Thyroid Dysfunction in Pregnancy

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THYROID ECONOMY IN EARLY PREGNANCY IS AFFECTED BY 3 MAIN FACTORS

DIETARY IODINE

FT4 ng/dL

TSH uU/ml

WEEKS GESTATION

TBG

hCG
TBG AND THYROID FUNCTION (4-10 WKS)

Pituitary gland

↑ TSH

\[ \text{TSH} \]

↓ FT\(_4\)

\[ \text{FT}_4 \]

↑ TBG

\[ \text{TBG} \]

Thyroid gland
TBG AND THYROID FUNCTION (4-10 WKS)

Pituitary gland → TSH → Thyroid gland → FT₄ → TBG

NORMAL TSH
FT₄
hCG AND THYROID FUNCTION (6-13 WKS)

- Pituitary gland
- Placental gonadotrophin (hCG)
- TSH
- FT4

Diagram:
- Thyroid gland
- TSH receptor
- Normal TSH, FT4
hCG vs. TSH Changes during Gestation

From: Glinoer et al. JCEM 71:276 (1990)
DECREASE THYROID RESERVE

chronic thyroiditis
post thyroid ablation
L-thyroxine Therapy

HIGH TSH
NORMAL OR LOW FT$_4$
CLINICAL OR
SUBCLINICAL
HYPOTHYROIDISM
TSH (uU/ml) and FT4 (ng/ml) levels during weeks of gestation.

- **TSH** levels:
  - Normal Thyroid Reserve: Stable from 3.0 to 0.4 uU/ml.
  - Decrease Thyroid Reserve: Fluctuates from 3.0 to 0.4 uU/ml.

- **FT4** levels:
  - Standard Range: 1.8 - 0.6 ng/ml.

Graph shows the typical thyroid function changes during pregnancy with labels indicating normal and decreased thyroid reserve.
## Thyroid Disorders in Pregnancy
### Physiological Changes

<table>
<thead>
<tr>
<th></th>
<th>Non pregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBG (mg/L)</td>
<td>7 – 15</td>
<td>20 – 40</td>
</tr>
<tr>
<td>Total T4 (μg/dL)</td>
<td>5 – 12.5</td>
<td>7 – 15</td>
</tr>
<tr>
<td>Total T3 (ng/dL)</td>
<td>70 – 200</td>
<td>100 – 250</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>0.8 – 2.3</td>
<td>0.8 – 2</td>
</tr>
<tr>
<td>Free T3 (ng/dL)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>TSH (ng/dL)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>FTI</td>
<td>4.5 – 12</td>
<td>4.5 – 12</td>
</tr>
<tr>
<td>R3TU (%)</td>
<td>25 – 35</td>
<td>15 – 25</td>
</tr>
</tbody>
</table>
Testing for Thyroid Disease

- Serum TSH
- Free T4
- Free T3
Testing for Thyroid Disease

Free thyroxin index

\[ \text{FT4I} = \text{Total T4} \times \text{patient RT3U} \]  
Normal RT3U
Additional Testing

- **Thyroid peroxidase antibodies (TPO)**
  Previously called thyroid microsomal antibodies

- **TSH receptor antibodies (TRAbs)**
  - Blocking (thyrotropin binding inhibitory immunoglobulin (TBII); thyroiditis)
  - Activating (thyroid stimulating immunoglobulin (TSI); hyperthyroidism)
  - Neutral

- **Thyroglobulin antibodies**
Radioiodines in Pregnancy

- Concentrated in fetal thyroid after 12 weeks
- Excreted in breastmilk
- Half life
  - 8 days for $^{131}$I (no breastfeeding for 4 weeks)
  - 13.5 hours for $^{123}$I (no breastfeeding for 2 weeks)
  - 6 hours for Tc (no breastfeeding for 2 days)
Hyperthyroidism in Pregnancy

1 per 2000 pregnancies

Etiology

- Graves disease
  - 90% of cases
  - autoimmune disorder
  - may improve in late pregnancy and flare postpartum
- Toxic diffuse nodule
- Toxic multinodular goiter
- Subacute thyroiditis
- Hashimoto’s thyroiditis
- GTN
Hyperthyroidism in Pregnancy
Maternal Risks

- High output heart failure
- Thyroid storm (25% mortality)
Hyperthyroidism in Pregnancy
Fetal Risks

⚠️ Thyroid antibodies and medications
  - Effect on fetal thyroid unpredictable
  - Neonatal thyrotoxicosis (10% of Graves’)
    • lasts for 2-3 months after delivery
    • TSI not useful
    • may cause craniosynostosis, exophthalmos, heart failure, hepatosplenomegaly

⚠️ Preterm delivery (11 - 25%)

⚠️ Stillbirths (8 - 15%)

⚠️ Decreased birthweight
Hyperthyroidism in Pregnancy
Diagnosis

† Signs and symptoms
  – Most confused with pregnancy changes
  – Exophthalmos in Graves’

† Laboratory
  – Free T4 ± free T3 (if pregnancy norms available)
  – Ultrasensitive TSH
  – FTI
  – Never use radioactive thyroid scan
Hyperthyroidism in Pregnancy
Management

FT4 +/- FT3
TSH

Both highly abnl
Rx

Both mildly abnl or Inconsistent
rTSH Ab
TSI

Normal
No further testing

Positive
RX

Negative
Sx
No Sx

Follow monthly

No Sx

Follow monthly
Hyperthyroidism in Pregnancy
Thioamide Therapy

- Block incorporation of iodine into tyrosine
- Propylthiouracil
  - Preferred (also inhibits peripheral conversion of T4 to T3)
  - Start with 100 mg Q 8
- Methimazole
  - Start with 10 mg Q 8
Hyperthyroidism in Pregnancy
Thioamide Side Effects

- Skin rash and pruritis
- Nausea, vomiting, diarrhea
- Aplasia cutis
- Agranulocytosis (0.2%) and granulocytopenia (5%)
  - Immediate CBC for sore throat or other
  - Immediate D/C
- Fetal goiter
- Transient neonatal hypothyroidism (1 - 5%)
Hyperthyroidism in Pregnancy

Beta Blockers

- Only for symptomatic relief
- Also blocks peripheral conversion T4 to T3
- Concomitant with thioamides
- Propranolol
  - Start with 10 mg Q 8
  - Side effects: bronchospasm, CHF, fetal growth abnormality, neonatal bradycardia, neonatal hypoglycemia
Hyperthyroidism in Pregnancy
Antepartum Maternal Follow up

- If on thioamide and propranolol
  - QOD
  - Adjust by 10 mg Q 8 to maintain pulse < 100 bpm
  - Should be able to D/C in 1 - 2 weeks

- If on thioamide only
  - Weekly check for signs and symptoms
  - Laboratory Q 4 weeks
  - Adjust dose by 1/4 - 1/3 as soon as change
  - Keep FT4 in upper normal range
Hyperthyroidism in Pregnancy
Fetal Follow up

- Ultrasound for growth and neck check Q every 3 weeks
- NST and AFI weekly after 32 weeks
Hyperthyroidism in Pregnancy
Postpartum Follow up

- Effect of immune tolerance decline on Graves’ disease postpartum
  - Initial diagnosis
  - Flare

- Rx
  - If breastfeeding
    - similar to antepartum
    - radioiodine contraindicated
    - follow up neonates
  - If not breastfeeding
    - may use radioiodine
2.1.3. Propylthiouracil (PTU), if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy because of the possible association of methimazole (MMI) with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. MMI 10 mg is considered to be
approximately equal to 100–150 mg of PTU. Recent analyses reported by the U.S. Food and Drug Administration (FDA) indicate that PTU may rarely be associated with severe liver toxicity. For this reason we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy,
including the potential difficulties involved in switching patients from one drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○○). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3–4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2|⊕○○○○).
Thyroid Storm
General

- Occurs in 1% of hyperthyroid pregnant women
- Maternal mortality up to 25% in older literature
- High risk of heart failure
Thyroid Storm in Pregnancy
Precipitating Factors

- Diabetic ketoacidosis/hypoglycemia
- Infection (pneumonia, pyelonephritis, meningitis, chorioamnionitis, sepsis)
- Labor or induction
- Preeclampsia/Molar pregnancy
- Pulmonary thromboembolism
- Trauma and Surgery (including cesarean section)
Thyroid Storm
Diagnosis

- Fever
- Change in mental status
  - restless
  - nervous
  - confusion
  - seizure
  - coma
- GI symptoms
  - vomiting
  - diarrhea
- Tachycardia out of proportion
- Inciting event
Thyroid Storm
Management

- High index of suspicion
- Obtain serum FT4, FT3, and TSH prior to therapy
- Do not wait for laboratory diagnosis
- Supportive care
Hyperthyroidism in Pregnancy
Management of Thyroid Storm

- Rapid intervention (do not wait for labs)
- Thioamides
  - PTU 600 - 800 mg po
  - Methimazole 60 - 100 mg pr
- Iodide 1 - 2 hours after PTU
  - SSKI 2 - 5 drops po Q 8
  - NaI 0.5 - 1 mg IV Q 8
- Dexamethasone 2 mg IV Q 6 x 4 doses
- Propranolol 1 - 10 mg IV Q 4
- IV fluids, electrolytes, antipyretics
Hypothyroidism in Pregnancy

Etiology

- Autoimmune
- Postablation
- Idiopathic
- Rarely: central
Hypothyroidism in Pregnancy
Maternal Risks

- Myxedema coma (20% mortality)
Hypothyroidism in Pregnancy
Fetal Risks

- Increased SAB
- Increased stillbirth
- Neurodevelopmental delay
MATERIAL HYPOTHYROIDEMIA AND INTELLECTUAL DEVELOPMENT OF THE OFFSPRING

- **LOWER IQ’S**

- **NORMAL IQ’s**
Table 2. Standardized Full-Scale Child IQ and Scores on the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function, Preschool Version (Brief-P), According to Study Group.* 3 years of age

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening Group (N=390)</th>
<th>Control Group (N=404)</th>
<th>Difference (95% CI) (Control Group – Screening Group)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>99.2±13.3</td>
<td>100.0±13.3</td>
<td>0.8 (−1.1 to 2.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>&lt;85 (% of children)</td>
<td>12.1</td>
<td>14.1</td>
<td>2.1 (−2.6 to 6.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>CBCL T score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.4±12.4</td>
<td>45.1±13.6</td>
<td>0.7 (−1.2 to 2.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Brief-P T score§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td>0.59</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>47–55</td>
<td>47–55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.4a. The committee could not reach agreement with regard to screening recommendations for all newly pregnant women. Two versions are therefore presented.

8.4a1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; evidence, fair (2(+++0)) (Authors supporting: L.D.G., J.R., J.H.L., N.A., C.J.E.).

8.4a2. Some members recommended neither for nor against universal screening of all pregnant women for TSH
Subclinical Hypothyroidism in Pregnancy

ABSTRACT: Subclinical hypothyroidism is diagnosed in asymptomatic women when the thyroid-stimulating hormone level is elevated and the free thyroxine level is within the reference range. Thyroid hormones, specifically thyroxine, are essential for normal fetal brain development. However, data indicating fetal benefit from thyroxine supplementation in pregnant women with subclinical hypothyroidism currently are not available. Based on current literature, thyroid testing in pregnancy should be performed on symptomatic women and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease (e.g., diabetes mellitus). Without evidence that identification and treatment of pregnant women with subclinical hypothyroidism improves maternal or infant outcomes, routine screening for subclinical hypothyroidism currently is not recommended.
Subclinical Hypothyroidism in Pregnancy

ABSTRACT: Subclinical hypothyroidism is diagnosed in asymptomatic women when the thyroid-stimulating hormone level is elevated and the free thyroxine level is within the reference range. Thyroid hormones, specifically thyroxine, are essential for normal fetal brain development. However, data indicating fetal benefit from thyroxine supplementation in pregnant women with subclinical hypothyroidism currently are not available. Based on current literature, thyroid testing in pregnancy should be performed on symptomatic women and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease (eg, diabetes mellitus). Without evidence that identification and treatment of pregnant women with subclinical hypothyroidism improves maternal or infant outcomes, routine screening for subclinical hypothyroidism currently is not recommended.
Hypothyroidism in Pregnancy

Diagnosis

► Signs and symptoms
  – Most confused with pregnancy changes
  – Eyelid edema and excessive weight gain

► Laboratory
  – Free T4 ± free T3 if pregnancy norms available
  – Ultrasensitive TSH
  – FTI
  – Never use radioactive thyroid scan
Hypothyroidism in Pregnancy
Management

FT4 +/- FT3
TSH

- Both abnl: Rx
- Inconsistent: Antimicrosomal Ab Anti-TGB Ab
- Normal: No further testing

Antimicrosomal Ab
Anti-TGB Ab

- Positive: Rx
- Negative: Sx
  - No Sx: Follow monthly
  - Sx: Rx
1.1. We recommend caution in the interpretation of serum free $T_4$ levels during pregnancy and that each laboratory establish trimester-specific reference ranges for pregnant women if using a free $T_4$ assay. The nonpregnant total $T_4$ range (5–12 $\mu$g/dl or 50–150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free $T_4$ index ("adjusted $T_4$") appears to be a reliable assay during pregnancy. U.S. Preventive Service Task Force (USPSTF) recommendation level: B; evidence, fair (GRADE 2 | ++ ○ ○).
1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception $T_4$ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|.tsv).

1.2.4. The $T_4$ dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1|.tsv).
1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. $T_4$ dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mIU/liter (in an assay using the International Standard) in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific TSH ranges. Thyroid function tests should be remeasured within 30–40 d and then every 4–6 wk. USPSTF recommendation level: A; evidence, good (1⃣⃣⃣⃣⃣⃣⃣).
1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored every 4–6 wk for elevation of TSH above the normal range for pregnancy. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕⊕).
Hypothyroidism in Pregnancy
Thyroid Hormone Replacement

- Only use levothyroxine (Synthroid)
- Start 0.1 mg/d
- Labs Q 4 weeks
- Adjust by 1/4 - 1/3

Postpartum
  - Return to pre-pregnancy dose over 2 - 4 weeks
  - Labs 4 weeks after stable dose
Postpartum Thyroiditis

- Affect 5 - 10% (often subclinical)

- Initial phase
  - Lymphocytic infiltration of thyroid
  - Thyrotoxicosis (often overlooked or ASx)
  - Starts 6 - 12 weeks PP and lasts for 4 - 8 weeks
  - Differentiate from Graves’
    - thyroid autoantibodies positive but TSI negative
    - radioiodine uptake decreased
  - Rx symptomatic with beta-blockers
  - Always resolves
Later phase
- Hypothyroidism
- Sx confused with postpartum changes (fatigue, weight gain, depression)
- Starts 3 - 6 months PP and lasts for 3 - 6 months
- Differential
  - Hashimoto’s disease (usually permanent)
  - lymphocytic hypophysitis and Sheehan’s (TSH elevated)
- Rx symptomatic with levothyroxine
- 50% recurrence in future pregnancies
7.2. Women known to be TPO-Ab+ should have TSH measured at 6–12 wk gestation and at 6 months postpartum, or as clinically indicated. USPSTF recommendation level: A; evidence, good (1|★★★★★).

7.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period after the episode of PPT. An annual TSH level should be performed in these women. USPSTF recommendation level: A; evidence, good (1|★★★★★).
Thyroid Enlargement in Pregnancy

Diffuse

- Normal increase in thyroid size (2x) is barely detectable clinically
- Any clinically detectable enlargement should be investigated
  - Check iodine intake (developing world)
  - Check TSH and FT4
Thyroid Enlargement in Pregnancy
Asymmetrical

- No radioisotope scanning
- Ultrasound not very useful for diagnosis
- Fine needle aspirate
  - Benign
  - Follicular neoplasm (indeterminate)
    - excision vs suppression (risk of carcinoma 20%)
  - Carcinoma (usually papillary)
    - thyroidectomy (may wait if close to term)
    - levothyroxin suppression postoperative
    - radioablation postpartum
5.1. Fine-needle aspiration (FNA) cytology should be performed for predominantly solid thyroid nodules larger than 1 cm discovered in pregnancy. Women with nodules 5 mm to 1 cm in size should be considered for FNA if they have a high-risk history or suspicious findings on ultrasound, and women with complex nodules 1.5 to 2 cm or larger should also receive an FNA. During the last weeks of pregnancy, FNA can reasonably be delayed until after delivery. Ultrasound-guided FNA is likely to have an advantage for maximizing adequate sampling. USPSTF recommendation level: B; evidence, fair (1|★★★★).
5.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women with a previously treated thyroid cancer, in those with an FNA positive for or suspicious for cancer, or in those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more than low-risk patients from a greater degree of TSH suppression. The free T₄ or total T₄ levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).
5.4. Radioactive iodine (RAI) with $^{131}$I should not be given to women who are breastfeeding or for at least 4 wk after nursing has ceased. USPSTF recommendation level: A; evidence, good (1★★★★★). Furthermore, pregnancy should be avoided for 6 months to 1 yr in women with thyroid cancer who receive therapeutic RAI doses to ensure stability of thyroid function and confirm remission of thyroid cancer. USPSTF recommendation level: B; evidence, fair (1★★★★★).
Hyperemesis Gravidarum

- TSH suppressed in 2/3 of patients
- Thyroid function tests only if either
  - Prior history
  - Thyroid enlargement
  - Other thyrotoxicosis signs or symptoms
  - Persists beyond 16 weeks
- Rx only if either
  - Lab abnormality does not improve
  - Dehydration and electrolyte imbalance
- If Rx: watch for maternal and fetal hypothyroidism