until approximately 12 weeks of gestation, does not appear to be at risk of damage (8).

Evaluation of thyroid cancer in pregnancy involves a multidisciplinary approach. Most cases of thyroid carcinoma are well differentiated and follow an indolent course. The possibility that thyroid cancer is part of a hereditary familial cancer syndrome is unlikely but should be considered. When thyroid

malignancy is diagnosed during the first or second trimester, thyroidectomy may be performed before the third trimester, but concern regarding inadvertent removal of parathyroid glands often leads to the choice to delay surgery until after delivery. In women without evidence of an aggressive thyroid cancer or women in whom thyroid cancer is diagnosed in the third trimester, surgical treatment can be deferred to the immediate postpartum period (26).

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