Hypethyroidism
&
Pregnancy

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The 2017 American Thyroid Association Guidelines for Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

An Expert Panel Discussion

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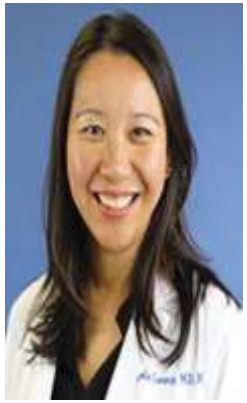

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Case presentation

- 31 y/o pregnant women with GA of 10 weeks seeks your opinion for thyroid evaluation. She complains of severe nausea and vomiting from 2 weeks age.
- **PMHx:** regular menses with no prior pregnancy or infertility
- **FHx:** hypothyroidism in mother
- **P/E:** within normal limit
- **Lab tests:**
- **TT4: 15 µg/dl(8-12)**
- **TT3: 200 ng/dl (85-170)**
- **TSH: 0.01µIU/ml (0.4-4)**

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 Graves' disease (GD) occurring **before pregnancy in 0.4-1.0 %** of women and in approximately **0.2 % during pregnancy**.

- **Less common non-autoimmune causes**

1. Toxic multinodular goiter
2. Toxic adenoma
3. Sub acute painful or painless thyroiditis
4. Overtreatment with or factitious intake of thyroid hormone.
5. TSH-secreting pituitary adenoma
6. Struma ovarii
7. Functional thyroid cancer metastases
8. Germline TSH receptor mutations

- More frequent than GD as the cause of thyroid function tests demonstrating hyperthyroxinemia is **'gestational transient thyrotoxicosis',** which is limited to the **first half of pregnancy**.

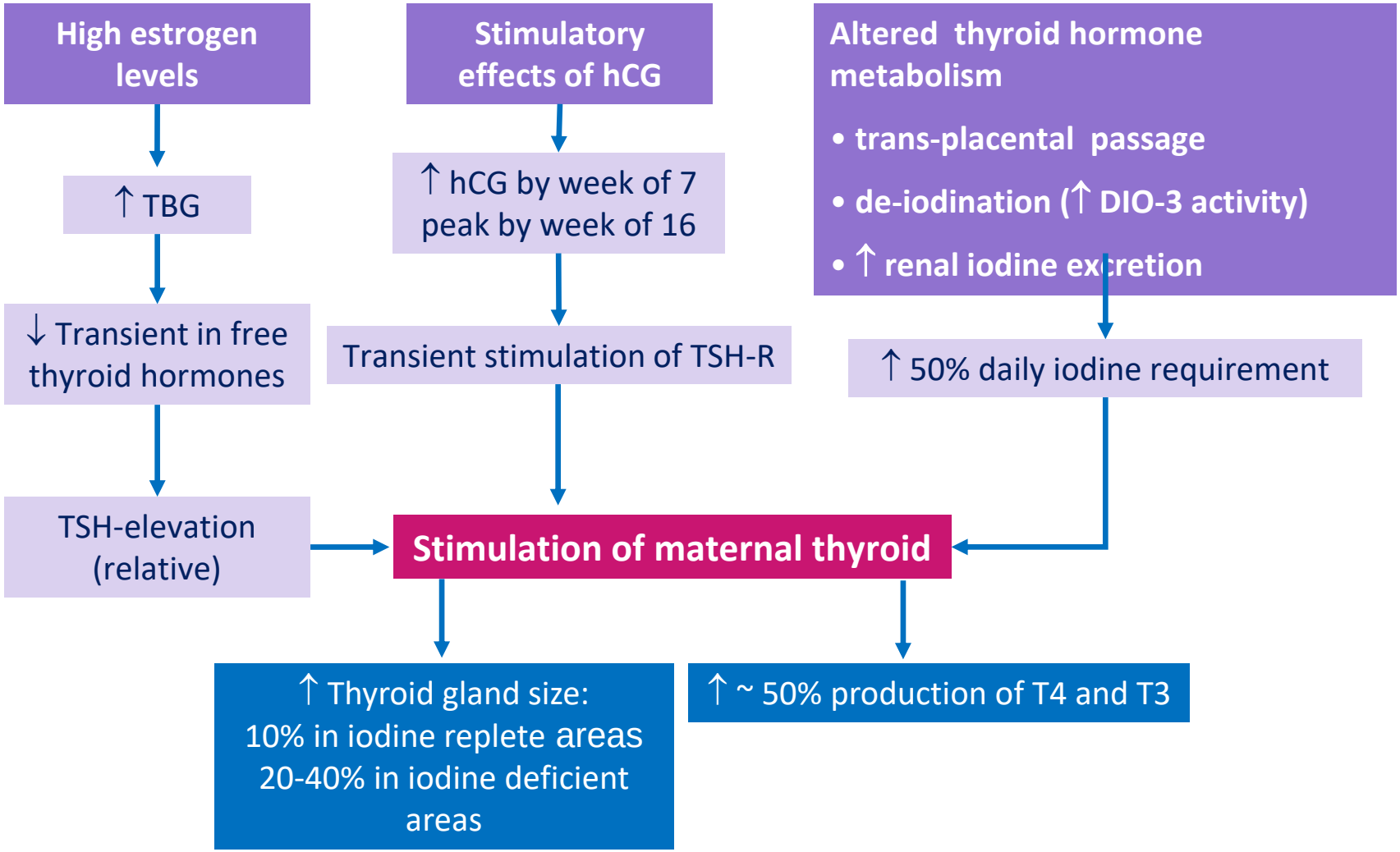
- Elevated FT4 and suppressed serum TSH, is diagnosed in about 1-3% of pregnancies.

- Often it is associated with:

1. Hyperemesis gravidarum, defined as severe nausea and vomiting in early pregnancy with more than 5% weight loss, dehydration, and ketonuria.
2. Multiple gestation
3. Hydatidiform mole
4. Choriocarcinoma

- Most cases present with marked elevations of serum hCG.

Thyroid adaption to pregnancy

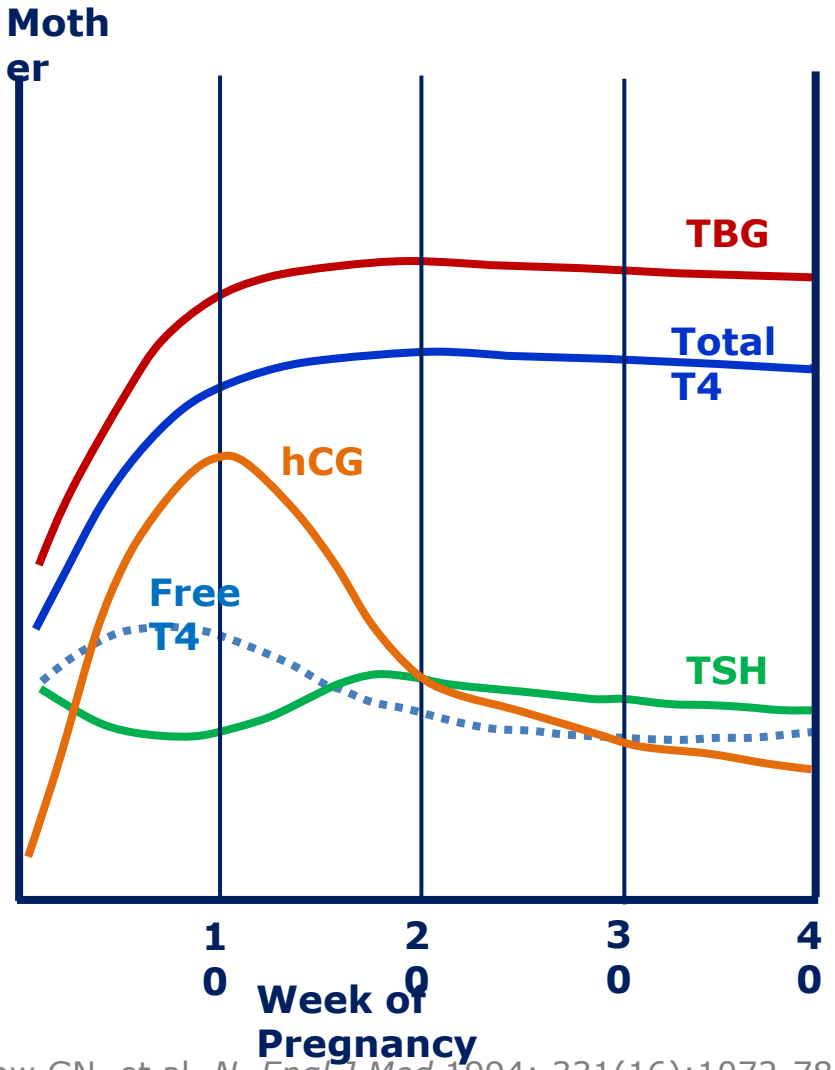


Alexander Erik K, et al. *Thyroid* 2017; 27(3):315-389.

WHAT IS THE APPROPRIATE INITIAL EVALUATION OF A SUPPRESSED SERUM TSH CONCENTRATION DURING THE FIRST TRIMESTER OF 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 7-11 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.

Changes in thyroid physiology during pregnancy



Pregnancy

Burrow GN, et al. *N. Engl J Med* 1994; 331(16):1072-78.

HOW CAN GESTATIONAL TRANSIENT THYROTOXICOSIS BE DIFFERENTIATED FROM GRAVES' HYPERTHYROIDISM IN PREGNANCY?

- In both situations, common clinical manifestations include palpitations, anxiety, tremor, and heat intolerance.
- A careful history and physical examination is of utmost importance in establishing the etiology.
- Gestational transient thyrotoxicosis:

1. No prior history of thyroid disease
2. No stigmata of Graves' disease (goiter, orbitopathy)
3. Self-limited mild disorder
4. Symptoms of emesis

- **TRAb:** If other causes for thyrotoxicosis are suspected, measurement of TSH receptor antibody (TRAb) is indicated.
- **Thyroid ultrasound:** If this is negative or thyroid nodules are suspected based on clinical examination, a thyroid ultrasound should be performed to evaluate nodularity.
- No study has demonstrated usefulness of thyroid ultrasonography for differentiating between gestational transient thyrotoxicosis and GD.
- **Serum hCG:** on average, higher in gestational transient thyrotoxicosis than in patients with GD, but overlap is considerable and the clinical usefulness of such measurement is limited.
- **T3:** TMNG, thyroiditis

- **Recommendation**
- When a suppressed serum TSH is detected in the first trimester (TSH less than the reference range), a medical history, physical examination, and measurement of maternal serum Free T4 or total T4 concentrations should be performed. Measurement of TSH receptor antibodies (TRAb), and maternal total T3, may prove helpful in clarifying the etiology of thyrotoxicosis.
- ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation**
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in
- pregnancy. ***(Strong recommendation, High quality evidence)***

- **Recommendation**
- The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. Antithyroid drugs are not recommended, though beta-blockers may be considered. ***(Strong recommendation, Moderate***
- ***quality evidence)***

Case presentation

- 25 y/o women known case of graves disease seeks your opinion for pre-pregnancy thyroid evaluation
- **PMHx:** regular menses
- **FHx:** hyperthyroidism in mother
- **P/E:** orbitopathy, mild diffuse goiter
- **DH:** metimazol 5 mg daily

HOW SHOULD WOMEN WITH GRAVES' DISEASE SEEKING FUTURE PREGNANCY BE COUNSELED?

- **Recommendation 43**
- In all women of childbearing age who are thyrotoxic, the possibility of future pregnancy should be discussed. Women with Graves' disease seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation, including the association of birth defects with antithyroid drug use.
- Preconception counseling should review the risks and benefits of all treatment options, and the patient's desired timeline to conception. **(*Strong recommendation, High quality evidence)***

- **Recommendation 44**
- Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy. Several treatment options exist, each of which are associated with risks and benefits. These include **131I ablation**, **surgical thyroidectomy**, or **ATD therapy**. ***(Strong recommendation, Moderate quality evidence)***

WHAT IS THE MANAGEMENT OF PATIENTS WITH GRAVES' HYPERTHYROIDISM DURING PREGNANCY?

- **Recommendation 45**
- Women taking MMI or PTU should be instructed to confirm potential pregnancy as soon as possible. If the pregnancy test is positive, pregnant women should contact their caregiver immediately. ***(Strong recommendation, High quality evidence)***

- **Recommendation 46**
- **a.** In a newly-pregnant woman with Graves' disease, who is euthyroid on a low dose of MMI (≤5-10 mg/day) or PTU (≤ 100-200 mg/day), the physician should consider discontinuing all antithyroid medication given potential teratogenic effects.
- The decision to stop medication should take into account the **disease history**, **goiter size**, **duration of therapy**, **results of recent thyroid function tests**, **TRAb measurement**, **and other clinical factors**.
- ***(Weak recommendation, Low quality evidence)***

- ***b.*** Following cessation of antithyroid medication, maternal thyroid function testing (TSH, and FT4 or TT4) and clinical examination should be performed every 1-2 weeks to assess maternal and fetal thyroid status. If the pregnant woman remains clinically and biochemically euthyroid, test intervals may be extended to 2-4 weeks during the 2nd and 3rd trimester. ***(Weak recommendation, Low quality evidence)***
- **c.** At each assessment, the decision to continue conservative management (withholding antithyroid medication) should be guided both by the clinical and the biochemical assessment of maternal thyroid status. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 47**
- In pregnant women with a high risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, continued antithyroid medication may be necessary.
- Factors predicting high clinical risk include:

1. Being currently hyperthyroid,
2. Requirement of> 5-10 mg/day MMI or > 100-200 mg/day PTU to maintain a euthyroid state.

- In such cases:
- **a.** PTU is recommended for the treatment of maternal hyperthyroidism through 16 weeks of pregnancy. ***(Strong recommendation, Moderate quality evidence)***
- **b.** Pregnant women receiving MMI who are in need of continuing therapy during pregnancy should be switched to PTU as early as possible. ***(Weak Recommendation, Low quality evidence)***

- **c.** When shifting from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g. MMI 5 mg daily = PTU 100 mg twice daily).
- ***(Strong recommendation, Moderate quality evidence)***
- **d.** If ATD therapy is required after 16 weeks gestation, it remains unclear whether PTU should be continued or therapy changed to MMI. As both medications are associated with potential adverse effects and shifting potentially may lead to a period of less-tight control, no recommendation regarding switching antithyroid drug medication can be made at this time. ***(No recommendation, Insufficient evidence)***

WHAT ARE THE PRINCIPLES OF THYROID TESTING AND ANTITHYROID MEDICATION ADMINISTRATION WHEN TREATING GRAVES' HYPERTHYROIDISM DURING PREGNANCY?

- **Recommendation 48**
- **a.** In women being treated with antithyroid drugs in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks.
- ***(Strong recommendation, Moderate quality evidence)***
- **b.** Antithyroid medication during pregnancy should be administered at the lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at or moderately above the reference range.
- ***(Strong recommendation, High quality evidence)***

- **Recommendation 49**
- A combination regimen of levothyroxine and an antithyroid drug should not be used in pregnancy, except in the rare situation of isolated fetal hyperthyroidism. ***(Strong recommendation, High quality evidence)***

WHAT ARE THE INDICATIONS AND TIMING FOR THYROIDECTOMY IN THE MANAGEMENT OF GRAVES' DISEASE DURING PREGNANCY?

- **Recommendation 50**
- Thyroidectomy in pregnancy may be indicated for unique scenarios.
- If required, the optimal time for thyroidectomy is in the second trimester of pregnancy.
- If maternal TRAb concentration is high (> 3x 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**.**

(Strong recommendation, High quality evidence)

HOW SHOULD PREGNANT PATIENTS WITH GRAVES' DISEASE BE PREPARED FOR URGENT NON-THYROID SURGERY?

- **Recommendation 51**
- 1) A pregnant woman should never be denied indicated surgery, regardless of trimester.
- 2) Elective surgery should be postponed until after delivery. 3) If possible, nonurgent surgery should be performed in the second trimester when preterm contractions and spontaneous abortion are least likely."
- In the setting of a patient with Graves' Disease undergoing urgent, non-thyroid surgery, if the patient is well controlled on ATD, no other preparation is needed. Beta-blockade should also be utilized if needed. (**Strong recommendation, Moderate quality evidence**)

WHAT IS THE VALUE OF TRAb MEASUREMENT IN THE EVALUATION OF A PREGNANT WOMAN WITH GRAVES' HYPERTHYROIDISM?

- Fetal risks in women with previous or current Graves' hyperthyroidism include:
- a) fetal hyperthyroidism
- b) neonatal hyperthyroidism
- c) fetal hypothyroidism
- d) neonatal hypothyroidism,
- e) central hypothyroidism.
- The above potential complications depend on several factors:

1. poor control of hyperthyroidism throughout pregnancy may induce transient central hypothyroidism
2. excessive amounts of ATDs may be responsible for fetal and neonatal hypothyroidism, even if the mother is biochemically euthyroid
3. high levels of thyroid stimulating antibodies in the 2nd 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.

- Indications for ordering a TRAb test in pregnant women with GD include: 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, or d) a known history of thyroidectomy for the treatment of
- hyperthyroidism in pregnancy (416). 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.

- The incidence of fetal and neonatal hyperthyroidism is between **1 and 5%** in all women with active or a past history of Graves' hyperthyroidism, and is associated with increased fetal/neonatal morbidity and mortality if unrecognized and untreated.
- A maternal TRAb serum concentration > 5 IU/L (approximately 3X the upper limit of normal for the assay) in the 2nd and 3rd trimester predicted neonatal hyperthyroidism with 100 % sensitivity and 43 % specificity.

- A determination of serum TRAb in early pregnancy is helpful in detecting pregnancies at risk.
- A value > 5 IU/L or 3 times the upper limit of normal in a mother who previously received ablative therapy for Graves' disease is an indication for establishing close follow-up of the fetus in collaboration with a Maternal-Fetal-Medicine physician.
- Cases of overlooked isolated fetal hyperthyroidism leading to fetal loss in such women have repeatedly been published.
- A determination of serum TRAb in late pregnancy in a mother who is still in need of ATD therapy to remain euthyroid, is helpful for detecting risk for neonatal hyperthyroidism.
- A value > 5 IU/L or 3 times the upper limit of normal in the mother indicates that the fetal thyroid may be strongly stimulated by TRAb passing through the placenta.
- After birth, any ATD from the mother is much more rapidly cleared in the neonate than are the TRAb, and the neonate may become hyperthyroid.
- If TRAb becomes undetectable in a pregnant woman taking ATD, this is an indication that it may be feasible to reduce or withdraw the ATD, to protect the fetus against hypothyroidism and goiter.
- In women who are in remission and euthyroid after a previous course of ATD therapy for Graves' disease, measurement of TRAb in pregnancy is not required.

- **Recommendation 52**
- a. If the patient has a past history of Graves' disease treated with ablation (radioiodine or surgery), a maternal serum determination of TRAb is recommended at initial thyroid function testing during early pregnancy. ***(Strong recommendation, Moderate quality***
- ***evidence)***
- b. If maternal TRAb concentration is elevated in early pregnancy, repeat testing should occur at weeks 18-22. ***(Strong recommendation, Moderate quality evidence)***
- c. If maternal TRAb is undetectable or low in early pregnancy, no further TRAb testing is needed**.** ***(Weak recommendation, Moderate quality evidence)***

- d. If a patient is taking ATDs for treatment of Graves' hyperthyroidism when pregnancy is confirmed, a maternal serum determination of TRAb is recommended. (***Weak recommendation, Moderate quality evidence)***
- e. If the patient requires treatment with ATDs for Graves' disease through mid pregnancy, a repeat determination of TRAb is again recommended at weeks 18-22. ***(Strong recommendation, Moderate quality evidence)***
- f. 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. ***(Strong recommendation,***
- ***High quality evidence)***

UNDER WHAT CIRCUMSTANCES SHOULD ADDITIONAL FETAL ULTRASOUND MONITORING FOR GROWTH, HEART RATE, AND GOITER BE PERFORMED IN WOMEN WITH GRAVES' HYPERTHYROIDISM IN PREGNANCY?

- Serial ultrasound examinations may be performed for the assessment of gestational age, fetal viability, amniotic fluid volume, fetal anatomy, and detection of malformations.
- Fetal wellbeing may be compromised in the presence of elevated TRAb, uncontrolled hyperthyroidism, and pre-eclampsia .
- Signs of potential fetal hyperthyroidism that may be detected by ultrasonography include fetal tachycardia (heart rate >170 bpm, persistent for over 10 minutes), intrauterine growth restriction, presence of fetal goiter, (the earliest sonographic sign of fetal thyroid dysfunction), accelerated bone maturation, signs of congestive heart failure, and fetal hydrops.
- A team approach to the management of these patients is required, including an experienced obstetrician or maternalfetal- medicine specialist, neonatologist, and anesthesiologist. In most cases, the diagnosis of fetal hyperthyroidism should be made on clinical grounds based on maternal history, interpretation of serum TRAb levels, and fetal ultrasonography.

- **Recommendation 53**
- Fetal surveillance should be performed:

1. In women who have uncontrolled hyperthyroidism in the second half of pregnancy,
2. In women with high TRAb levels detected at any time during pregnancy (greater than 3x 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. ***(Strong recommendation, Moderate quality evidence)***

WHEN SHOULD UMBILICAL BLOOD SAMPLING BE CONSIDERED IN WOMEN WITH GRAVES' DISEASE IN PREGNANCY?

- **Recommendation 54**
- Cordocentesis should be used in rare circumstances and performed in an appropriate setting.
- It may occasionally be of use when fetal goiter is detected in women taking antithyroid drugs to help determine whether the fetus is hyperthyroid or hypothyroid.
- ***(Weak recommendation, Low quality evidence)***

HOW SHOULD HYPERTHYROIDISM CAUSED BY AUTONOMOUS THYROID NODULES BE HANDLED IN PREGNANCY

- **Recommendation 55**
- If ATD therapy is given for hyperthyroidism caused by autonomous nodules, the fetus should be carefully monitored for goiter and signs of hypothyroidism during the 2nd half of pregnancy.
- A low dose of ATD should be administered with the goal of maternal FT4 or TT4 concentration at or moderately above the reference range. ***(Strong recommendation, Low quality evidence)***

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