
قال الله تعالى
بسم الله الرحمن الرحيم

Hyperthyroidism during pregnancy

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AGENDA

- ***INTRODUCTION***
- ***THYROID PHYSIOLOGY DURING NORMAL PREGNANCY***
- ***Pregnancy complications***
- ***What are the causes of thyrotoxicosis in pregnancy?***
- ***TREATMENT***
- ***POSTPARTUM ISSUES***

INTRODUCTION

- Overt hyperthyroidism is relatively uncommon during pregnancy, occurring in 0.1 to 0.4 percent of all pregnancies
- The diagnosis of pregnant women with hyperthyroidism parallels that of nonpregnant women and men but presents some unique problems.

- Endocr Rev 2010; 31:702/Thyroid 2015; 25:698.

THYROID PHYSIOLOGY DURING NORMAL PREGNANCY

- To meet the increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests. These changes include the following:
- TBG excess results in high serum total T4 and total T3 concentrations but not high serum free T4 or free T3 concentrations.
- High hCG concentrations during early pregnancy and even higher concentrations in women with hyperemesis gravidarum or multiple pregnancies may result in transient subclinical or rarely overt hyperthyroidism.

THYROID PHYSIOLOGY DURING NORMAL PREGNANCY

- Serum TSH may decrease in the first trimester of normal pregnancy as a physiological response to the stimulating effect of hCG upon the TSH receptor.
- A peak hCG level typically occurs between 7 and 11 weeks gestation

In particular, a serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in approximately 5% of women by week 11 of pregnancy

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What is the appropriate initial evaluation of a suppressed serum TSHconcentration during the first trimester of pregnancy?

- Any subnormal serum TSH value should be evaluated in conjunction with serum TT4 (or FT4) and T3 values.
- The biochemical diagnosis of overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or T3 (free T4 and/or T3 levels that exceed trimester-specific normal reference ranges or total T4 and T3 that exceed 1.5 times the nonpregnant range)

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Pregnancy complications

- Pregnancy complicated by poorly controlled overt hyperthyroidism with increased rates of the following:
- Spontaneous abortion
- Premature labor
- Low birth weight
- Stillbirth
- Preeclampsia
- Heart failure

Am J Obstet Gynecol 1989; 160:63/Am J Obstet Gynecol 2004; 190:211/Obstet Gynecol 1994; 84:946/..

Pregnancy complications

- **Subclinical hyperthyroidism** -In contrast to the findings in women with overt hyperthyroidism, in one report of 433 women with subclinical hyperthyroidism, there was no evidence of adverse pregnancy outcomes
- In another report, women with subclinical hyperthyroidism during weeks 4 to 8 of pregnancy had a lower incidence of spontaneous abortion and a higher risk of preeclampsia
- **Free T4 in the upper-normal quintile** – A normal free T4 in the upper quintile with a normal TSH has been associated with lower birth weight and maternal hypertension ,but not adverse pregnancy outcomes
- bstet Gynecol 2006; 107:337/ Womens Health (Larchmt) 2019; 28:842/J Clin Endocrinol Metab 2013; 98:59/J Clin Endocrinol Metab 2014/ Clin Endocrinol Metab 2014; 99:E2591.

What are the causes of thyrotoxicosis in pregnancy?

- The most common cause of thyrotoxicosis is hyperfunction of the thyroid gland (hyperthyroidism), and the most common cause of hyperthyroidism in women of childbearing age is autoimmune GD
- Less common non-autoimmune causes include TMNG,toxic adenoma,

Subacute painful or painless thyroiditis with passive release of thyroid hormones from a damaged thyroid gland are less common causes of thyrotoxicosis in pregnancy and a number of other conditions such as a TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, or germline TSH receptor mutations are very rare

- More frequent than GD as the cause of thyroid function tests demonstrating hyperthyroxinemia is ‘‘gestational transient thyrotoxicosis

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Graves' disease

- Graves' disease is a syndrome that may consist of hyperthyroidism, goiter, eye disease (orbitopathy), and occasionally a dermopathy referred to as pretibial or localized myxedema
- Hyperthyroidism is the most common feature of Graves' disease, affecting nearly all patients, and is caused by TRAbs that activate the receptor, thereby stimulating thyroid hormone synthesis and secretion as well as thyroid growth
- The presence of TRAbs in serum and orbitopathy on clinical examination distinguishes the disorder from other causes of hyperthyroidism. The thyroid gland is usually, but not always, diffusely enlarged.

HCG-mediated hyperthyroidism

- Hyperthyroidism mediated by the effects of hCG include gestational transient thyrotoxicosis (GTT), hyperemesis gravidarum, and trophoblastic hyperthyroidism.
- Only the last requires treatment of the hyperthyroidism.
- During normal pregnancy, serum hCG concentrations rise soon after fertilization and peak at 10 to 12 weeks gestation, after which time the levels decline. There is considerable homology between the beta-subunits of hCG and TSH. As a result, hCG has weak thyroid-stimulating activity and may cause hyperthyroidism during the period of highest serum hCG concentrations

Gestational transient thyrotoxicosis

- During the time of peak hCG concentrations , total serum T4 and T3 concentrations increase. Serum free T4 and T3 concentrations increase slightly, usually within the normal range, and serum TSH concentrations are appropriately reduced.
- Thus, in some women, the high serum concentration of hCG during early pregnancy can lead to subclinical or mild overt hyperthyroidism characterized by slightly low serum TSH concentrations and high-normal or mildly elevated serum free T4 concentrations .This phenomenon is called GTT. 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)
- *J Clin Endocrinol Metab 1990; 71:276.*

Hyperemesis gravidarum

- Hyperemesis gravidarum is 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.
- Women who develop hyperemesis gravidarum have higher serum hCG and estradiol concentrations than normal pregnant women ,in addition, their hCG has more thyroid-stimulating activity
- Therefore, their serum TSH concentrations are often lower than those in normal pregnant women
- A few of these women have high serum free T4 concentrations and, therefore, have overt hyperthyroidism.
- J Clin Endocrinol Metab 1992; 75:1333/J Clin Endocrinol Metab 1995; 80:473/Clin Endocrinol (Oxf) 1993; 38:345/Thyroid 1999; 9:653.

Hyperemesis gravidarum

- Features that distinguish the transient hyperthyroidism of hyperemesis gravidarum from hyperthyroidism of other causes ,are the 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). In addition, serum free T4 concentrations are only minimally elevated and serum T3 concentrations may not be elevated in women with hyperemesis gravidarum, whereas both are usually unequivocally elevated in pregnant women with true hyperthyroidism from Graves' disease.
- J Clin Endocrinol Metab 1992; 75:1333

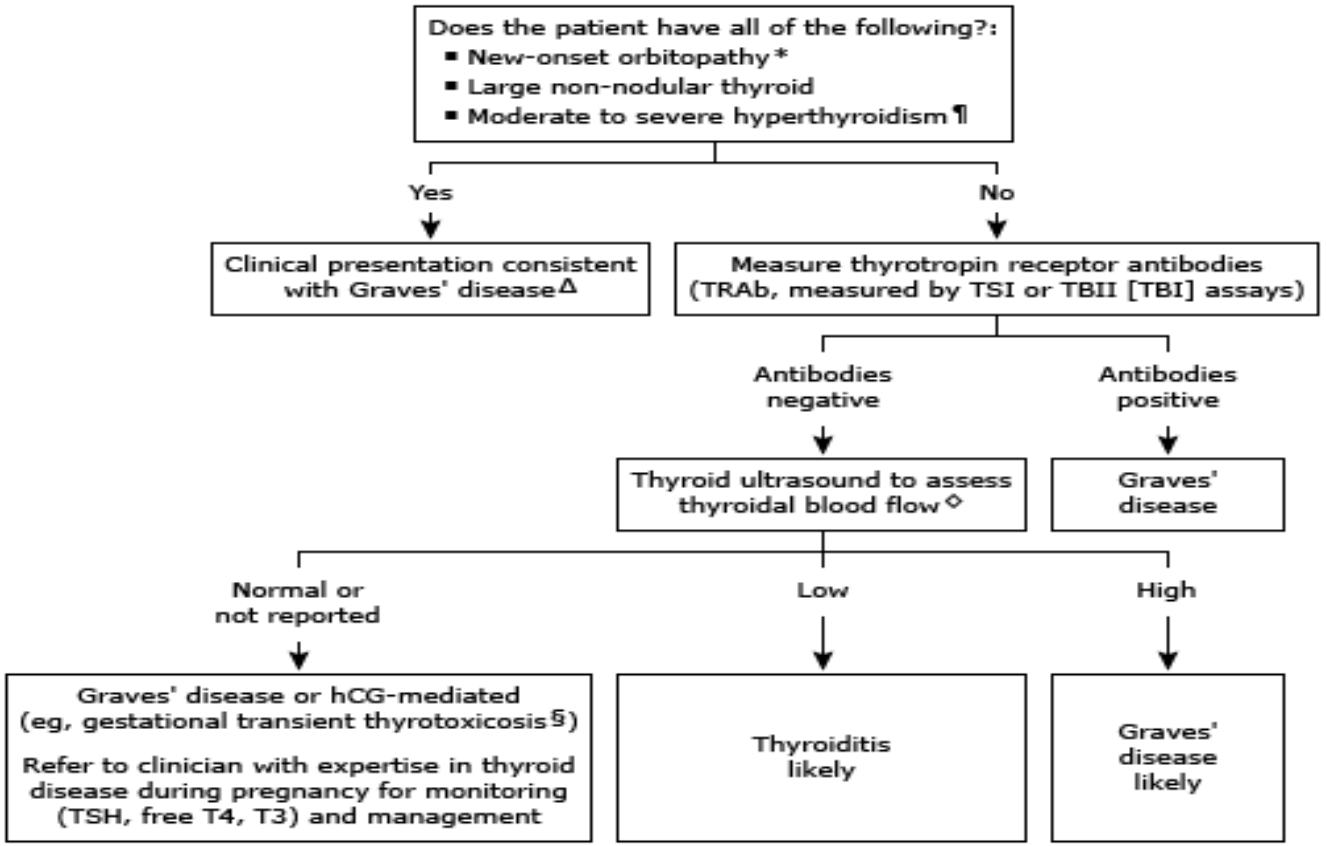
How can gestational transient thyrotoxicosis be differentiated from Graves' hyperthyroidism in pregnancy?

- A careful history and physical examination is of utmost importance in establishing the etiology.
- The findings of 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.
- If other causes for thyrotoxicosis are suspected, measurement of TRAb is indicated

Hyperemesis gravidarum

- The thyroid hyperfunction in women with hyperemesis gravidarum usually does not require treatment, because it is mild and subsides as hCG production falls (as does the vomiting). Like the thyroid hyperfunction, the vomiting is also proportional to the elevation in serum hCG and estradiol concentrations, and it is thought to be caused by estradiol
- If overt hyperthyroidism persists for more than several weeks or beyond the first trimester, it is probably not hCG mediated.
- J Clin Endocrinol Metab 1992; 75:1333

ESTABLISHING THE CAUSE



- Graves' disease (occurring in 0.1 to 1 percent of all pregnancies) and hCG-mediated hyperthyroidism due to gestational transient thyrotoxicosis (1 to 3 percent of pregnancies) are the most common causes of hyperthyroidism

How should women with GD seeking future pregnancy be counseled?

- Preconception counseling should review the risks and benefits of all treatment options and the patient's desired timeline to conception
- Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy.
- As a guide, two sets of thyroid function test within the reference range, at least 1 month apart, and with no change in therapy between tests, can be used to define a stable euthyroid state.
- The use of contraception until the disease is controlled is strongly recommended
- Several treatment options exist, each of which are associated with risks and benefits.
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Advantages and Disadvantages of Therapeutic Options for Women with Graves' Disease Seeking Future Pregnancy

Therapy	*Advantages*	*Disadvantages*
Antithyroid drugs	Effective treatment to euthyroid state within 1–2 months	Medication adverse effects (mild 5%–8%; severe 0.2%)
	Often induces gradual remission of autoimmunity (decreasing antibody titers)	Birth defects associated with use during pregnancy (MMI 3%–4%; PTU 2%–3% though less severe)
	Easily discontinued or modified. Treatment easy to take. Relatively inexpensive	Relapse after drug withdrawal likely in 50%–70%
Radioactive iodine	Easy oral administration	Repeat therapy at times necessary
	Reduction in goiter size	Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk
	Future relapse of hyperthyroidism very rare	Lifelong need of levothyroxine therapy following ablation
Thyroidectomy	Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy	Life-long need for levothyroxine supplementation
	Post surgery, gradual remission of autoimmunity occurs	Surgical complications occur in 2%–5%
	Goiter disappears	Healing and recovery from surgery Permanent neck scar

What is the management of patients with Graves' hyperthyroidism during pregnancy?

- **Goals:** The goal of treatment is to maintain persistent but mild hyperthyroidism in the mother in an attempt to prevent fetal hypothyroidism since the fetal thyroid is more sensitive to the action of antithyroid drugs
- Overtreatment of maternal hyperthyroidism with ATDs can cause fetal goiter and primary hypothyroidism. On the other hand, transient central hypothyroidism may be seen in infants whose mothers had poorly controlled hyperthyroidism during pregnancy, presumably due to suppression of the fetal pituitary-thyroid axis
- N Engl J Med 1986; 315:24/Am J Obstet Gynecol 2004; 190:211

What is the management of patients with Graves' hyperthyroidism during pregnancy?

- To attain the goal of mild hyperthyroidism, the mother's serum free T4 concentration should be maintained at or just above the trimester-specific normal range for pregnancy or (especially if the trimester-specific reference range is not available) the total T4 and T3 should be maintained at 1.5 times above the nonpregnant reference range. The serum TSH concentration should be below the reference range for pregnancy (eg, goal TSH approximately 0.1 to 0.3 mU/L), using the lowest possible dose of medication.
- Attaining these goals requires assessment of thyroid function frequently (ie, at four-week intervals) with appropriate adjustment of medication.

TREATMENT

- **Indications:**
- Women with symptomatic, moderate to severe, overt hyperthyroidism due to Graves' disease, toxic adenoma, toxic multinodular goiter, or gestational trophoblastic disease require treatment of hyperthyroidism. Such patients will almost always have TSH values below 0.05 mU/L and elevations in trimester-specific free T4 concentrations and/or total T4 and T3 concentrations that exceed 1.5 times the upper limit of normal for nonpregnant patients.
- Although hyperthyroidism due to gestational trophoblastic disease resolves with treatment of the underlying gestational trophoblastic disease and subsequent normalization of hCG levels, symptomatic women require treatment prior to surgery.

TREATMENT

- Treatment of hyperthyroidism is not required in the following settings:
- Transient, subclinical hyperthyroidism
- hCG-mediated, overt hyperthyroidism (also called gestational transient thyrotoxicosis
- Hyperemesis gravidarum-associated hyperthyroidism, because it is usually mild and subsides as hCG production falls (typically by 16 to 18 weeks gestation). Women with severe hyperemesis, however, require treatment of dehydration with intravenous fluids
- Subclinical and mild, asymptomatic, overt hyperthyroidism due to Graves' disease, toxic adenoma, or toxic multinodular goiter
- In women who are being monitored without therapy, we measure TSH, free T4 (if there is a trimester-specific reference range), and/or total T4 or total T3 every four to six weeks.

What is the management of patients with Graves' hyperthyroidism during pregnancy?

- ATDs are the mainstays of treatment for hyperthyroidism during pregnancy
- The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia
- In general, initial doses of ATDs during pregnancy are as follows: MMI, 5–30mg/d (typical dose in average patient 10–20mg); and PTU, 100–600mg/d(typical PTU dose in average patient 200–400mg/d).
- The equivalent potency of MMI to PTU is approximately 1:20

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Antithyroid drugs

- The increased risk of birth defects associated with both PTU and MMI use during early pregnancy should be reviewed
- If possible, ATDs should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored.
- Consideration can be given to discontinuing PTU after the first trimester and switching to MMI to decrease the risk of liver failure in the mother
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Beta-adrenergic blocking agents

- Beta-adrenergic blocking agents may be used until patients have become euthyroid on ATD therapy.
- The dose should be reduced as clinically indicated.
- Long-term treatment with b-blockers has been associated with intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia
- Beta-blocking drugs may be used as preparation for thyroidectomy.

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Should antithyroid medication be withdrawn or modified in early pregnancy?

- when pregnancy is diagnosed in a woman receiving ATD therapy for GD and who, based on clinical and biochemical findings appears to be in remission, is to withdraw ATD medication and perform repeated thyroid function testing during the first trimester of pregnancy.

- If ATD therapy is needed during the first trimester, PTU is preferred over MMI because the risk for severe birth defects is lower. Cessation of medication has to be recommended early in gestation, before the major teratogenic periods(gestational weeks 6–10)
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What are the principles of thyroid testing and ATD administration when treating Graves' hyperthyroidism during pregnancy?

- In women being treated with ATDs in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks.

- Antithyroid medication during pregnancy should be administered at the lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at the upper limit or moderately above the reference range.

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What are the indications and timing for thyroidectomy in the management of GD during pregnancy?

- Thyroidectomy should be considered in cases of allergies/contraindications to both ATDs, in the patient who is not compliant with drug therapy, and in women in whom euthyroidism cannot be achieved even on large doses of ATDs
- If required, the optimal time for thyroidectomy is in the second trimester of pregnancy.
- If maternal TRAb concentration is high (>3 times the upper reference for the assay) the fetus should be carefully monitored for development of fetal hyperthyroidism throughout pregnancy, even if the mother is euthyroid post thyroidectomy

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What is the value of TRAb measurement in the evaluation of a pregnant woman with Graves' hyperthyroidism

- High levels of thyroid stimulating antibodies in the second half of pregnancy may induce fetal and neonatal hyperthyroidism

- TRAb is measurable in around 95% of patients with active Graves' hyperthyroidism, and levels may remain high following ablation therapy, even more so after radioiodine treatment than surgical removal

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Indications for ordering a TRAb

- (a) mothers with untreated or ATD-treated hyperthyroidism in pregnancy
- (b) a previous history of GD with past treatment with radioiodine or total thyroidectomy
- (c) a previous history of delivering an infant with hyperthyroidism,
- (d) a known history of thyroidectomy for the treatment of hyperthyroidism in pregnancy
- In the majority of patients, maternal TRAb concentrations decrease with the progression of pregnancy; however, as in non pregnant patients, the course of GD is variable
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Indications for ordering a TRAb

- If maternal TRAb concentration is elevated in early pregnancy, repeat testing should occur at weeks 18–22.
- If maternal TRAb is undetectable or low in early pregnancy, no further TRAb testing is needed
- If elevated TRAb is detected at weeks 18–22 or the mother is taking ATD in the third trimester, a TRAb measurement should again be performed in late pregnancy(weeks 30–34) to evaluate the need for neonatal and postnatal monitoring

Additional fetal ultrasound monitoring

- Fetal surveillance should be performed in women who have uncontrolled hyperthyroidism in the second half of pregnancy, and in women with high TRAb levels detected at any time during pregnancy (greater than 3 times the upper limit of normal).
- A consultation with an experienced obstetrician or maternal–fetal medicine specialist is recommended.
- Monitoring may include ultrasound to assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter

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POSTPARTUM ISSUES

- **Breastfeeding**
- Given the concerns about potential PTU-associated hepatotoxicity, methimazole is suggested rather than PTU for nursing mothers.
- Methimazole should be administered following a feeding in divided doses.
- When the maternal dose of methimazole is >20 mg daily, infants should have thyroid function tests assessed after one and three months.

J Clin Endocrinol Metab 2000; 85:3233/Clin Endocrinol (Oxf) 2000; 53:177.

POSTPARTUM ISSUES

- The largest study investigating the effects of maternal MMI consumption during lactation was performed by Azizi and colleagues
- These data have led experts to confirm the safety of low to moderate doses of both PTU and MMI/CM in breastfeeding infants. However, given the relatively small size of the studied population, maximal daily doses of 20 mg MMI or 450 mg PTU are advised

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POSTPARTUM ISSUES

- PTU is less soluble than methimazole and is more bound to plasma proteins, whereas methimazole is free in serum, so that relatively more methimazole reaches the infant via breast milk .Nonetheless, there is little difference in serum thyroid hormone concentrations or thyroid function in infants of mothers given moderate doses of either drug

J Clin Endocrinol Metab 2000; 85:3233/Clin Endocrinol (Oxf) 2000; 53:177.

How should breastfeeding children of mothers who are treated with antithyroid medications be monitored?

- Breastfed children of women who are treated with ATDs should be monitored for appropriate growth and development during routine pediatric health and wellness evaluations.
- Routine assessment of serum thyroid function in the child is not recommended.

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SUMMARY AND RECOMMENDATIONS

- Women with symptomatic and/or moderate to severe, overt hyperthyroidism due to Graves' disease, toxic adenoma, toxic multinodular goiter, or gestational trophoblastic disease require therapy for the treatment of hyperthyroidism
- Pregnant women with subclinical and pregnant women with asymptomatic and/or mild, overt hyperthyroidism may be followed with no treatment.
- In women who are being monitored without therapy, measure TSH, free T4 (if there is a trimester-specific reference range), and/or total T4 or total T3 every four to six weeks.

SUMMARY AND RECOMMENDATIONS

- For pregnant women with moderate to severe hyperthyroidism due to Graves' disease, toxic adenoma, or toxic multinodular goiter, a thionamide is first choice of treatment
- Given the concerns about potential PTU-associated hepatotoxicity, some experts suggest methimazole rather than PTU for nursing mothers


Questions?

Relapse

- Postpartum hyperthyroidism may be due to a relapse of Graves' disease or to postpartum thyroiditis. The disorders can be differentiated from one another based upon the clinical presentation, the number of months postpartum (earlier onset favors thyroiditis), thyrotropin receptor antibody (TRAb) measurement, and evaluation of serum T3-to-T4 ratio
- Women with Graves' disease who have been treated during pregnancy need careful monitoring during the postpartum period as they may experience an exacerbation. One approach is to measure thyroid function tests (TSH, free T4) six weeks postpartum, then every six weeks if an adjustment in thionamide dose is needed or every four months if thyroid tests remain normal [57].

Thanks for your attention

Trophoblastic hyperthyroidism

- Hyperthyroidism can also occur with gestational trophoblastic disease. A hydatidiform mole (molar pregnancy) is benign but may give rise to choriocarcinoma. Both are associated with high serum hCG concentrations and abnormal hCG isoforms
- Many patients with hyperthyroidism caused by trophoblastic disease have a normal thyroid gland and few symptoms of thyroid hormone excess. However, some patients have more typical clinical findings of hyperthyroidism and a diffuse goiter, but ophthalmopathy is not present. Nausea and vomiting may predominate, as in hyperemesis gravidarum.
- *J Clin Endocrinol Metab 1994; 78:862*.

Laboratory findings

- Because of the changes in thyroid physiology during normal pregnancy, thyroid function tests may be difficult to interpret. Most pregnant women with significant overt hyperthyroidism in the first trimester have a serum TSH below that which is seen in asymptomatic healthy pregnant women (ie, <0.01 mU/L), associated with an elevated free T4 and/or free T3 (or total T4 and/or total T3) measurement that exceeds the normal range during pregnancy
- Transient subclinical hyperthyroidism in the first trimester of pregnancy is considered a normal physiologic finding. True subclinical hyperthyroidism may occur, but it is not typically associated with adverse outcomes during pregnancy and does not require therapy
- Reference ranges for free T4 are assay method specific, and trimester-specific reference ranges should be provided with the assay kits.
- Obstet Gynecol 2006; 107:337/Obstet Gynecol 2002; 100:387/Thyroid 2017; 27:31