



ANTEPARTUM THYROID DISEASE DIAGNOSIS AND TREATMENT

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The normal physiological changes that occur during pregnancy, particularly increases in renal blood flow and glomerular filtration rate, lead to an increase in iodide clearance and a fall in plasma iodine concentrations.¹ In addition, there is an increased requirement for iodine in pregnant women as the fetal thyroid gland initiates synthesis of thyroid hormone after the first trimester.

In iodine-sufficient populations, this concomitant drop in plasma iodine concentration and increase in iodine requirement usually has no impact on thyroid hormone homeostasis.¹ An increase in thyroid hormone synthesis and a decrease in thyroid hormone degradation during pregnancy can maintain thyroid hormone concentrations within the normal range in the face of increasing plasma volume.²

In iodine-insufficient regions and in women predisposed to thyroid disease, however, the physiological changes associated with pregnancy can have an impact on thyroid function and lead to the development of thyroid disease. Iodine deficiency in pregnancy may lead to persistent stimulation of the thyroid gland and development of goiter.³ Goiter formation can be prevented by increasing iodine intake (to at least 200 µg/d) prior to conception and through pregnancy.⁴

Many of the physical characteristics of mild hyper- and hypothyroidism appear during pregnancy, including tachycardia, heat intolerance, and fatigue, making it difficult to diagnose thyroid disease in pregnant patients. Overt thyroid disease is present in approximately 1% to 2% of pregnant women, though mild forms of hyper- or hypothyroidism may be more prevalent.⁵

Hypothyroidism

In normal pregnancy, the maternal immune system undergoes a dramatic change to allow implantation and development of the fetus, a perceived foreign body. This shift may induce a general autoimmune response resulting in thyroid autoimmunity or gestational diabetes mellitus. Approximately 2% to 4% of women have some degree of hypothyroidism as they enter pregnancy,^{4,6-8} and the most common cause of primary hypothyroidism in women of child-bearing age is autoimmune thyroiditis. Between 1% and 2% of women who become pregnant are already receiving levothyroxine sodium (LT₄). The development of maternal hypothyroidism in pregnancy can lead to adverse health effects in both the mother and the fetus; in particular, low maternal thyroid hormone has been linked to neuropsychological deficiencies in children.⁹⁻¹² Hypothyroidism, either overt or mild, carries an increased risk for gestational hypertension, miscarriage, premature delivery, and fetal death.^{8,12-14}

Because of the risks posed by thyroid hypofunction to both mother and fetus, thyroid-stimulating hormone (TSH, thyrotropin) screening of pregnant women within the first trimester may be warranted, particularly in women with symptoms of hypothyroidism, goiter, high antithyroid antibody titer, or family history of thyroid disease (Figure 1).^{8,9,15} Diagnosis of primary hypothyroidism is made by measuring serum TSH and free thyroxine (FT₄) levels. Because of the normal increase in thyroxine binding globulin that occurs during pregnancy,¹ FT₄ in the pregnant patient should be within the normal range, whereas total T₄ may be increased by 4-5 µg/dL. Thyroid autoimmunity is accompanied by a measurable increase in thyroid peroxidase

antibodies (TPOab), which has led to the recommendation that all pregnant patients be screened for the presence of TPOab during the first trimester.^{16,17} The American Association of Clinical Endocrinologists has also recommended that women considering pregnancy should have their TSH levels checked to detect and treat hypothyroidism before pregnancy.¹⁵

Maternal hypothyroidism can be treated with LT₄ therapy. In a newly diagnosed hypothyroid pregnant patient, the full replacement dose of LT₄ should be initiated.¹⁵ If FT₄ is normal, patients should begin with 25-75 µg/d LT₄; if FT₄ is low, patients should be given 1.6 µg/kg/d LT₄. Thyrotropin levels should be retested every 5-6 weeks and LT₄ titrated in 12.5 µg/d to 25 µg/d increments as needed to maintain TSH levels within the normal range (0.5 to 2.0 mIU/L).

Several studies have shown that T₄ requirements increase in pregnancy; thus, patients with preexisting hypothyroidism who are already receiving LT₄ therapy should undergo TSH testing and have their LT₄ dose retitrated early in gestation.^{15,18,19} Patients should have their TSH levels assessed as soon as possible after conception, and again at 8-12 weeks and 20 weeks gestation. Levothyroxine sodium should be titrated in 12.5 µg/d to 25 µg/d increments as needed to maintain TSH levels within the normal range (0.5 to 2.0 mIU/L).

Hyperthyroidism

Hyperthyroidism in pregnancy is relatively rare, occurring in 0.2% of pregnancies in the US, with the most common cause being pre-existing Graves disease.^{4,20-22} Uncontrolled hyperthyroidism can adversely affect not only the mother's health, but can cause congenital abnormalities, fetal goiter, thyrotoxicosis, neonatal Graves disease, and an increase in fetal mortality.²¹ The signs and symptoms of hyperthyroidism in nonpregnant and pregnant patients are similar, and fatigue, palpitations, and heat intolerance are also common in normal pregnancies. The most telling sign of hyperthyroidism in pregnancy is weight loss or absence of customary weight gain despite an increased appetite.

Human chorionic gonadotropin (hCG) has weak thyrotropic properties. The normal rise in hCG in early pregnancy will induce a small increase in thyroid hormone levels and a decrease in TSH within the first trimester (peak hCG at 10-12 weeks gestation).^{1,17} An increase in hCG of 10 000 IU/L correlates with a decrease in TSH of 0.1 mIU/L and an increase in FT₄ of 0.6 pmol/L (0.05 ng/dL). As hCG levels decrease with the progression of pregnancy, TSH levels normalize. Thus, a slightly decreased TSH level in early pregnancy should not be misdiagnosed as hyperthyroidism. Low TSH accompanied by sustained supranormal FT₄ concentration is characteristic of gestational transient thyrotoxicosis (GTT).^{1,17,22}

Hyperemesis gravidarum is a transient thyrotoxic condition in which there are additional increases in both triiodothyronine (T₃) and T₄, and it may be hard to distinguish this disease from coexistent thyrotoxicosis.²² Hyperemesis gravidarum may be caused by excessive levels of hCG and resolves as hCG levels fall with progression of gestation.²³ At times, it may be necessary to treat patients with antithyroid drugs (ATDs).

As described above, pregnant patients should have their TSH and TPOab titer checked early in gestation (6-12 weeks) (Figure 2).²² If TSH is low, T₄ should also be checked, as well as TSH receptor antibody (TSH-Rab) to determine whether the observed hyperthyroidism is due to

autoimmune disease or a transient rise in hCG.²² Patients with FT₄ levels above 2.5 ng/mL should begin ATD therapy.²⁴ If a patient has been previously treated for hyperthyroidism by radioactive iodine (RAI) therapy or surgery, TSH-Rab should be tested. If a patient has previously taken or is taking ATDs, TSH-Rab should be checked in the third trimester. The presence of significant TSH-Rab titers places the newborn at risk for neonatal thyrotoxicosis even when the mother may be euthyroid.

Because ATDs can pass from mother to child, administration of ATDs during pregnancy can affect fetal thyroid development and may lead to fetal hypothyroidism and goiter. Thus, the goal of treatment for hyperthyroidism in pregnancy is to maintain the patient at a high-normal euthyroid state (TSH 0.1-1.0 mIU/L, high-normal T₄) throughout pregnancy using the lowest dose of ATDs possible. Treatment with ATDs such as propylthiouracil (PTU) should begin at 50-100 mg twice daily and should not be given at doses greater than 300 mg/d (equivalent to about 20 mg/d mercaptomethylimidazole).²⁴ To ensure that the lowest dose of ATDs is used, these drugs should not be co-administered with LT₄.²⁴

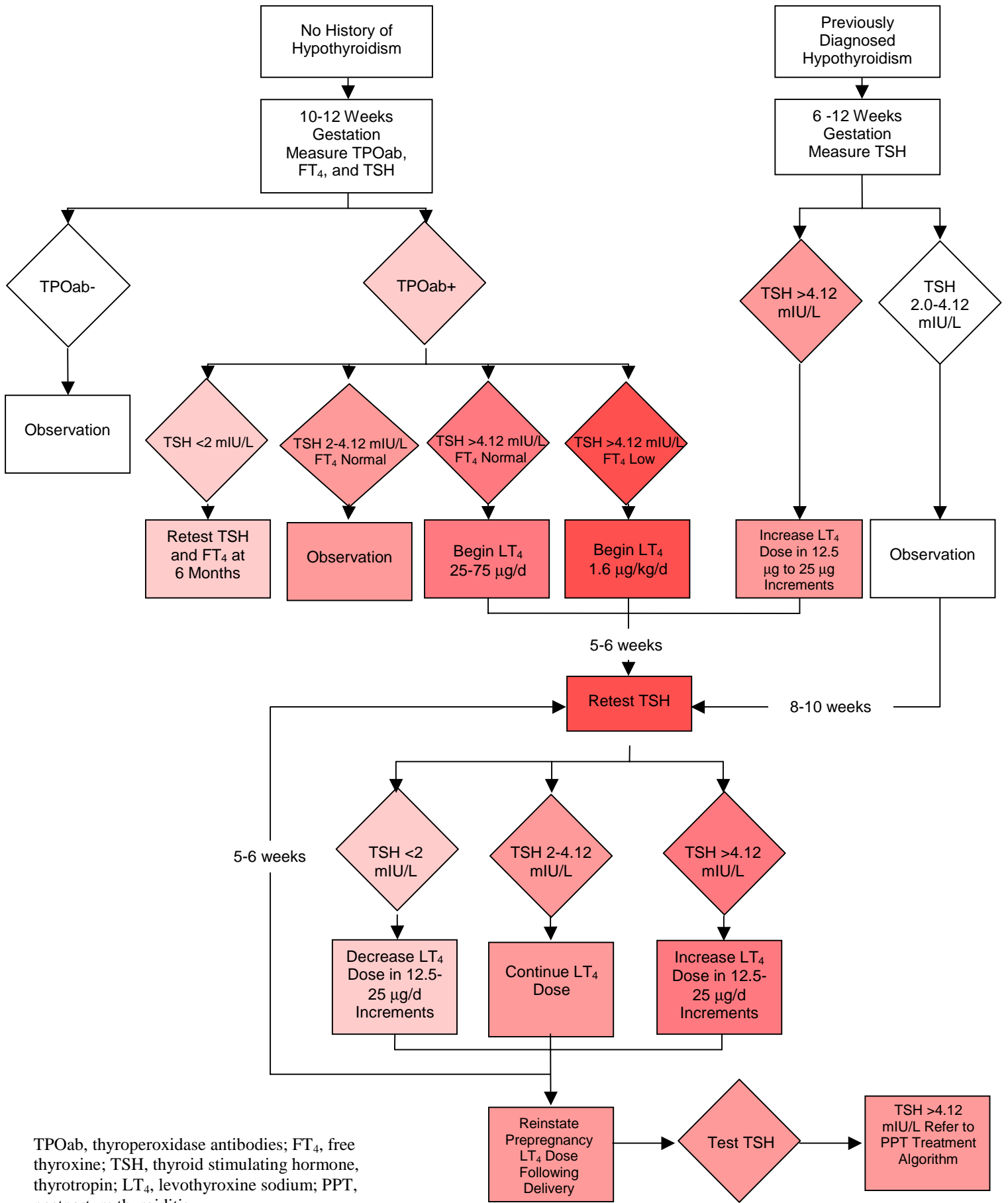
Monthly monitoring of pregnant patients receiving ATD therapy is necessary,²⁴ and the dose of ATDs usually can be adjusted downward as gestation continues. Antithyroid drugs should be discontinued as early in gestation as possible. Once thyroid function has been normalized (TSH 0.1 to 0.4 mIU/L), the ATD dose can be gradually discontinued.

If thyroidectomy is necessary because of nonresponse to the highest doses of ATDs, it should be performed in the second trimester. Levothyroxine sodium therapy should be instituted at 2.2 µg/kg/d following surgery, and then reduced to 1.6 µg/kg/d after delivery.

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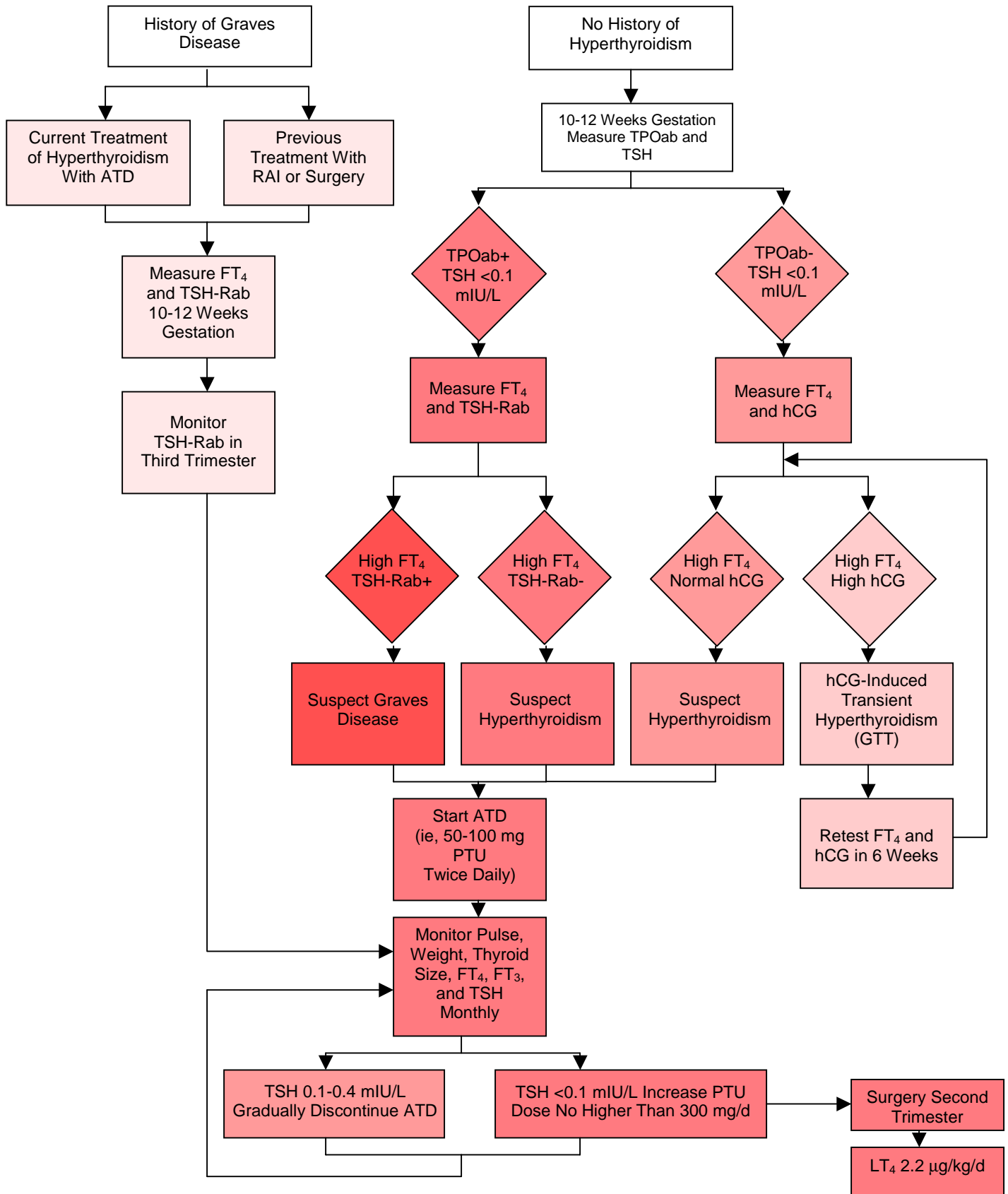
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Figure 1. Diagnosis and Treatment of Hypothyroidism in Pregnancy



TPOab, thyroperoxidase antibodies; FT₄, free thyroxine; TSH, thyroid stimulating hormone, thyrotropin; LT₄, levothyroxine sodium; PPT, postpartum thyroiditis.

Figure 2. Diagnosis and Treatment of Antepartum Hyperthyroidism



ATD, antithyroid drug; RAI radioactive iodine; TSH, thyroid-stimulating hormone, thyrotropin; TSHR-ab, TSH receptor antibody; TPOab, thyroperoxidase antibody; FT₄, free thyroxine; hCG, human chorionic gonadotropin; GTT, gestational transient thyrotoxicosis; FT₃, free triiodothyronine; PTU, propylthiouracil; LT₄, levothyroxine sodium.