
بسم الله الرحمن الرحیم

THYROTOXICOSIS IN PREGNANCY

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DEFINITION

Thyrotoxicosis is the clinical syndrome of hypermetabolism and hyperactivity that occurs when a person is exposed to supraphysiological concentrations of thyroid hormones (TH).

Hyperthyroidism is the hyperfunction of the thyroid gland leading to thyrotoxicosis.

PREVALENCE AND ETIOLOGY

Thyroid disorders constitute one of the most common endocrine disorders in pregnancy and occur in about 4% of all pregnancies, with primary hypothyroidism being the most common. Overt thyrotoxicosis can affect between 0.2 and 0.4% of pregnancies, although the prevalence of subclinical thyrotoxicosis can be as high as 1%

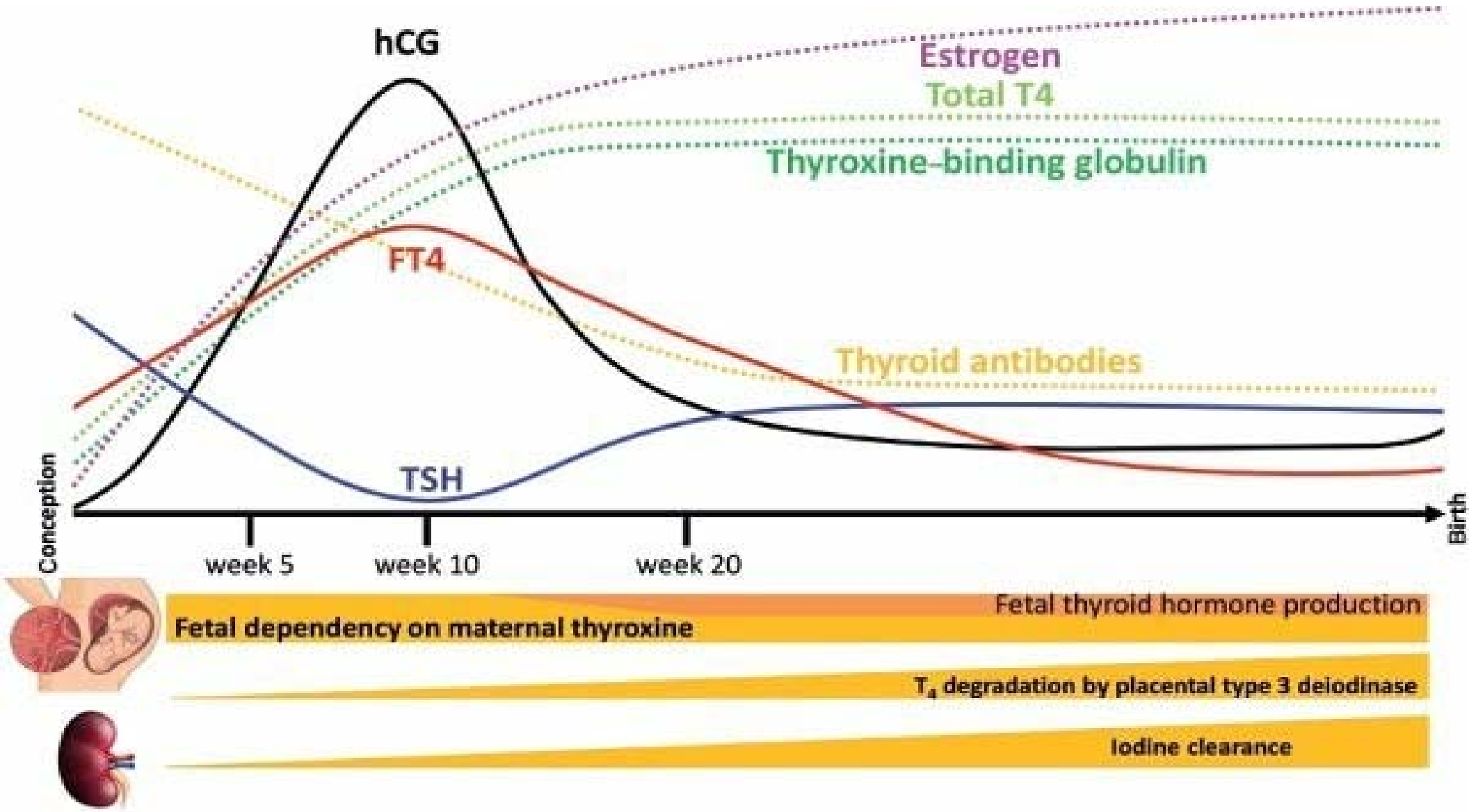
THYROID ADAPTAITION DURING PREGNANCY

The major changes in thyroid function during pregnancy are :

- An increase in serum thyroxine-binding globulin (TBG)
- Stimulation of the thyrotropin (thyroid-stimulating hormone [TSH]) receptor by human chorionic gonadotropin (hCG).

PHYSIOLOGIC CHANGES IN PREGNANCY THAT INFLUENCE THYROID FUNCTION TESTS

Physiologic change	Thyroid function test change
↑ Thyroid-binding globulin (TBG)	↑ Serum total T4 and T3 concentrations
↑ First trimester hCG elevation	↑ Free T4 and ↓TSH
↑ Plasma volume	↑ T4 and T3 pool size
↑ Type III 5-deiodinase (inner ring deiodination) due to increased placental mass	↑ T4 and T3 degradation resulting in requirement for increased hormone production
Thyroid enlargement (in some women)	Serum thyroglobulin
↑ Iodine clearance	↕ Hormone production in iodine-deficient areas


hCG
Estrogen
Total T4
Thyroxine-binding globulin
FT4
Thyroid antibodies
TSH
Conception
Birth
week 5
week 10
week 20
Fetal thyroid hormone production
Fetal dependency on maternal thyroxine
T_4 degradation by placental type 3 deiodinase
Iodine clearance

INITIAL EVALUATION OF A SUPPRESSED TSH IN PREGNANCY

It is important to recognize that the standard values of TSH are shifted downward in pregnancy. The first trimester 5th percentile TSH was 0.1 mIU/L and the second trimester was 0.39 mIU/L. These lower values correspond with the peak hCG levels that occur between weeks 8–11 .

The decrease in the lower reference limit of TSH in the first trimester is due to human chorionic gonadotropin, which is structurally similar to TSH and is weakly capable of stimulating the TSH receptor, leading to reduced TSH levels.

Thyroxine-binding globulin (TBG) levels increase during pregnancy and peak at approximately 16–20 weeks.

With the rise in TBG, total hormone levels also increase .TBG has a 20-fold greater affinity for T4 than T3, so the rise in T4 parallels the rise in TBG more closely .The magnitude of the increase in TBG is greater than the increase in T4, resulting in a progressively decreasing T4/TBG ratio.

This leads to a 10–15% decrease in free hormone values in the latter part of pregnancy .

TRIMESTER-SPECIFIC REFERENCE RANGES

Weeks 7 to 12 : Reduce the lower limit of the reference range of TSH by approximately 0.4 mU/L and the upper limit by 0.5 mU/L (corresponding to a TSH reference range of approximately 0.1 to 4 mU/L).

Second and third trimester : There should be a gradual return of TSH towards the nonpregnant normal range.

The upper reference range for total T4 increases by approximately 5 percent per week, beginning at week 7.

At approximately 16 weeks, total T4 (and T3) levels during pregnancy are 1.5-fold higher than in nonpregnant women (due to TBG excess).

Disorders of Excessive TSH Receptor Stimulation

- Graves' disease via TSH receptor autoantibodies
- Gestational transient thyrotoxicosis (hCG induced)
- Familial gestational hyperthyroidism (TSH receptor mutation)
- Trophoblastic disease (hCG induced)
- TSH-producing pituitary adenoma

DISORDERS OF AUTONOMOUS THYROID HORMONE SECRETION

- Toxic adenoma or toxic multinodular goiter
- Activating TSH receptor mutation

EXTRATHYROIDAL SOURCES OF THYROID HORMONE

- Overtreatment with thyroid hormone
- Factitious intake of thyroid hormone
- Functioning struma ovarii
- Functional thyroid cancer metastases

DESTRUCTION OF THYROID FOLLICLES WITH SUBSEQUENT RELEASE OF PREFORMED THYROID HORMONE

- Subacute thyroiditis
- Painless thyroiditis
- Acute thyroiditis

MATERNAL AND FETAL EFFECTS OF THYROTOXICOSIS

Excessive thyroid hormone levels increase cardiac contractility indirectly, by diminishing systemic vascular resistance with resultant increased heart rate and cardiac output.

These two mechanisms can result in increased left ventricular mass and a high-output state.

Nonpregnant patients with overt thyrotoxicosis rarely develop heart failure, but by contrast, nearly 10% of women with untreated thyrotoxicosis develop heart failure during pregnancy .

Poorly controlled thyrotoxicosis during pregnancy is associated with an increased risk of miscarriage, IUGR , preterm birth ,stillbirth, gestational hypertension, preeclampsia, and thyroid storm . It was also associated with, intensive care unit admission, low birth weight, neurocognitive development, and fetal thyrotoxicosis/Graves' disease as well as fetal goiter and subclinical hypothyroidism.

FETAL OR NEONATAL HYPERTHYROIDISM

Approximately 1 to 5 %of mothers with hyperthyroidism caused by graves disease active or treated have fetus or neonate with hyperthyroidism.

Manifestations of fetal hyperthyroidism :

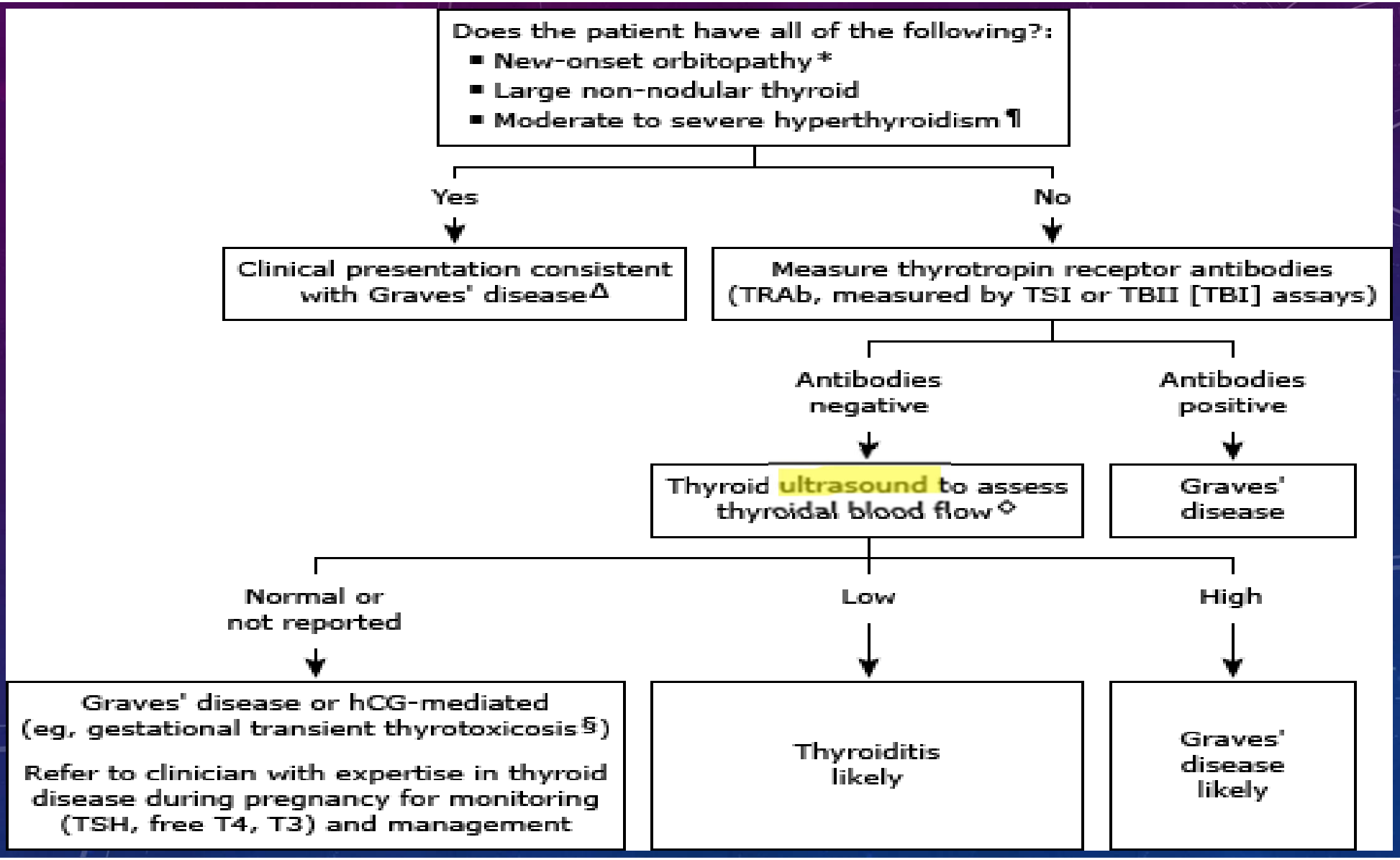
- High fetal heart rate >160
- fetal goiter
- advanced bone age
- poor growth
- craniosynostosis
- cardiac faiure and hydrops with sever disease

COMMON CAUSE OF THYROTOXICOSIS IN PREGNANCY

- GTT
- Graves' disease

If a cause of thyrotoxicosis other than GTT is suspected, TRAb levels, thyroid ultrasonography, or the TT3/TT4 ratio may be helpful.

The TT3/TT4 ratio is typically >20 incases of overproduction such as Graves' disease and <20 in cases such as thyroiditis.


Does the patient have all of the following?:
New-onset orbitopathy *
Large non-nodular thyroid
Moderate to severe hyperthyroidism ¶
Yes
No
Clinical presentation consistent with Graves' disease Δ
Measure thyrotropin receptor antibodies (TRAb, measured by TSI or TBII [TBI] assays)
Antibodies negative
Antibodies positive
Thyroid ultrasound to assess thyroidal blood flow ◇
Graves' disease
Normal or not reported
Low
High
Graves' disease or hCG-mediated (eg, gestational transient thyrotoxicosis §)
Refer to clinician with expertise in thyroid disease during pregnancy for monitoring (TSH, free T4, T3) and management
Thyroiditis likely
Graves' disease likely

GESTATIONAL TRANSIENT THYROTOXICOSIS (GTT)

Transient non-autoimmune hyperthyroidism of early pregnancy or

Transient hyperthyroidism of hyperemesis gravidarum .

Gestational transient thyrotoxicosis is thought to have an incidence of 2–3% of all pregnancies .

It is seen most commonly in women diagnosed with hyperemesis gravidarum, in whom transient hyperthyroidism is seen in up to 67% .

GTT

- no symptoms of hyperthyroidism prior to pregnancy
- symptom onset in the first trimester
- no family history of Graves' disease
- minimal or absent signs of hyperthyroidism
- Hyperemesis
- similar vomiting in prior pregnancy
- family history of hyperemesis gravidarum.
- self-limited

GTT

During the physical exam, there is no evidence of ophthalmopathy, dermopathy (pretibial myxedema), goiter, or Graves' acropachy.

Biochemically, GTT is associated with a low or suppressed TSH, elevated free T4 , negative antibodies for thyroid autoimmunity (TRAb and TPO), and a TT3/TT4 ratio of <20 .

It occurs near the end of the first trimester, and symptoms (if present) and thyroid hyperfunction subside as hCG production falls (typically 14 to 18 weeks gestation)

HYPEREMESIS GRAVIDARUM

A syndrome of nausea and vomiting associated with weight loss of 5 percent or more during early pregnancy that occurs in **0.1 to 0.2**percent of pregnancies.

vomiting, **absence of goiter** and **ophthalmopathy**, and absence of the common symptoms and signs of hyperthyroidism (tachycardia greater than 100 beats/minute, hyperdefecation, muscle weakness, tremor).

serum free T4 concentrations are only minimally elevated and serum T3 concentrations may not be elevated, whereas both are usually unequivocally elevated in pregnant women with true hyperthyroidism from Graves'disease.

FAMILIAL GESTATIONAL HYPERTHYROIDISM

Familial gestational hyperthyroidism is due to rare variants of the TSH receptor that are very sensitive to hCG and have been reported to cause hyperthyroidism in pregnancy in the absence of hyperemesis gravidarum .

TREATMENT

Supportive care is all that is typically needed. Short courses of beta-blockers can be used for symptomatic relief if needed .

It is reasonable to repeat thyroid levels in 4 weeks. women with persistent vomiting, significant weight loss, and presence of ketones in urine, hospitalization is very frequently required .

ATDs may be given transiently as there is a correlation between **FT4/FT3 levels** and the **severity of the hyperemesis** and in extreme cases HG has been associated with cardiovascular complications and even cardiac arrest .

If overt hyperthyroidism persists for more than several weeks or beyond the first trimester, it is probably not hCG mediated.

GRAVES' DISEASE (GD)

Graves' disease is the most common cause of hyperthyroidism in all populations, with the highest incidence seen in women between 40–60 years of age .

Graves' disease in pregnancy can be divided into two categories:

Graves' disease diagnosed during pregnancy and

Graves' disease diagnosed before pregnancy, with the latter being the far more common.

GD

The course of hyperthyroidism due to Graves' disease *tends to improve during pregnancy* because of three independent factors: (1) immunosuppression related to pregnancy tends to decrease production of TRAbs

(2) increased TBG and reduced free thyroid hormone concentrations tend to blunt the effect of excessive thyroid hormone production

(3) in iodine restricted areas, increased iodine demand along with decreased supply blunts excessive production. This being said, not everyone is protected from hyperthyroidism by these changes .

MANAGEMENT OPTIONS FOR PATIENTS WITH GRAVES' DISEASE

For patients with Graves' disease, the three established treatment modalities are:

- antithyroid drug(methimazole, propylthiouracil),
- ablation with radioactive iodine and surgery.

Antithyroid drugs (ATDs) are used most commonly.

RADIOACTIVE IODINE (RAI)

Contraindicated in pregnancy, Fetal exposure to radioiodine before implantation may increase the risk of miscarriage and death of the embryo in a dose-dependent manner, but surviving embryos will probably escape any major malformations or thyroid problems. Exposure during thyroid development, from **10 weeks** of gestation onwards, will result in fetal hypothyroidism and fetal thyroid ablation needing lifelong thyroxine replacement. In these cases the management includes maintain maternal thyroxine levels towards the upper end of normal for the rest of the pregnancy and immediate treatment of the neonate with thyroxine .

ANTITHYROID DRUGS

- MMI & carbimazol
- PTU

In a nonpregnant patient, methimazole is preferred because it has a lower risk of hepatotoxicity and the convenience of once or twice daily dosing versus three times daily for PTU. Both methimazole and PTU work by inhibiting the oxidation and organic binding of thyroid iodide, leading to an intrathyroidal iodine deficiency and decreasing output of thyroid hormone. PTU also has the abillity to block type 1 deiodinase (D1) which is the major source of peripheral conversion of T4 to T3.

American Thyroid Association guidelines recommend PTU through **16 weeks'** gestation and they cite insufficient evidence to recommend switching back.Both PTU and MMI are able to cross the placenta and are equally effective at controlling hyperthyroidism. The starting dose of PTU in pregnancy is typically 50 mg two to three times daily, while MMI is dosed at 5–10 mg once daily.

The goal during pregnancy is to use the lowest dose possible .

SIDE EFFECTS

The minor side effects occur in 5–10% of patients include rash, pruritus, nausea, and fever ,30–50% of patients with a rash or pruritus from MMI will have a similar reaction to PTU .

The two most serious side effects – **agranulocytosis** and **hepatotoxicity** are quite rare.

The most common symptoms of agranulocytosis are fever and sore throat.

SIDE EFFECTS

Hepatotoxicity is another potential serious adverse drug reaction. MMI- associated hepatotoxicity has typically been described as cholestatic but can also be hepatocellular in nature.

PTU, can cause fulminant hepatic necrosis that can be fatal or require liver transplantation.

children to be at higher risk of this reaction.

SIDE EFFECTS

A CBC and liver function tests should be obtained before starting ATD therapy. These medications should be avoided when the *absolute neutrophil count is less than 1500 or when liver function tests are greater than three to five times the upper limit of normal*.

SIDE EFFECTS

The third and least common major side effect of ATDs is antineutrophil cytoplasmic antibody-mediated **vasculitis** (ANCA). This condition is seen predominantly in Asian patients treated with PTU but can rarely be seen with MMI.

ANTITHYROID DRUGS: SPECIAL CONSIDERATIONS IN PREGNANCY

PTU is preferred over MMI in the first 16 weeks due to increased risk of birth defects with methimazole, about **2-4%** of exposed children during the first trimester. The defects that comprise what is known as methimazole embryopathy include choanal atresia, omphalocele, esophageal atresia, omphalomesenteric duct anomalies, athelia and aplasia cutis .

PTU has also been linked to birth defects in some studies. urinary system malformations and malformations in the face and neck region ,situs invertus.

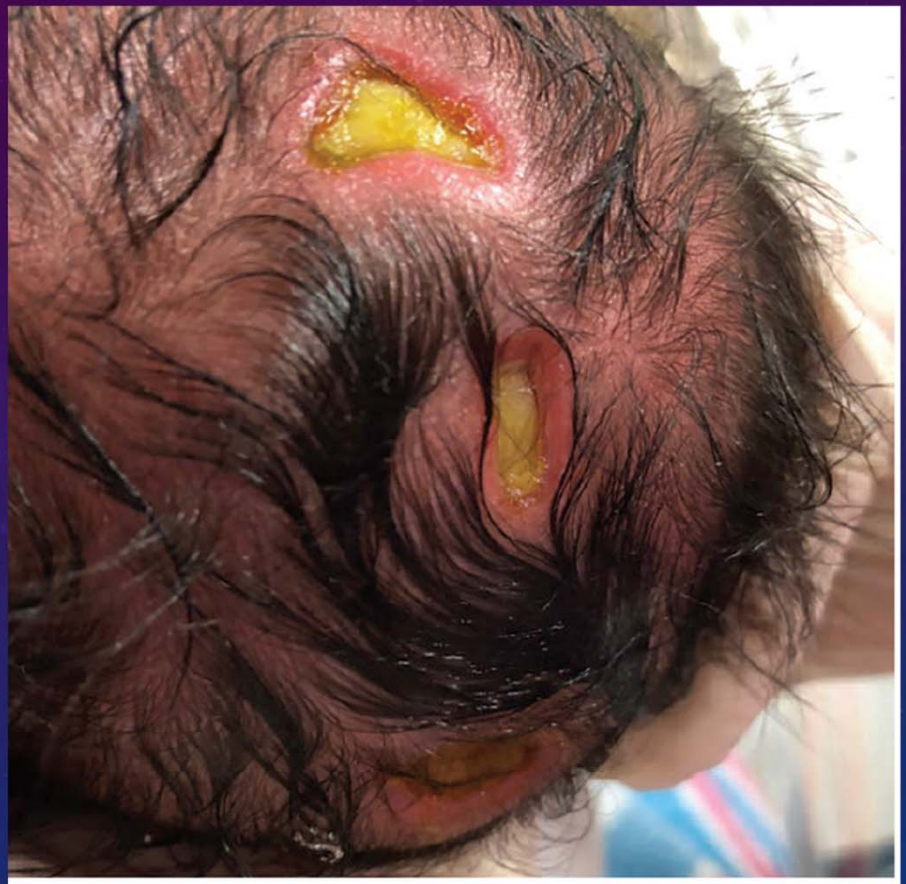


FIGURE 2. After 5 days of activated *Leptospermum* honey, slow progress and thickening of edges.

TRAB

For women with hyperthyroidism during pregnancy who will be taking thionamids serum TRAb should be measured at dignosis and , if elevated, again at 18 to 22 weaks and at 30 to 34 gestation.

GOALS OF THERAPY

The goal of treatment is to maintain

Mild maternal hyperthyroidism

GOALS OF THERAPY

Screening for fetal hypothyroidism found that 25% of cases were due to maternal ingestion of ATDs . the goal of therapy is to maintain the FT4 values in the range of high normal or just above the nonpregnant normal range or total T4 and T3 ,1.5 times above nonpregnant refrence range and goal TSH shoud be 0.1 to 0.3.**Overtreatment should be avoided**.Due to decreases in thyroid autoimmunity as pregnancy progresses, discontinuation of ATDs is possible in 20–30% of patients .

TT4 or FT4 and TSH should be monitored every 2–4 weeks and 2 weeks after a dose of medication change.

THYROIDECTOMY

Thyroidectomy is typically the last resort due to the associated maternal and fetal risks. fetal complications including induced, spontaneous, or missed abortion, early or threatened labor, fetal distress, intrauterine death, stillbirth, neonatal hypocalcemic tetany.

INDICATIONS FOR THYROIDECTOMY IN PREGNANCY

Anaphylactic or severe allergic reactions to ATDs
Agranulocytosis or hepatotoxicity with ATDs
Failure to control thyrotoxicosis despite high dose of ATDs (400 mg/day of PTU and 30–40 mgday of MMI)
Compressive symptoms (stridor or dysphagia) from a large goiter

THYROIDECTOMY

In a patient intolerant of ATDs, a short course (7to 10 days)of beta-blockers and potassium iodide (50–100 mg/day) 1 to 3 drops daily should be given in preparation for surgery.

Potassium iodide leads to a decrease in thyroidal iodine uptake, a decrease in iodide oxidation, and organification and blocks the release of thyroid hormone .

The optimal time for surgery is during the second trimester.

CONSIDERATIONS IN THE POSTPARTUM PERIOD

Many women with Graves' disease will go into remission during the course of pregnancy . These women still need close monitoring, as many have a **rebound** after pregnancy, during the postpartum period ATDs are the first-line therapy.

In general, MMI is the preferred agent due to the risk of idiosyncratic hepatic damage with PTU.

HYPERTHYROIDISM AND LACTATION

PTU and MMI are secreted in breast milk at very low levels Breastfeeding is safe if the daily dose of PTU or MMI is less than 450 mg or 20 mg/day, respectively, and thyroid function testing of infants is not required.

PRECONCEPTION COUNSELING OF WOMEN WITH PREEXISTING HYPERTHYROIDISM

Women on methimazole for Graves' disease should be transitioned to PTU before attempting pregnancy and should not switch back to methimazole until at least 16 weeks gestation .Patients undergoing radioactive iodine ablation should wait at least 6 months after treatment before attempting to conceive and should demonstrate stable euthyroidism off or on LT4 therapy. Finally, thyroidectomy can offer the benefit of faster time to definitive therapy and a decrease in maternal TRAbs. Pregnancy after surgery should be delayed at least 3 months to ensure stable euthyroidism before proceeding with surgery .

PRECONCEPTION COUNSELING

Determination of TRAb: All women with Graves' disease must be followed during pregnancy for the presence of TRaB . The gradual disappearance from the circulation posttherapy depends on the type of treatment chosen; following thyroidectomy, there is a gradual disappearance of TRAb titers, while following 131I therapy, there is an **increase** in TRAb titers that may last for 12 months followed by a gradual fall in titers .