Thyroid Disease During Pregnancy: What's New in 2016?

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Case 1

- 32 year old lawyer reads online that mild hypothyroidism in pregnancy may have an impact on a child's intellectual capacity.
- Asks her PCP to check her TFTs 10 weeks after her last menstrual period.
- TSH 0.22 uU/ml (0.4- 4.2)
- Repeat TSH 0.15
  - FT4 1.2 ng/dL (0.93 - 1.7)
  - TT3 230 ng/dL (80 – 200)

ARS Question 1

- Which of the following statements are consistent with this clinical presentation?

1. This patient is likely in her 1st trimester.

2. This TSH level diagnoses hyperthyroidism.

3. A normal FT4 rules out hyperthyroidism.

4. This TT3 level diagnoses hyperthyroidism.

ATA Guidelines 2016
Recommendation 37

- When a suppressed serum TSH is detected in the first trimester (TSH less than the reference range), a medical history, PE, maternal FT4 or TT4 should be obtained.
- TSH receptor antibodies (TRAb) +/- TT3 may help in diagnosis and determination of etiology of the thyrotoxicosis.

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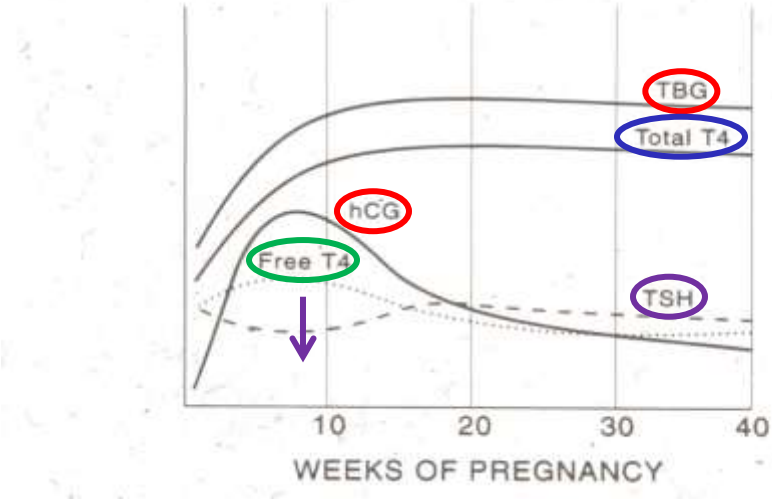
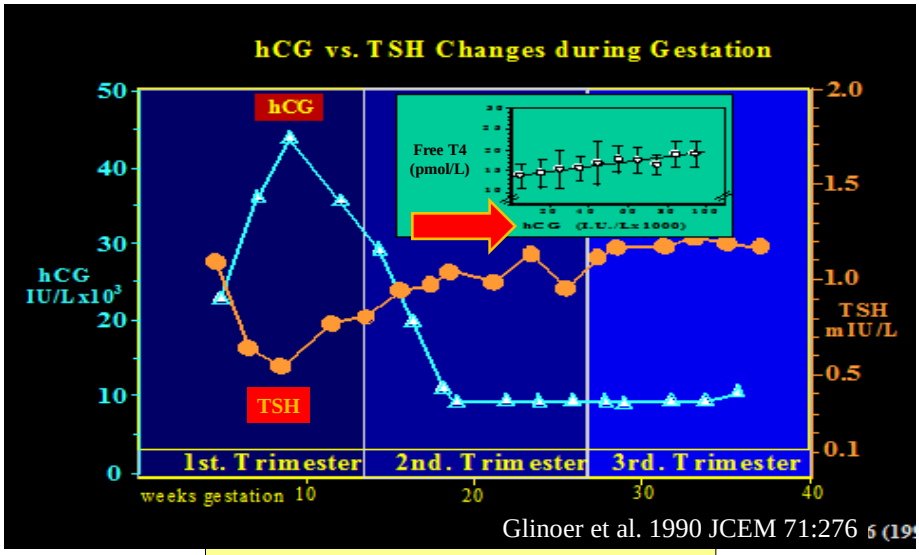
Maternal Thyroid Function: Pregnancy



Mandel SJ et al. 2005 Thyroid 15:44-53

hCG Stimulates Thyroid Activity



Glinoer et al. 1990 JCEM 71:276

Glinoer D 2010 www.thyroidmanager.org Ch. 14

Trimester-Specific TSH Ranges

Thyrotropin reference ranges in different populations

Reference	Population	Thyrotropin reference range (mIU/L) 1st trimester	2nd trimester	3rd trimester
Stagnaro-Green[8]	US*	0.1-2.5	0.2-3.0	0.3-3.0
De Groot[9]	US†	0.1-2.5	0.2-3.0	0.3-3.5
Yan[19]	Chinese	0.03-4.51	0.05-4.50	0.47-4.54
Li[20]	Chinese	0.14-4.87		
Marwaha[21]	Indian	0.6-5.0	0.44-5.78	0.74-5.7
Korevaar[22]	Mixed (Dutch, Moroccan, Turkish, Surinamese)	0.06-4.51		

*American Thyroid Association guideline recommendations.
†Endocrine Society guideline recommendations.

Negro & Stagnaro-Green BMJ 349 g4929.2014

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Recommendation 1

A. When possible, use trimester-specific TSH ranges, defined by local population data representative of a healthcare providers practice.

- Determinations should only include pregnant women without thyroid disease, optimal iodine intake and negative TPO ab status.

Strong Recommendation, Moderate quality evidence

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Recommendation 1

- **B.** When this is not feasible, reference ranges obtained from similar patient populations and performed using similar TSH assays can be substituted.
- **C.** If internal or transferable reference ranges are not available, the upper limit of TSH in non-pregnant patients (≈ 4.0 mU/l) should be used.

Strong recommendation, moderate quality evidence

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Recommendation 2

- The accuracy of serum **Free T4** measurement by the indirect analog immunoassays is **influenced** by pregnancy and also **varies** significantly by **manufacturer**.
- If measured in pregnant women, assay method specific and **trimester-specific** pregnancy **reference** ranges should be applied.

Strong recommendation, Moderate quality evidence

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Recommendation 3

- In lieu of measuring FT4, **total T4**, measurement (with a pregnancy adjusted reference range), is a highly **reliable** means of estimating hormone concentration during pregnancy.
- Accurate estimation of the free T4 concentration can be done by calculating a free thyroxine index.

Strong recommendation, Moderate quality evidence

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ATA Pregnancy Guidelines 2011

- **Recommendation 3**
  - Optimal method to assess FT4 is in dialysate or ultrafiltrate of serum by **LC/MS/MS**
    - Level A – USPSTF
- **Recommendation 4**
  - If LC/MS/MS **not available**, estimate FT4 by whatever method available (limitations)
  - **TSH more accurate** indication of thyroid status than any of the alternatives.
    - Level A - USPSTF

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Case 1

- Follow up TFT's @ 14 weeks
- TSH 0.62 uU/ml (0.4- 4.2)
- FT4 1.1 ng/dL (0.93 - 1.7)
- TT3 232 ng/dL (80 – 200)
  - FT3I wnl

ATA Guidelines 2016
Recommendation 39

- The appropriate management of abnormal maternal thyroid function 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, but beta-blockers may be used.

Strong recommendation, Moderate quality evidence

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Case 2

- A 28 year old woman consults with her PCP prior to stating her family.
- PMHx: S/P total thyroidectomy @ 14 years
  - Stage 1 (T1a[0.5 cm], N0, Mx) FV-PTC (NI)
  - Post operative hypothyroidism (LT4 100 mcg/d)
- Most recent neck US negative
  - TSH 4.2
  - Tg < 0.1 ng/Ml
  - Tg-ab < 20 IU/mL

ARS Question 2

What recommendations would you make to this patient as she prepares for pregnancy?

1. Restaging of the thyroid cancer is the priority.

2. Increase the LT4 dose to 125/d, recheck TSH prior to encouraging this patient to conceive.

3. Once cleared, no dose adjustments expected.

4. Stop LT4 as it not recommended in pregnancy.

ATA Guidelines 2016

Recommendation 93

- All patients seeking pregnancy, or newly pregnant should undergo clinical evaluation.
- If any of the following risk factors are identified, testing TSH is recommended.

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- Women at high risk of thyroid dysfunction
  - Hx or Sx of hyper or hypothyroidism
  - Thyroid antibody positivity or goiter
  - Hx H/N irradiation or prior thyroid surgery
  - Age > 30 years
  - Personal or FHx of DM 1 or other AI disease
  - Hx miscarriage, preterm delivery or infertility
  - Multiple prior pregnancies ($\geq$ 2)
  - Morbid obesity (BMI $\geq$ 40 kg/m2)
  - Amiodarone, Lithium or IV Contrast exposure
  - Residence in area of moderate to severe iodine deficiency

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Recommendation 93

- All patients seeking pregnancy, or newly pregnant should undergo clinical evaluation.
- If any of the following risk factors are identified, testing TSH is recommended.

- **TSH ≥ 10** should receive LT4 treatment
- **TSH > 2.5 and < 10** check TPO antibody
  - **TPO ab positive** women:
    - TSH > normal (SCHypo) LT4 **recommended**
    - TSH > 2.5 and upper normal **consider** LT4 Rx

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Recommendation 65

- ATA 2015 Excellent Response to treatment
  - No clinical, biochemical (LT4 Tg <0.2, Stim Tg <1), nor structural evidence of disease.
- US and Tg **monitoring** during pregnancy **not** required.

Strong recommendation, Moderate quality evidence

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TSH and Miscarriage Risk

- 55,501 individuals received 1st LT4 Rx
  - 2001-2009 in UK General Practice Database
- 7978 women of childbearing age (18-45 yrs.)
- 1031 with ≥ 6 month LT4 Rx pre-conception
- Main outcomes measured:
  - TSH
  - Miscarriage/ Delivery Status

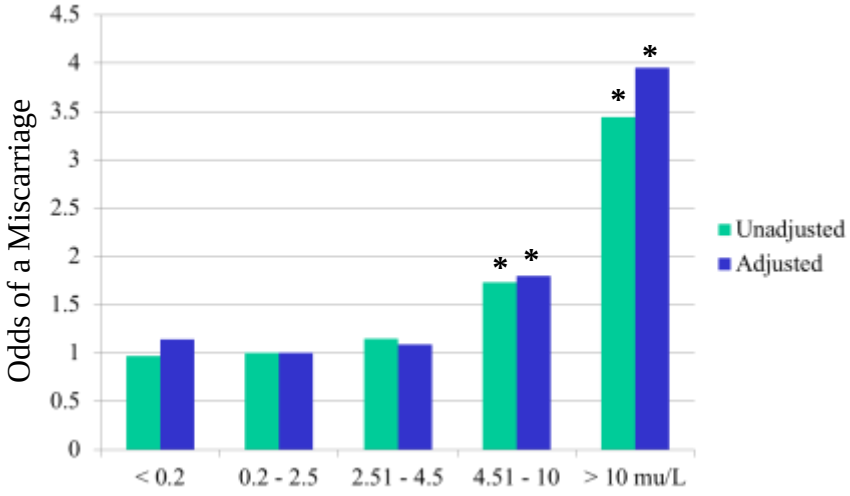
Taylor PN et al. JCEM 2014 99(10):3895-902

LT4 Rx Results

- 46% of LT4 treated patients 18-45 TSH > 2.5
- Among pregnant women:
  - 62.8% had 1st Trimester TSH > 2.5 mIu/L
    - 29.1% had TSH > 4.5 mIu/L
    - 7.41% had TSH > 10 mIu/L
  - Only 37.1% had TSH 0.2-2.5 as recommended
  - 6.5% had TSH <0.2

Taylor PN et al. JCEM 2014 99(10):3895-902

Odds of Miscarriage by 1st Trim TSH



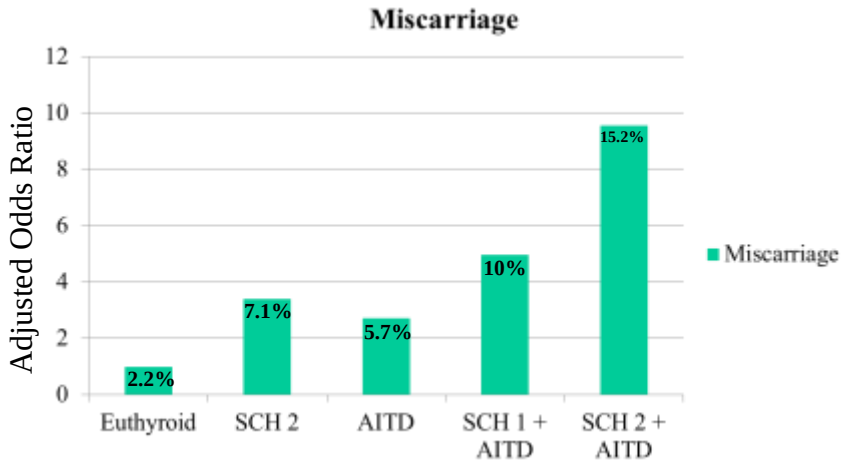
Taylor PN et al. JCEM 2014 99(10):3895-902

SCHypo & Thyroid Autoimmunity

- 3315 low risk women followed prospectively
- Initial TFTs drawn at 4-8 weeks gestation
- Clinical Classification based on results:
  - Euthyroid
  - Isolated SCHypo
    - SCHypo 1 (≥ 2.5 TSH <5.22 mIu/L)
    - SCHypo 2 (5.22 ≤ TSH < 10 mIu/L)
  - Isolated AITD (TPO &/or Tg-ab +)
  - SCH + TAI

Liu H et al. 2014 Thyroid 24(11):1642-1649

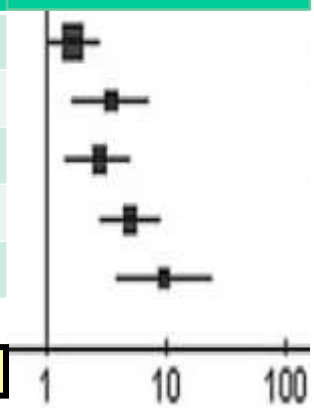
Miscarriage (Preg. loss < 20 weeks)



Liu H et al. 2014 Thyroid 24(11):1642-1649

SCHypo and Miscarriage

Group	Miscarriage	Odds Ratio (95% CI)
TSH 2.5-5.1	22/628	1.62 (0.96-2.73)
TSH 5.2-10	9/127	3.40 (1.62-7.17)
TAI only	13/227	2.17 (1.43-5.12)
TSH 2.5-5.1 + TAI	17/170	4.96 (2.76-8.90)
TSH 5.2-10 + TAI	6/34	9.56 (3.76-24.28)



Liu H et al. 2014 Thyroid 24(11):1642-1649

ATA Pregnancy Guidelines 2016

Recommendation 3

- Subclinical hypothyroidism in pregnancy should be approached as follows:

A. Levothyroxine therapy is **recommended** for:

– TPO ab positive women with TSH greater than the reference range (See recommendation 1)

Strong recommendation, Moderate quality evidence

– TPO ab negative with a TSH greater than 10.0 mIu/L.

Strong recommendation, Low quality evidence

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ATA Pregnancy Guidelines 2016

Recommendation 3

B. Levothyroxine therapy may be **considered** for:

– **TPO ab positive** women with **TSH** concentration **> 2.5 mIu/L** and the upper limit of the reference range.

Weak recommendation, Low quality evidence

– **TPO ab negative** women with **TSH** concentrations greater than the reference range though **< 10 mIu/L**.

Weak recommendation, Low quality evidence

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Recommendation 3

C. Levothyroxine is **not recommended** for:

– **TPO** ab **negative** women with **normal TSH**

- TSH within the pregnancy specific reference range, or
- TSH < 4.0 mIu/L if unavailable

Strong recommendation, Good quality evidence

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ATA pregnancy Guidelines 2016

- **TPO ab positive**
  - TSH > reference range — LT4 recommended
  - TSH > 2.5 < reference — LT4 considered
  - TSH ≤ 2.5 mIu/L — **NO** LT4
- **TPO ab negative**
  - TSH > 10 mIU/L — LT4 recommended
  - TSH > reference < 10 — LT4 considered
  - TSH in reference range — **NO** LT4

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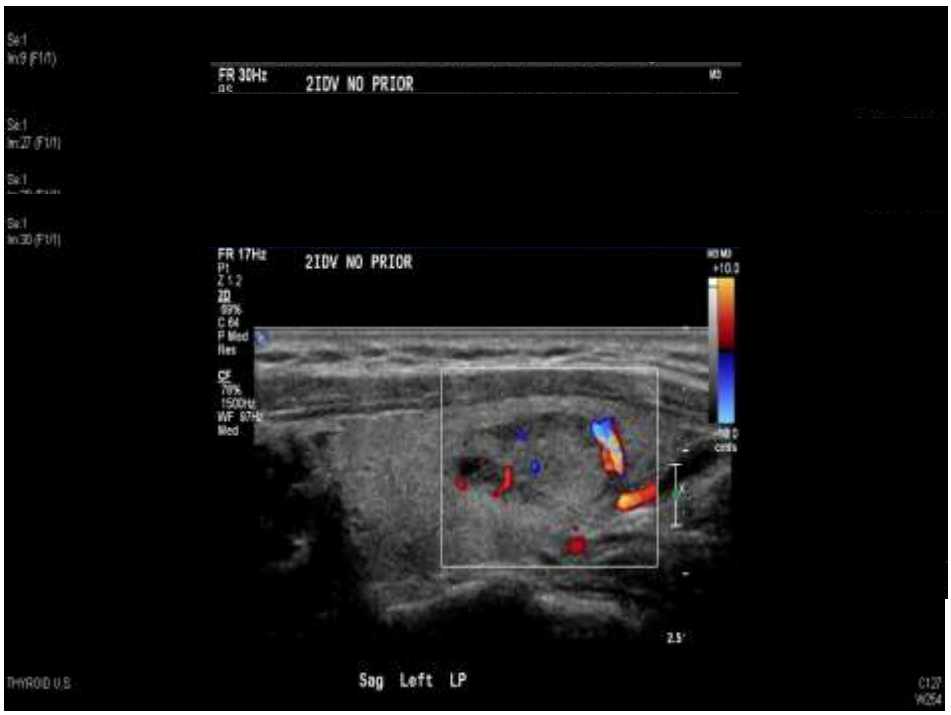
Case 3

- 31 year old G1, P0 (12 weeks gestation)
- PMHx: Negative
- FHx: Mother and M-G mother Breast cancer
- ROS: Fatigue, dry flaky right upper eyelid
- PE: VS wnl, Neck + thyromegaly, L > R
- Labs: TSH 0.63, FT4 1.3
- US: 1.6 X 0.8 X 1.1 cm LLL thyroid nodule



ARS Question 3

Which of the following is your next best move?

A. Reassure her that this lesion is too small to deserve any further attention at this time.

B. Proceed with FNA and book surgery as soon as possible if result is indeterminate or PTC.

C. Plan an FNA with solely with genetic testing as this is the preferred approach in 2016.

D. Proceed with FNA if she desires, after explaining that surgery for papillary thyroid cancer could likely be deferred until she delivers her baby.

Thyroid Malignancy in Pregnancy

- Prevalence estimates:
  - Retrospective 3 referral centers
    - 12% (Marley EF et al. 1997 Diag Cytopath 16:122)
    - 15% (Tan GH et al. 1996 Arch Intern Med 156:2317)
    - 43% (Rosen IB et al. 1985 Surgery 98:1135)
  - Prospective study of pregnant women
    - 0% malignant (Kung AW 2002 JCEM 87:1010)
  - Population/ Cancer Registry linkage
    - 14.4/100,000 (Smith LH 2003 A J Ob-Gyn 189:1128)
      - 3.3/100K before, 0.3/100K @ and 10.8/100K $\leq$ 1 yr. delivery

History and PE

- Family History
  - Thyroid disease
  - Familial Medullary, MEN2
  - Familial PTC, Familial polyposis coli
- Previous XRT during childhood
- Rapid nodule growth, cough or dysphonia
- Palpable cervical LNs

Stagnaro-Green A et al. Thyroid 2011 21:1081-1125

Fine Needle Aspiration in Pregnancy

- Recommendation 48: Level A
  - FNA Appears to be safe in any trimester
- Recommendation 49: Level I
  - Cytologic diagnoses appear accurate
    - **Tan GH et al. 1996 Arch Intern Med. 156:2317**
    - **Marley EF et al. 1997 Diagn Cytopathol 16:122**
  - FNA of nodules thought to be benign by U/S criteria may be deferred until after delivery

Stagnaro-Green A et al. Thyroid 2011 21:1081-1125

Recommendation 30

- A. FNA of clinically relevant thyroid nodules (see Rec 10) should be performed in euthyroid and hypothyroid pregnant women.
  - **Strong recommendation, Moderate-quality evidence**
- B. For women with suppressed serum TSH beyond 16 weeks gestation, FNA may be deferred until after pregnancy and cessation of lactation. A radionuclide scan can then be performed to evaluate nodule function if the TSH remains suppressed.
  - **Strong recommendation, Moderate-quality evidence**

Haugen BR et al. Thyroid 2016 26(1):1-133

ATA Guidelines 2016
Recommendation 58

- Thyroid nodule FNA is generally recommended for newly detected nodules in pregnant women with non-suppressed TSH.
- The nodule's sonographic pattern determines which nodule requires FNA.
- Assessment of cancer risk or patient preference determines the timing of FNA during pregnancy.

Strong recommendation, Moderate quality evidence

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Thyroid Ultrasound FNA Indications

- Nodules ≥ 10 mm with US suspicion category:
  - **High** based on US appearance
  - **Intermediate** based on US appearance
- Nodules ≥ 1.5 cm with US suspicion category:
  - **Low** based on US appearance
- Nodules ≥ 2 cm if very low suspicion
- FNA is **not required** for nodules:
  - NOT meeting above criteria
  - Purely cystic nodules

Recommendation 8
I-III, A-F

Haugen BR et al. Thyroid 2016 26(1):1-133

What do Endocrinologists Do?

- 22 year old, 1.5 cm nodule, 8th week pregnancy
  - TSH normal, no suspicious US findings
- 821 respondents:
  - 36% would sample the nodule in the 1st trimester
  - 11.3% would wait on FNA until second trimester
  - 18.3% would FNA only if nodule grew
  - 34.1% would defer the FNA until after pregnancy

52.4 %

Burch HB et al. 2016 JCEM doi: 10.1210/jc.2016-1155

Case 3: FNA, left middle lobe

- **DIAGNOSIS:** ATYPIA OF UNDETERMINED SIGNIFICANCE.
- Cellular aspirate, follicular cells with enlarged and crowded nuclei with no nuclear membrane irregularity.
- There is a prominent component of a single cell population, and occasional lymphoid tangles suggesting a background of lymphocytic thyroiditis. Some follicular cells with microfollicular architecture. Colloid is also seen.
- Cells immunoreactive for TTF-1 and negative for calcitonin, chromogranin and synaptophysin.
- Thyroglobulin shows high background staining**.**

ATA Pregnancy Guidelines 2016 **Recommendation 57-58**

- **57.** Pregnancy does not alter surveillance strategies in nodules with **benign** FNA.

  Strong recommendation, Moderate quality evidence

- **58.** Indeterminate FNA without suspicious LNs on US or metastatic disease, DEFER surgery to PP.

  Strong recommendation, Moderate quality evidence

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ATA Guidelines 2016
Recommendation 59-60

- 59. Molecular testing of indeterminate nodules is NOT recommended during pregnancy.

  Strong recommendation, Moderate quality evidence

- 60. If there is suspicion of aggressive behavior in a patient with indeterminate FNA, surgery may be considered.

  No recommendation, Insufficient evidence

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ATA Pregnancy Guidelines 2016
Recommendation 62

- The impact of pregnancy on newly diagnosed medullary or anaplastic thyroid cancer is unknown.
- **Delay** in treatment is **likely** to **adversely** impact **outcome**.
- Surgery should be strongly considered following assessment of clinical factors.

  Strong recommendation, Low quality evidence

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Case 3 Outcomes

- Re-FNA for molecular testing
  - Indeterminate for malignancy, follicular lesion with some features suggestive of but not diagnostic for papillary thyroid carcinoma.
    - Cellular aspirate, nuclear enlargement, powdery chromatin, small nucleoli and occasional nuclear grooves.
- Further outcomes pending

Optimal Timing of Surgery in Pregnancy

- Surgery **after delivery** recommended **for most** patients with non-aggressive DTC.
- When indicated, surgery during pregnancy best performed during the **second trimester**.
- When indicated, surgery should be performed by an experienced, **high volume** thyroid surgeon.

Uruno T et al. W J Surg 2014; 38:704-708

Goodwin TM 1995 Endo Metab Clin NA 24:41-47

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