Thyrotoxicosis in Pregnancy: Diagnose and Management

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Pregnancy has profound impact on thyroid gland and its function.

Interpretation of laboratory testing differs from the non-pregnant.

Potential side effects and teratogenic effects of anti-thyroid drugs.

Uncontrolled maternal hyperthyroid: Potential risks of complicating pregnancy and reducing the quality of the offspring.
Interpretations of Biochemical Parameters of Thyroid Function During Pregnancy

• Physiologically:
  • HCG $\rightarrow$ impacts on TSH levels
  • TBG $\uparrow$ $\rightarrow$ impacts on FT4 levels
  • TBG $\uparrow$, NEFA $\uparrow$, Albumin$\downarrow$: impacts on Laboratories methods
The downward shift of TSH reference range according to trimester of pregnancy.

- **J. E. Haddow et al. 2004**: 5th and 95th centiles.
- **R. Stricker et al. 2007**: 2.5th and 97.5th centiles.
- **N. S. Panesar et al.: 2001**: 5th and 95th centiles.

Nonpregnant TSH range (0.40–4.0 mIU/liter).
What is the normal reference range for serum TSH concentrations in each trimester of pregnancy?

- In the 1st TM
  - The lower reference range can be reduced by approximately 0.1-0.2 mU/L,
  - The upper reference range is reduced by approximately 0.5-1.0 mU/L.
  - This reference limit should generally be applied beginning with the late 1st TM, weeks 7–12.
- Gradual return towards nonpregnant range in the 2nd and 3rd TM
What is the optimal method to assess serum T4 concentration during pregnancy?

• Sera of pregnant women are characterized by ↑ TBG and NEFA and ↓ albumin relative to the sera of nonpregnant women,

→ many current FT4 analog immunoassays fail dilutional assessment.
Free T4 measurements in 29 women in the 9th month of gestation, using equilibrium dialysis (ED), and 9 different immunoassays
What is the optimal method to assess serum T4 concentration during pregnancy?

- **TT4** measurements superior to immunoassay measurement of FT4 measurements in pregnant women.

- A clinically acceptable upper range determination can be calculated by shifting the nonpregnant limit 50% higher — can only be used after week 16 of pregnancy ( > 16 weeks GA).
Calculation method to assess serum T4 concentration during weeks 7-16 of pregnancy

• On weeks 7–16 of pregnancy, a calculation can be made based on increasing the nonpregnant upper reference limit by 5% per week, beginning with week 7.

• For example, at 11 weeks of gestation (4 weeks beyond week 7), the upper reference range for T4 is increased by 20% (4 weeks x 5%/week)
Diagnose
Thyrotoxicosis in Pregnancy:
Type of case

Undiagnosed before pregnancy

Pictures: https://www.google.co.id/search?safe=strict&hl=en&tbs isch&q=thyrotoxicosis+in+pregnancy&chips=q:hyperthyroid+in+pregnancy,g_1:person,online_chips:during+pregnancy&usg=AI4_-kS0qZ-8ipsKhtSgmTXkYVTXTKk1Ng&sa=X&ved=0ahUKEwjPg_7_gKneAhXLw18KHyfHMIQ4IYIMigI&biw=1280&bih=610&dpr=1.5#imgrc=
Thyroid function: TSHS, FT4, TT4, TT3, FT3

Etiology of thyrotoxicosis: Thyroid USG, TRAb or: Pelvic USG, HCG

1st TM of pregnancy: Severe hyperemesis gravidarum

HCG ↑↑

Gestational transient thyrotoxicosis

Thyroid disease? Lumps? Hypermetabolic?

Thyrotoxicosis

Graves Disease? Toxic nodul? Thyroiditis? Molar disease?

Thyrotoxicosis in Pregnancy: steps to D/
1. Evaluation of clinical signs & symptoms and the history of thyroid disorders
Clinical features suggesting the possibility of hyperthyroidism due to Graves' disease in a pregnant patient

<table>
<thead>
<tr>
<th>ANAMNESIS</th>
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<tbody>
<tr>
<td>History of hyperthyroidism, autoimmune thyroid disease (patient or family)</td>
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<tr>
<td>Typical symptoms of hyperthyroidism including weight loss (failure to gain weight), palpitations, proximal muscle weakness, emotional lability.</td>
</tr>
<tr>
<td>Suggesting Graves' disease such as ophthalmopathy or pretibial myxedema</td>
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<tr>
<td>Thyroid enlargement.</td>
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<tr>
<td>More prominent of normal symptoms of pregnancy such as heat intolerance, diaphoresis, and fatigue.</td>
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</table>

Clinical features suggesting the possibility of hyperthyroidism due to Graves' disease in a pregnant patient

<table>
<thead>
<tr>
<th>PHYSICAL EXAMINATION</th>
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<tbody>
<tr>
<td>Pruritus.</td>
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<tr>
<td>Pulse rate &gt; 100/mnt</td>
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<tr>
<td>Widened pulse pressure</td>
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<tr>
<td>Eye signs of Graves' disease or pretibial myxedema</td>
</tr>
<tr>
<td>Thyroid enlargement especially in iodine sufficient geographical areas</td>
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<tr>
<td>Onycholysis</td>
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Step 2: Laboratory confirmation of thyrotoxicosis
What is the appropriate initial evaluation of a suppressed serum TSH concentration during the first trimester of pregnancy?

• Serum TSH < 0.1 mU/L (even could undetectable) may be present in approximately 5% of women by week 11 of pregnancy.

• Any subnormal serum TSH value should be evaluated in conjunction with serum TT4 (or FT4 by specific, not wide use, assay) and TT3 values.
What is the biochemical diagnosis of overt thyrotoxicosis in pregnancy?

Overt thyrotoxicosis is confirmed in the presence of:

- suppressed or undetectable TSH

plus

- inappropriately elevated TT4/ (FT4 by specific, not wide use, assay), or TT3
Step 3 : Clarifying the etiology of thyrotoxicosis
Clarifying the etiology of thyrotoxicosis

- A careful history and physical examination is of utmost importance in establishing the etiology.
- Measurement of TRAb and maternal TT3
- Thyroid ultrasound should be performed to evaluate nodularity.
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.
Clarifying the etiology of thyrotoxicosis

- No prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), a self-limited mild disorder, and symptoms of emesis favor to gestational transient thyrotoxicosis
Gestational transient thyrotoxicosis

• Characterized by elevated FT4 and suppressed TSH.
• 1%–3% of pregnancies, depends on the geographic area.
• Associated with hyperemesis gravidarum defined as:
  • severe nausea and vomiting in early pregnancy,
  • more than 5% weight loss,
  • dehydration, and ketonuria.
Management of Thyrotoxicosis in Pregnancy
Anti Thyroid Drugs (ATD) during pregnancy

- Remains an important clinical question.
- Potential teratogenic effects of the methimazole (MMI) and propylthiouracil (PTU).
  - Mild hyperthyroidism appears safe for the mother and fetus.
  - Moderate to severe hyperthyroidism can prove dangerous.
Hepatotoxic effect of PTU

- PTU had been found on the list of drugs leading to liver transplantation in the US.
- PTU should limited use during first trimester of pregnancy, exceptions on MMI allergy or those with thyroid storm.
- Monitoring hepatic enzymes during administration of PTU.
- No prospective data have demonstrated that the monitoring of liver enzymes is effective in preventing fulminant PTU-induced hepatotoxicity.

Should not we treat thyrotoxicosis during pregnancy?
Poor control of thyrotoxicosis

- Poor control of thyrotoxicosis is associated with:
  - Pregnancy loss, pregnancy induced hypertension
  - Prematurity, low birth weight
  - Intrauterine growth restriction, stillbirth
  - Thyroid storm, maternal congestive heart failure

Implications of excessive levels of maternal thyroid hormone on fetal

• Fetal exposure to excessive levels of maternal thyroid hormone may program the offspring to develop diseases such as seizure disorders and neurobehavioral disorders in later life.
Management of Graves Disease in Pregnancy
Antithyroid medication in early pregnancy

- Cessation of medication has to be recommended early in gestation, before the major teratogenic periods (gestational weeks 6–10).
- Perform repeated thyroid function testing during the 1st TM.
- Consider the risk of rapid relapse of hyperthyroidism after medication withdrawal.
- If ATD is needed during 1st TM, PTU is preferred over MMI.
Risk of rapid relapse of hyperthyroidism after medication withdrawal in early pregnancy

- Risk is high in patients:
  - treated for a short period (<6 months),
  - suppressed or low serum TSH while on medication pre-pregnancy,
  - require >5–10mg of MMI per day to stay euthyroid,
  - active orbitopathy or large goiter, high levels of TRAb

- Risk is considered high, medication should not be withdrawn, and PTU is preferred over MMI in 1st TM.
Management of patients with Graves’ hyperthyroidism during pregnancy

• The initial dose of ATD depends on the severity of the symptoms and degree of hyperthyroxinemia.

• MMI, 5–30mg/d (typical dose 10–20mg); CM, 10–40mg/d ➔ 1-2x/day

• PTU, 100–600mg/d (typical dose 200–400mg/d) ➔ 2-3x/day

• The equiv. potency of MMI to PTU is ~1:20 (5mgMMI = 100mg of PTU)

• 10 mg of CM is rapidly metabolized to approximately 6mg of MMI
Beta adrenergic blocking agents

• Propranolol 10–40 mg every 6–8 hours may be used for controlling hypermetabolic symptoms until patients have become euthyroid on ATD therapy.

• The dose should be reduced as clinically indicated. Majority, can be discontinued in 2–6 weeks.

• Long-term treatment with b-blockers has been associated with intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycaemia.
How should women with GD seeking future pregnancy be counseled?

• Pregnancy should be postponed until a stable euthyroid state:
  • 2 sets of thyroid function test within the reference range:
    • at least 1 month apart,
    • with no change in therapy between tests.
  • The use of contraception until the disease is controlled.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Antithyroid drugs</td>
<td>Effective treatment to euthyroid state within 1–2 months</td>
<td>Medication adverse effects (mild 5%–8%; severe 0.2%)</td>
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<td></td>
<td>Often induces gradual remission of autoimmunity (decreasing antibody titers)</td>
<td>Birth defects associated with use during pregnancy (MMI 3%–4%; PTU 2%–3% though less severe)</td>
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<td></td>
<td>Easily discontinued or modified. Treatment easy to take. Relatively inexpensive</td>
<td>Relapse after drug withdrawal likely in 50%–70%</td>
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<tr>
<td>Radioactive iodine</td>
<td>Easy oral administration</td>
<td>Repeat therapy at times necessary</td>
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<tr>
<td></td>
<td>Reduction in goiter size</td>
<td>Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk</td>
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<tr>
<td></td>
<td>Future relapse of hyperthyroidism very rare</td>
<td>Lifelong need of levothyroxine therapy following ablation</td>
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<tr>
<td>Thyroidectomy</td>
<td>Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy</td>
<td>Life-long need for levothyroxine supplementation</td>
</tr>
<tr>
<td></td>
<td>Post surgery, gradual remission of autoimmunity occurs</td>
<td>Surgical complications occur in 2%–5%</td>
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<tr>
<td></td>
<td>Goiter disappears</td>
<td>Healing and recovery from surgery</td>
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<td></td>
<td>Permanent neck scar</td>
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MMI, methimazole; PTU, propylthiouracil.