Review Article

A look at Graves' hyperthyroidism in pregnancy

Caroline T. Nguyen[1], Jorge H. Mestman[2]

[1]Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, [2]Division of Endocrinology, Diabetes & Metabolism, Department of Medicine and Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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Correspondence to: Caroline T. Nguyen, MD. 1540 Alcazar Street, CHP 204, Los Angeles, CA 90033, USA. Email: Caroline.Nguyen@med.usc.edu.

Abstract: Maternal, obstetrical, and neonatal complications are increased in women with poorly controlled thyroid disease during pregnancy. Establishing the correct diagnosis and effectively managing Graves' hyperthyroidism (GH) remains challenging for physicians due to several reasons including, but not limited to changes in thyroid physiology during pregnancy, effect of pregnancy on laboratory testing, and teratogenicity associated with anti-thyroid drugs. This paper will review the diagnosis and management of GH in pregnancy and address: (I) preconception counseling; (II) alterations in thyroid physiology in pregnancy; (III) thyroid laboratory testing; (IV) etiologies of hyperthyroidism; (V) pregnancy-related complications; (VI) maternal management; (VII) neonatal management; (VIII) ATDs and the associated maternal and fetal complications; and (IX) post-partum management. Establishing the diagnosis of GH early, maintaining euthyroidism throughout the duration of pregnancy, and avoiding overtreatment of the fetus with antithyroid drugs (ATDs) is essential to reducing the risk of complications for the mother, fetus, and newborn. The successful care of these complex patients requires close collaboration between the endocrinologist, maternal-fetal-medicine specialist, obstetrician, neonatologist, and pediatric endocrinologist.

Keywords: Hyperthyroidism; Graves' hyperthyroidism (GH); pregnancy; preconception counseling; antithyroid drugs (ATDs)

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Introduction

The management of Graves' hyperthyroidism (GH) in pregnancy remains a challenge for the physician who must recognize the signs and symptoms of thyrotoxicosis; assess any history of thyroid disease along with its course and management; correctly interpret thyroid labs, which are complicated by the changes that occur in thyroid physiology during pregnancy; and choose the best treatment plan for the patient and the fetus. Furthermore, treatment of GH with antithyroid drugs (ATDs) has been associated with teratogenicity.

Maternal, obstetrical, and neonatal complications are increased in women with poorly controlled thyroid disease. In 1975, a study of 26 pregnancies of hyperthyroid women treated with ATDs resulted with four infants born with goiter, three with hyperthyroidism, and five with congenital abnormalities (1). Today, complications due to uncontrolled GH still occur.

The key to the successful management of GH in pregnancy begins with preconception counseling. In addition, early recognition of the symptoms of disease and a multidisciplinary approach involving the endocrinologist, maternal-fetal-medicine specialist, anesthesiologist, neonatologist, and pediatric endocrinologist are essential.

This review will discuss: (I) preconception counseling; (II) alterations in thyroid physiology in pregnancy; (III) thyroid laboratory testing; (IV) etiologies of hyperthyroidism; (V) pregnancy-related complications; (VI) maternal management; (VII) neonatal management; (VIII) ATDs and

the associated maternal and fetal complications; and (IX) post-partum management.

Preconception counseling

GH is an autoimmune disease characterized by antibodies that stimulate the thyroid stimulating hormone receptor (TSHR). The likelihood that a pregnant woman age 20–45 years old has had a prior history of GH is 0.5% to 1.3% (2). All women of reproductive age with GH or a past history of GH should receive preconception counseling. These women should be advised to plan their pregnancies and contact their physician before or as soon as pregnancy has been confirmed (3).

Women with a history of GH treated with either radioactive iodine ablation (RAIA) or surgery will need an increase in their levothyroxine dose early in pregnancy due to the 30–50% increase in thyroid hormone demand in the first half of pregnancy (4,5). Some studies have shown that a TSH greater than 2.5 mIU/L in the first trimester of pregnancy increases the incidence of miscarriages, premature labor, and intellectual deficiencies in the offspring later in life (6,7). However, other studies have shown no clinically important association between maternal thyroid dysfunction in early pregnancy and impaired educational achievement (8). Abalovich *et al.* showed that a TSH of 1.2 mIU/L before conception prevents development of hypothyroidism after conception in almost 85% of hypothyroid women on thyroid replacement therapy (9).

Counseling should take into consideration the woman's desired timeline to conception and a discussion of the potential risks and benefits of treatment options including ATD, 131-RAIA, and surgery. Women should not become pregnant until hyperthyroidism is controlled. Women with difficult to control GH on high doses of ATD should consider definitive therapy prior to conception. Women should be educated about the frequency of medical and obstetric visits during pregnancy, need for serial thyroid blood tests, the potential for congenital abnormalities of ATDs, the risks of uncontrolled hyperthyroidism in pregnancy, the possibility of recurrence of hyperthyroidism in pregnancy and postpartum, and breastfeeding.

Women who are on ATDs for GH should be on contraception and counseled to pay close attention to their menstrual cycles. If a period is missed, a pregnancy test should be done immediately. The risk of birth defects due to ATDs is greatest during weeks 6–10 during organogenesis (10). Methimazole (MMI) is generally preferred to propylthiouracil (PTU) in the treatment of GH for ease of once daily dosing compared to PTU, which is dosed three times daily. PTU also is associated with an increased risk for hepatotoxicity. However, women are often switched to PTU in the first trimester of pregnancy because the teratogenic effects associated with PTU are considered less severe than those associated with MMI. Patients may be switched from MMI to PTU once pregnant or in anticipation of pregnancy. An argument for the latter is that pregnancy is typically not diagnosed until a missed period and the switch from MMI to PTU often occurs after week 6 when the risk of potential side effects from the medication is highest (11).

In women who will be treated with RAIA, a pregnancy test should be done beforehand and conception should be delayed for 6 months until the woman is euthyroid on levothyroxine therapy. The risks to the fetus of inadvertent treatment with RAIA during pregnancy are dependent on the timing of exposure and the radiation dose (12). Spontaneous miscarriage is more likely when exposure occurs in the first two weeks after fertilization, prior to implantation (13). A surviving embryo exposed at this early stage would be less likely to have a major malformation. Exposure at later stages in pregnancy such as during organogenesis or thyroidogenesis (from week 10) may result in fetal thyroid ablation or birth defects (12).

After RAIA therapy, TSH receptor antibodies (TRAb), which are measurable in 95% of patients with GH (14), may increase and stay elevated for months to years (15-17). Persistently elevated TRAb levels throughout pregnancy are prognostic of fetal thyroid dysfunction (18). Therefore, women with very elevated TRAb levels prior to conception may be better candidates for thyroidectomy as TRAb levels tend to decrease and normalize within months to one year after surgery (15,16). Rarely, TRAb levels may remain elevated years after surgery (19).

Changes in thyroid physiology during pregnancy

The increased demand for thyroid hormone production during pregnancy is attributed to (I) an almost two-fold increase in thyroxine-binding globulin (TBG) due to the stimulatory effects of estrogen on the production of TBG by the liver and possibly the prolonged half-life of sialylated TBG in pregnancy (20) (II) stimulatory effects of human chorionic gonadotropin (hCG), a glycoprotein that has structural similarity to TSH, on the TSHR (21), and high concentrations of Deiodinase Type 3 in the placenta, which

deactivates thyroxine and triiodothyronine (22).

The thyroid compensates for this increased demand by increasing T4 synthesis and secretion. Requirements of iodine, essential to thyroid hormone synthesis, consequently increase in pregnancy. The suggested daily iodine ingestion for pregnant women varies between 220–250 µg/day (23). Prenatal vitamins should contain 150 µg of iodine in the form of potassium iodine and are meant to supplement daily dietary iodine intake (24). However, not all prenatal vitamins contain iodine. The physician should alert the patient to obtain prenatal vitamins containing the proper iodine supplementation.

In the setting of adequate iodine intake, the normal thyroid gland is able to compensate for the increased thyroid hormone demands. However, in patients with thyroid abnormalities or in women on thyroid hormone replacement, this demand may not be met and hypothyroidism may result. The fetus relies entirely on the mother for thyroid hormone until 10–12 weeks when the fetal gland begins to secrete thyroid hormone. Significant fetal thyroid hormone production occurs around week 20 (25).

Laboratory tests

TSH is the screening test used for detection and diagnosis of thyroid dysfunction along with levels of thyroxine when TSH values are abnormal. In early pregnancy, hCG rises contributing to TSH concentrations that may be below the non-pregnant reference range in up to 10% of normal pregnant women. The American Thyroid Association Thyroid and Pregnancy Guidelines (ATATPG) recommended an adjusted reference range (decreases of the lower limit of the reference range of TSH by 0.4 mU/L and upper limit by approximately 0.5 mU/L) be used in weeks 7–12 with a gradual return to non-pregnancy reference ranges in the second and third trimester (23). Notably, 0.5–1% of women may have completely suppressed TSH levels in early pregnancy (26). TSH below 0.10 mIU/L in the first trimester is not associated with obstetric complications (27).

The most common commercially available tests in clinical practice for measurement of free thyroxine (FT4) are automated immunoassays by non-equilibrium methods. However, in the latter half of pregnancy, increased thyroid-binding globulin (TBG) and decreased serum albumin concentration lead to inconsistency between available FT4 immunoassays and falsely low FT4 levels (28-30) making trimester-specific pregnancy reference ranges necessary if FT4 is used (30). A comparison of FT4, total T4 (TT4) levels, and FT4 index (FT4I) found that the latter two more accurately demonstrate changes in thyroxine throughout gestation (30,31).

As TBG increases, TT4 rises from the first trimester until mid-gestation when TT4 stabilizes. After 16 weeks, the non-pregnancy reference range for TT4 may be adjusted by a factor of 1.5 and used to assess thyroid status. For example, the normal reference range of 4.5–12.5 µg/dL multiplied by 1.5 becomes 6.75–18.75 µg/dL (30). Alternatively, the FT4I can be calculated by adjusting the TT4 for alterations in TBG using the T3 resin uptake test (32). Equilibrium dialysis technique and tandem mass spectrometry are more accurate at FT4 measurement, but they are also more expensive and less commonly available (33).

The role of serum FT3 or TT3 is limited in pregnancy. If TSH is suppressed, but FT4/FT4I is normal, an elevated FT4/TT3 would be suggestive of an autonomous functioning nodule or exogenous triiodothyronine (T3) hormone. T3 may be elevated in GH as well, more commonly when being treated with ATDs.

TRAb

TSH receptor antibodies (TRAb) may be stimulating (TSAb), neutral, or blocking antibodies of the TSH receptor. TSAbs are the pathogenetic hallmark of GH with 97% sensitivity and 99% specificity for GH (14). TRAbs cross the placenta, act on the fetal TSHR, and can cause thyroid dysfunction. Consequently, TRAb levels play an important role in assessing the risk of fetal and neonatal hyperthyroidism (34,35).

TRAbs may be measured by two different methods, a "receptor assay" and a "bioassay." The receptor assay measures TRAbs by TRAbs' capacity to compete with radiolabeled TSH to bind to a TSHR preparation. The first generation receptor assay was referred to as TSH-binding inhibiting immunoglobulins (TBII). The second and third generation receptor assays are now referred to as TRAb. The sensitivity and specificity of each subsequent generation of the assay has improved. The third-generation TRAb assay is 98% and 99.2% sensitive and specific respectively (36,37).

The major limitation of the TRAb receptor assays is that they do not differentiate between the TSAB, neutral, or blocking antibodies. Furthermore, there has not been an established association between TRAb and the clinical and biochemical severity of the disease. In the bioassays, the functional property of the TRAbs may be

Table 1 Hyperthyroidism in pregnancy etiologies (41)

Thyroid disease
Graves' hyperthyroidism
Chronic thyroiditis
Painless thyroiditis
Subacute thyroiditis
Toxic adenoma
Multinodular goiter
Iatrogenic
Excessive thyroid hormone intake
Drugs (iodine, amiodarone, lithium)
Gestational transient thyrotoxicosis (see *Table 2*)

Table 2 Gestational transient thyrotoxicosis etiologies (42)

Mild nausea and vomiting
Hyperemesis gravidarum
Twin or multiple pregnancies
Mutation in the TSH receptor (47)
Hyperplacentosis (48)
Hyperreactio luteinalis (49)
Hydatidiform mole
Choriocarcinoma

measured and the antibodies may be distinguished from one another, providing useful clinical information. The bioassay entails incubating the patient's serum with cells expressing TSHR and measuring cyclic AMP production by radioimmunoassay or chemiluminescent assay (35).

In patients with active GH, a positive TRAb level via either the receptor or bioassay method is indicative of TSAb. In patients with GH treated by RAIA or surgery, TRAb may be stimulating, neutral, or blocking antibodies. A bioassay can provide clinically relevant information on the function of the TRAb, and in pregnancy its effect on the fetus. A recent study by Diana *et al.* demonstrated that 4.2% of non-pregnant patients with GH had detectable blocking antibodies (38). However, in another study of 788 neonates who had neonatal screening suggestive of neonatal hypothyroidism, only 9 had blocking antibodies (39).

TRAb levels tend to decrease after week 20 due to the immunosuppressive effects of pregnancy and are often undetectable towards the term of pregnancy coinciding with the subsiding of hyperthyroid symptoms often observed in GH patients. However, if TRAb levels remain elevated over 3 times the upper limit of normal (3× >ULN) in the latter half of pregnancy, there is an increased risk of fetal and neonatal hyperthyroidism (16) with 100% sensitive and 43% specificity (40).

TPO-Ab

Thyroid peroxidase antibody (TPO-Ab) is a nonspecific marker of thyroid autoimmunity. It has been associated with increased risk of miscarriage and premature delivery in euthyroid women. It does not have a role in GH.

Etiology of hyperthyroidism

Gestational transient thyrotoxicosis (GTT)

The etiology of hyperthyroidism in pregnancy is broad (*Table 1*), but the majority of cases are due to GTT. GTT affects 1–5% of all pregnant women, making it much more common than GH, which affects 0.2% of pregnancies (2,42). Differentiating GH from GTT is important because the latter is a transient, mild hyperthyroidism that does not require treatment with ATD and in most cases is not associated with adverse pregnancy outcomes (43,44).

Negative TRAb along with absence of Graves' ophthalmopathy, goiter, and prior history of hyperthyroidism is suggestive of GTT. TSH is typically suppressed and FT4 is mildly elevated. The clinical course coincides with hCG levels, which begin to rise week 7 of gestation and decrease between weeks 14 and 20 (45,46). TSH levels may exhibit a "lag phase" and remain suppressed weeks after resolution of the GTT.

The etiologies of GTT are many (*Table 2*), but the most common cause of thyrotoxicosis in the first trimester of pregnancy is hyperemesis gravidarum (HG) (50). It is characterized by significant nausea, vomiting, and weight loss of up to 5 kg. Patients frequently present to the hospital for IV hydration (51). Symptoms of hyperthyroidism are typically mild, although patients may present with palpitations, tremors, and night sweats.

Twin and multiple pregnancies have increased and prolonged levels of hcG production and may present with GTT. Trophoblastic diseases such as hydatidiform moles, choriocarcinoma, and hyperplacentosis are also associated

with increased levels of hcG, but are rare (52). Women with a prior history of GTT have a higher likelihood of having a repeat episode (42).

GH

In pregnancy, GH may present as: a first-time diagnosis, a patient undergoing treatment with ATD, a patient with recurrence of hyperthyroidism after treatment with ATD, radioiodine ablation therapy, and less commonly today, surgery (53). The diagnosis of GH should be suspected in a hyperthyroid pregnant woman who was having symptoms prior to pregnancy, had a prior diagnosis of hyperthyroidism, or gave birth to an infant with a thyroid dysfunction. The signs and symptoms of GH are similar to those seen in non-pregnant patients. Although the clinical diagnosis may be difficult in pregnancy as mild palpitations, HR 90–100 bpm, mild heat intolerance, shortness of breath on exertion, and warm skin can be seen in normal pregnancy. Clinical clues such as ophthalmopathy, goiter, frequent bowel movements, persistent tachycardia, weight loss, or inability to gain weight despite increased appetite are suggestive of GH

Worsening GH symptoms in early pregnancy along with a small increase in GH incidence is thought to be from the increase in hCG and or elevation in TRAb levels during the first trimester (54-57). With the progression of pregnancy, changes in the immunologic response lead to improvement in symptoms. Some women are able to discontinue ATD. In the postpartum period, however, GH may recur as the immune system rebounds (58).

Autonomous functioning thyroid nodule or toxic adenoma

A rare cause of maternal hyperthyroidism, a toxic adenoma typically presents with a palpable thyroid nodule on exam. Clinical signs of GH such as ophthalmopathy are absent. Thyroid function tests may reveal a FT4 or FT4Index mildly to moderately elevated. Thyroxine may be normal and the nodule may be predominantly T3 secreting. This is one occasion when a T3 measurement is useful. Management of these patients is different in that the hyperthyroidism does not improve with progression of pregnancy. Rather ATD requirements stay stable or may increase. These patients are TRAb negative. Consequently, the fetus is at greater risk for hypothyroidism in the setting of overtreatment with ATD.

Management and treatment of GH in pregnancy

Successful management of a pregnant woman with hyperthyroidism consists of controlling the hyperthyroidism and early detection of fetal thyroid dysfunction. Considerations include when to initiate ATD treatment, ATD choice, and titration of ATD throughout pregnancy. The lowest effective dose to maintain TT4 1.5× the upper limit of the non-pregnant reference range or the FT4I in the upper limit of the reference range should be used. If FT4 is used, one should maintain the FT4 towards the upper limit of normal or use trimester-specific reference ranges if available.

The concern is overtreatment and resulting hypothyroidism in the fetus. This is especially true of women with negative or low TRAb. TSH may remain suppressed during treatment and throughout the pregnancy. ATD should be lowered if TSH becomes detectable (3). "Block and replace" approach in which ATD is used in conjunction with levothyroxine therapy is not recommended in pregnancy (59).

In the first trimester, PTU is traditionally the preferred ATD because the side effects associated with PTU as compared to MMI are considered less severe (discussed further below). PTU is dosed 50–150 mg every 8 hours. Thyroid function tests (TSH along with Total T4, FT4 or FT4 index) should be reassessed every 2–4 weeks depending on patient's symptomatology and biochemical response. If the risk of relapse or worsening hyperthyroidism is considered low, the physician may consider holding ATD treatment with frequent monitoring of thyroid function. The period of maximum sensitivity to teratogenic effects of ATDs is during weeks 6–10, the period of fetal organogenesis. As most pregnancies are not detected until a menstrual period is missed, the window for intervention is narrow (60).

In the second trimester, patients may be switched from PTU to MMI or remain on PTU (23). Reasons to switch to MMI include ease of once daily dosing and risk of maternal hepatotoxicity associated with PTU (61,62). While both drugs have been associated with hepatotoxicity, the effects associated with MMI generally consist of cholestasis rather than fulminant liver failure (63). The ATATPG recommends using a ratio of 1:20 when switching from MMI to PTU (23). For example, 15 mg of MMI would be equivalent to 300 mg of PTU per day, dosed 100 mg every 8 hours. Higher doses are rarely required, but in very symptomatic patients, up to MMI 40 mg per day have been used. Reasons to remain on

PTU include a period of potentially worse control of the hyperthyroidism.

Propranolol 10–20 mg every 6–8 hours may be used to control the hyperadrenergic symptoms and tapered as tolerated. Long-term treatment with ß-blockers has been associated with intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia (64). In the majority of patients, clinical improvement is generally seen in two to three weeks and biochemical improvement in the first two weeks of therapy, with normalization of the FT4/FT4I/TT4 within three to seven weeks. TSH may remain suppressed throughout the rest of pregnancy (27).

Because of the immunologic changes that occur with the progression of pregnancy, TRAb levels decrease in the majority of women after week 20 and the requirement of ATD decreases in the latter half of pregnancy. In women with mild disease requiring low doses of ATD (MMI 2.5–5 mg daily or PTU 50–100 mg daily) with negative or mildly elevated TRAb, ATDs may be discontinued and the women monitored for evidence of recurrence. ATD may be successfully discontinued in up to 40% of women after 30–34 weeks of gestation (3). Fetal hypothyroidism is an indication to stop treatment and follow maternal thyroid labs every one to two weeks as clinically indicated. Low levels of TRAb may be an indication to use the minimal amount of ATD (65).

Thyroidectomy in pregnancy is reserved for rare cases of large goiters causing compressive symptoms, patients who are intolerant, allergic, or nonresponsive to ATD, or non-consistent with drug therapy. In pregnancy, surgery is best performed between 18–24 weeks gestation. Beta-blockers should be used to control hyperadrenergic effects before, during, and after the surgery. Potassium iodide (50–100 mg/day) may be used 8–14 days prior to surgery to decrease the vascularity of the thyroid gland in preparation for surgery and is considered safe for the fetus (66). TRAb levels should be checked prior to surgery given the increased risk of fetal hyperthyroidism with TRAb levels >3× ULN as mentioned above. Even if the mother becomes euthyroid after surgery, the TRAb levels may remain elevated as discussed above.

TRAb levels should also be tested at time of presentation with pregnancy in all women with a past history of GH treated with RAIA or surgery. If TRAb is elevated, repeat testing should occur at weeks 18–22. If TRAb is undetectable or low, no further TRAb testing is needed. If the TRAb level is elevated >3× ULN at weeks 18–22, close fetal monitoring for fetal thyrotoxicosis (FT) is warranted and the TRAb level should be checked again at weeks 30–34 to evaluate the need for neonatal and postnatal monitoring (23).

Pregnancy outcomes

Early recognition and treatment of hyperthyroidism helps avoid most pregnancy complications. In women with poorly controlled hyperthyroidism in pregnancy, pregnancy-induced hypertension (PIH) is one of the most common complications. Millar *et al.* described the risk of preeclampsia in uncontrolled patients as five times greater than those with controlled disease and risk of low-birth weight (LBW) was nine times greater (67). In women who became euthyroid after 20 weeks gestation, the risk remained 2.3 times greater compared to those who became euthyroid before or very early in pregnancy. Women with uncontrolled hyperthyroidism were 16.5 times as likely to undergo preterm delivery.

Other complications associated with poor control of hyperthyroidism include placental abruption, intrauterine growth restriction, stillbirth, miscarriage, maternal congestive heart failure, and thyroid storm (TS) (68-71). The rates of untreated maternal Graves' disease was associated with perinatal mortality rates of 20–45% prior to the introduction of ATDs (68,72). Nowadays, the rate of complications has improved drastically. A cohort study of 180 cases of 180 pregnancies complicated by overt hyperthyroidism in 2011 showed a 1.7% rate of perinatal death (71). Fetal and neonatal outcomes will be discussed below.

TS

In patients with thyrotoxicosis, the stress of infection or operation may precipitate clinical deterioration (73). In extreme cases, this can lead to TS. TS is a rare complication of uncontrolled GH. Davis *et al.* described one case in 120,000 deliveries over the span of 11 years at a single institution (68). TS occurs when a chronically hyperthyroid patient encounters a precipitating stressor such as pregnancy, infection, preeclampsia, labor, or surgery and decompensates. Altered mental status should raise suspicion of TS in the setting of tachycardia and fevers. Early recognition and appropriate treatment is crucial as mortality is significant, 10–30% (74,75). Patients require ICU level care and treatment entails beta-blockers, ATD, and supportive care (*Table 3*).

Table 3 Management of thyroid storm (3,76,77)

Target	Treatment
ATD management (decreases the synthesis and release of T4 and T3)	• PTU 100–150 mg PO every 8 hours (PO, NGT) or • MMI 20 mg PO every 12 hours (PO, NGT) or • MMI 40 mg in 200 cc water (Per rectum)
Non-selective beta blockade (symptomatic relief) to target B_1—Heart rate B_2—Vasodilation B_3—Basal metabolic rate and heat production	• Propranolol 1 mg IV bolus followed by 1 mg/hr (target heart rate of 90–100 bpm if adequately hydrated)
T4 and T3 release	• SSKI (potassium iodide) 5 drops or • Lugol's solution 10 drops every 8 hours 1 hour after MMI (PO, NGT)
Generation of T3	• Decadron 4mg IVPB every 6 hours • PTU at above doses decreases peripheral conversion of T4 to T3
Incorporation of T4 and T3 into the nucleus	• L-carnitine 1–2 grams twice a day (78)*
Fever	• Aspirin may increase thyroid hormones and acetaminophen can interfere with steroids. • Should improve with other treatment modalities
Supportive care	• Antibiotics as infection common precipitating event • IVF—TS patients are at a fluid deficit. Fluid balance should be net positive • Recommend against active cooling as can lead to peripheral vasoconstriction and hinder release of heat • Cautious use of diuretics. Intravascular depletion can lead to cardiovascular collapse • ICU level care • Low threshold to Intubate

*, no studies in pregnant patients. PO, per oral; NGT, nasogastric tube; PR, per rectum; IVF, intravenous fluids.

Complications of anti-thyroid drugs for mother and fetus

ATDs remain the treatment of choice of GH during pregnancy. They are relatively well tolerated with 3–5% of women experiencing side effects, the most common being an allergic reaction such as a skin rash (23,79). More serious side effects such as agranulocytosis or liver failure are rare, occurring in 0.15% and <0.1% of patients respectively (80,81). If a patient has a mild reaction such as skin rash, the patient may be switched to the other ATD. However, if the reaction is more severe, the patient may need to undergo surgery, generally performed in the second trimester. As mentioned above, PTU is also associated with an increased risk of maternal hepatotoxicity.

However, the greatest concern regarding the use of ATDs in pregnancy is the risk of teratogenic effects. PTU and MMI both cross the placenta and can affect the fetus. Rate of birth defects is elevated in patients exposed to ATDs in early pregnancy compared to non-exposed euthyroid patients (82). Rates of fetal defects is similar for both PTU and MMI (2–4%) (82-84) with greater risk associated with ATD exposure during weeks 6–10, the teratogenic period of pregnancy (63,85). However, the fetal defects associated with MMI are considered more severe than those associated with PTU (*Table 4*) (63,83). The fetal defects associated with PTU are limited to face and neck defects or the urinary system (82,86-88). The American Thyroid Association

Table 4 Congenital defects associated with ATD (77)

Methimazole
Aplasia cutis
Choanal atresia
Esophageal atresia
Omphalocele
Urinary tract malformations
Eye defects
Ventral septal defects
Dysmorphic facies
Athelia
Developmental delay
Propylthiouracil
Pre-auricular sinus/fistula and cysts
Urinary tract abnormalities in males

ATD, antithyroid drug.

currently recommends treatment with PTU through week 16 (23). Consideration to switch to PTU prior to pregnancy should be had in preconception counseling as there may be a delay in the diagnosis of pregnancy until after the critical week 6–10. Switching after this period has been shown to have no effect in rates of embryopathies (10,82).

Fetal management

Fetal and neonatal thyroid function

The fetal thyroid gland develops between 5 to 6 weeks gestation (89) and begins to secrete thyroxine at ten weeks gestation (90). However, fetal thyroid hormone production is minimal until 18 weeks of gestation when the fetal TSH receptor begins to function and becomes responsive to TSH and TRAb (19,91-93). Prior to this, the fetus is dependent on mother for TH via transplacental passage (94).

FT

Maternal TRAb levels are prognostic of FT (18,34,35). Studies evaluating TRAb levels using different methodologies have resulted in various TRAb level thresholds associated with increased risk of fetal and neonatal thyrotoxicosis (NT). ATATPG recommends a TRAb threshold of 3× the ULN (~5 IU/L with a second generation assay) as an indicator of increased risk of FT (23,40). TRAb levels >3× ULN in early pregnancy warrants close monitoring and repeat testing. TRAb levels >3× ULN in the second and third trimester predicts neonatal hyperthyroidism with 100% sensitivity and 43%specificity (40,95). In a recent systematic review by van Dijk *et al.*, the lowest level of maternal TRAb leading to NT was 4.4 U/L (3.7× ULN) via a second-generation assay (96).

The rate of FT is hard to establish, but NT occurs in 1–5% of children born to mothers with GH (93,97-99). Women who have poorly controlled GH, elevated TRAb titers, a prior fetus or neonate with a thyroid disorder, or who are requiring high doses of ATD in the second half of gestation are at risk for FT. On US, signs of FT include a HR greater than 160 bpm for more than ten minutes, intrauterine growth restriction, oligo/polyhydramnios, goiter, and advanced bone age that can lead to neonatal craniosynostosis (100). Severe FT can result in fetal heart failure, hydrops, and fetal demise (76,100).

The literature reports that the earliest sonographic sign of fetal thyroid dysfunction is a fetal goiter (100). However, this has not been our experience. Patients may present with fetal tachycardia before a goiter is diagnosed. The US is generally performed at 18–22 weeks and then every 4 weeks thereafter to assess for gestational age, fetal heart rate, amniotic fluid volume, fetal growth, the presence of fetal goiter, and fetal anatomy (23,76). Fetal goiter may lead to fetal, obstetric, and neonatal complications. Polyhydramnnios may result from reduced ability of the fetus to swallow or labor dystocia may occur from hyperextension of the fetal neck due to goiter (101). Consequently, cesarean section may be preferred in the presence of a goiter (102).

A fetal goiter may be due to FT or fetal hypothyroidism. If the thyroid status of the fetus remains unclear, cordocentesis may be used. This involves US-guided placement of a needle into the fetal circulation typically via a free loop of umbilical cord or at the cord insertion site. Risk of fetal complications with cordocentesis is low (0.5–1%) when performed at experienced centers (91,101). Alternatively, TH concentrations in amniotic fluid may be measured. This is a less invasive procedure, but remains to be validated (90).

Treatment of FT involves treatment of the mother with ATDs, which cross the placenta. FT can involve a mother that is euthyroid (i.e., status-post thyroidectomy or RAIA) or hypothyroid (103-105). In these scenarios, a euthyroid mother is treated with MMI 10–20 mg daily or larger

doses as clinically indicted. Doses are adjusted every few days based on fetal tachycardia and goiter size (3), using the lowest dose necessary to normalize fetal heart rate (110–160 beats per minute). This is one situation in which the mother is treated with ATD in addition to replacement levothyroxine. Assessment of fetal heart tones with hand-held doppler should be performed every 1–2 weeks or as necessary. US should also be utilized to assess growth, size of fetal thyroid gland, and amniotic fluid index.

Fetal hypothyroidism

In the case of overtreatment of the fetus with ATDs, fetal hypothyroidism may develop. Signs on US include goiter, intrauterine growth restriction, delayed bone age, and bradycardia (76). In this situation, ATD dose is reduced or stopped. Most of the time, this is enough to restore normal thyroid function to reduce the size of the fetal goiter. Rarely, intra-amniotic levothyroxine injection is necessary in conjunction with stopping of ATD dose (106). If the diagnosis of fetal hypothyroidism is not clear, cordocentesis may be considered to determine the fetal thyroid status (91,107). Alternatively, measuring thyroid hormone concentration in the amniotic fluid is a less risky procedure (92,108).

Neonatal management

Uncontrolled GH can lead to significant thyroid dysfunction in the neonate. In a study by Papendieck *et al.*, 28 children were born of hyperthyroid mothers and seen in a pediatric clinic prior to one month of age. Nine of these infants were born with neonatal hyperthyroidism, eleven infants were born with primary hypothyroidism, ten from mothers treated with ATD. Lastly, five infants were born with hypothalamic-pituitary hypothyroidism (61).

Neonatal thyroid function

Immediately after birth TSH, T4, and T3 rise. TSH peaks in the first 24 h of life and remains elevated for up to 3 to 5 days. T4 and T3 levels increase by 6-fold within the first few hours of life and peak 24 to 36 h after birth (91,109). By 3 to 4 days of life, thyroid function tests will gradually decrease to normal levels (110).

NT

NT occurs in 1–5% of offspring of mothers with GH (93,98,99). Those with FT should have thyroid tests checked at birth and every few days as clinically indicated. Neonates with NT may present with tachycardia, tachypnea, pulmonary hypertension, systemic hypertension, and heart failure. They may be small for gestational age with accelerated bone maturation and in more severely affected newborns, craniosynostosis, microcephaly, and psychomotor disabilities may occur (3,76,93,111).

Newborns with a TSH level less than 0.9 mIU/L between days 3 to 7 of life predicted neonatal hyperthyroidism with a sensitivity of 78% and a specificity of 99%, a positive predictive value of 90%, and a negative predictive value of 98% (112). All newborns born to mothers with GH on ATD without evidence of FT should be screened for thyroid dysfunction within two to five days after birth. ATD may cross the placenta and remain in the neonate's system for up to 48–72 hours, delaying the diagnosis of the hyperthyroidism.

Neonatal hyperthyroidism is generally transient. Typically infants are treated for 1–2 months, but TRAb may remain elevated in the infant's circulation for up to four months after delivery (3,113). Neonates with positive TRAb should be followed weekly with repeat clinical and laboratory studies until TRAb is normal (95). Banigé *et al.* recently described an equation to estimate the time it would take for TRAb to be eliminated from the newborn's circulation: TRAb elimination time (day) = [7.28 + 2.88 × log(TRAb) + 11.62 log(TRAb^2)] (112). This may assist clinicians in anticipating the frequency of testing and timing of follow-up.

The recommended regimen for neonatal hyperthyroidism is MMZ 0.5–1 mg/day with propranolol 2 mg/kg/day if severe (23). MMZ is preferred over PTU due to frequency of hepatotoxicity, liver failure, and death in children (114).

Neonatal hypothyroidism

Neonates are at risk for hypothyroidism secondary to maternal ATD therapy, central hypothyroidism from untreated women with suppression of fetal TSH, and impaired hypothalamic-pituitary-thyroid maturation (115). In term neonates with non-transient hypothyroidism, the recommended starting dose of levothyroxine is 10–15 mcg/kg/day. For optimal outcomes, therapy should be initiated within two weeks of life. Most infants and children do well with treatment. The shorter time to normalization of thyroid levels contributes to improved neurodevelopmental

outcome (110).

Maternal postpartum care

Women with GH and hyperthyroid at time of delivery will need to be monitored closely and treated according to standard treatment practices. Women with GH who are euthyroid at time of delivery should be followed during the first year postpartum. TSH and FT4 should be checked periodically starting at six weeks postpartum. Women with GH, including those in remission during pregnancy, are at risk for recurrence for up to one year after delivery (116). A report from Japan found that 40% of women ages 20–39 years old with GH had developed GH during the postpartum period (117).

A recurrence of hyperthyroidism in women with Graves' disease who are euthyroid at delivery may recur as early as six weeks postpartum and needs to be distinguished from postpartum thyroiditis (PPT). PTT occurs in roughly 5% of pregnancies and does not require treatment with ATD (118). It is characterized by a transient hyperthyroid phase that typically resolves within a few weeks, leading to a brief euthyroid phase and then to a transient hypothyroid phase before returning to euthyroidism in the majority of patients (119). High TRAb titers would support a diagnosis of GH (120). Onset of the hyperthyroidism in the first few months postpartum would be more consistent with PPT while onset after four to six months would suggest GH. If a diagnosis is still not clear, 123-I RAIA uptake is an option. If the patient is breastfeeding, the breast milk must be discarded for several days until the radioactive iodine has cleared from the body (23,121).

Breastfeeding

Patients on ATD at delivery should continue ATD after delivery even if breastfeeding as it has been shown to be safe (122-124). Both ATDs appear in the breast milk in very small concentrations (125-127). Experts recommend using the lowest effective dose possible < MMI 20 mg daily and PTU 300 mg total daily (128). The ATD should be taken just after the mother has breastfed (79). 131-Iodine therapy is contraindicated in lactating mothers. If definitive therapy is needed in a lactating mother, surgery is preferred.

Conclusions

Women with a history of GH, either previously treated or those with active disease at the time of pregnancy are at a higher risk for maternal and obstetrical complications compared to euthyroid women. The goal in the care of women with GH is the delivery of a healthy euthyroid newborn. The first step to achieving this begins prior to pregnancy during the preconception counseling. All women of reproductive age with thyroid disease should be counseled on the role of thyroid and pregnancy, management considerations of GH in pregnancy, including the potential side effects of ATDs, definitive treatment options, and postpartum care. Close collaboration between a medical team comprising of an endocrinologist, obstetrician, maternal fetal medicine physician, anesthesiologist, neonatologist, and pediatric endocrinologist during pregnancy and in the postpartum period is essential to reducing the risk of maternal, fetal, and newborn complications.

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