Thyroid Disease in Pregnancy: A 2022 Update

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Disclosures

- Co-Chair, planned update to the American Thyroid Association thyroid and pregnancy guidelines (in progress)
- Board of Directors, American Thyroid Association

Learning Objectives

- Describe the changes in thyroid physiology that occur in pregnancy.
- Review the available evidence of the risks of maternal hypothyroidism and/or thyroid antibody positivity during pregnancy.
- Understand the challenges of the diagnostic workup and treatment of hyperthyroidism in pregnancy.
- Discuss the current understanding of the associations between pregnancy and thyroid cancer.
- Summarize the risks and benefits of longterm therapies for thyroid cancer during pregnancy.

Outline

- Maternal hypothyroidism
- Maternal thyroid autoimmunity
- Maternal hyperthyroidism
- Thyroid nodules and thyroid cancer in pregnancy

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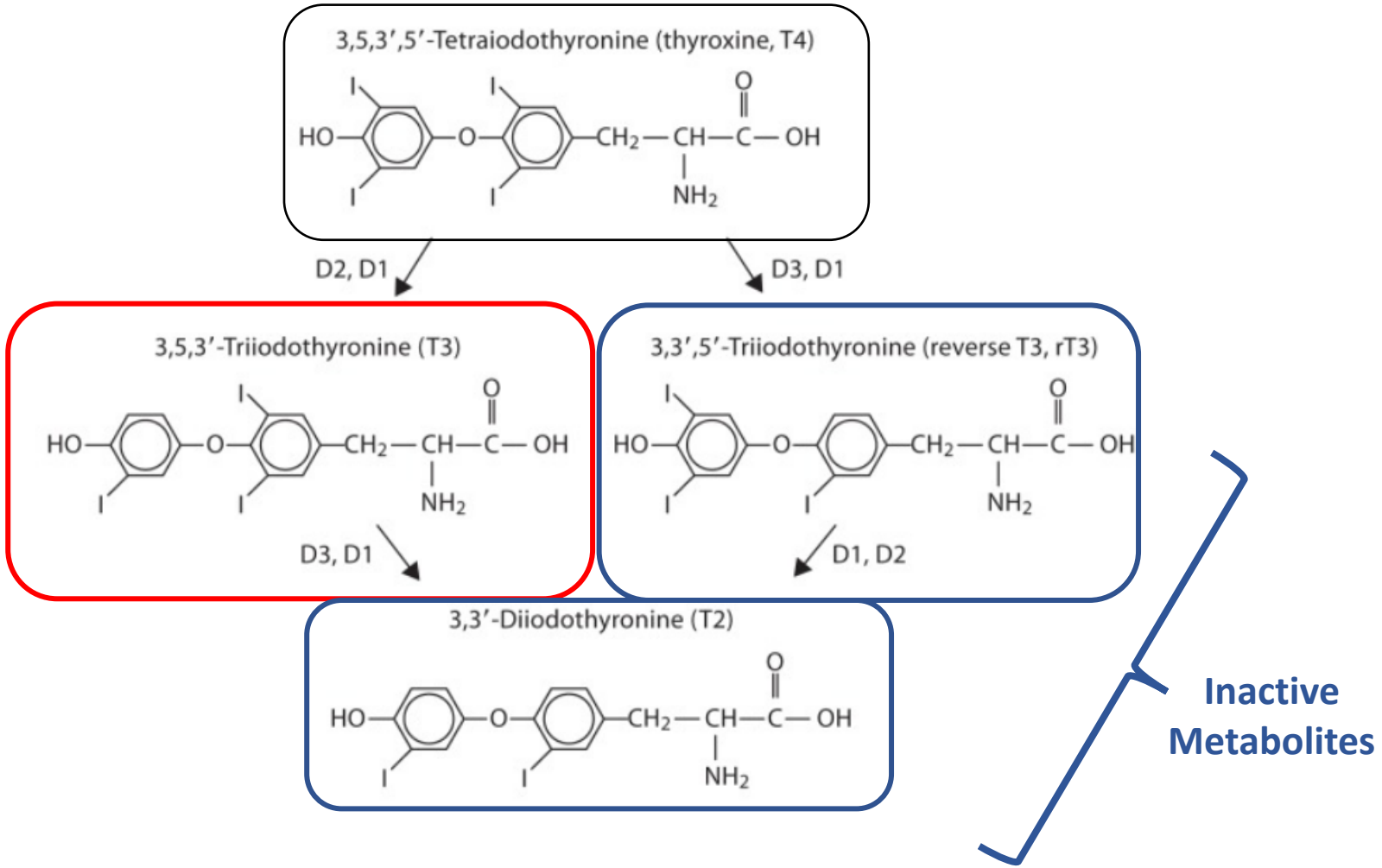
- **Maternal hypothyroidism**
- **Maternal thyroid autoimmunity**
- Maternal hyperthyroidism
- Thyroid nodules and thyroid cancer in pregnancy

Deiodination of Thyroxine (T4)

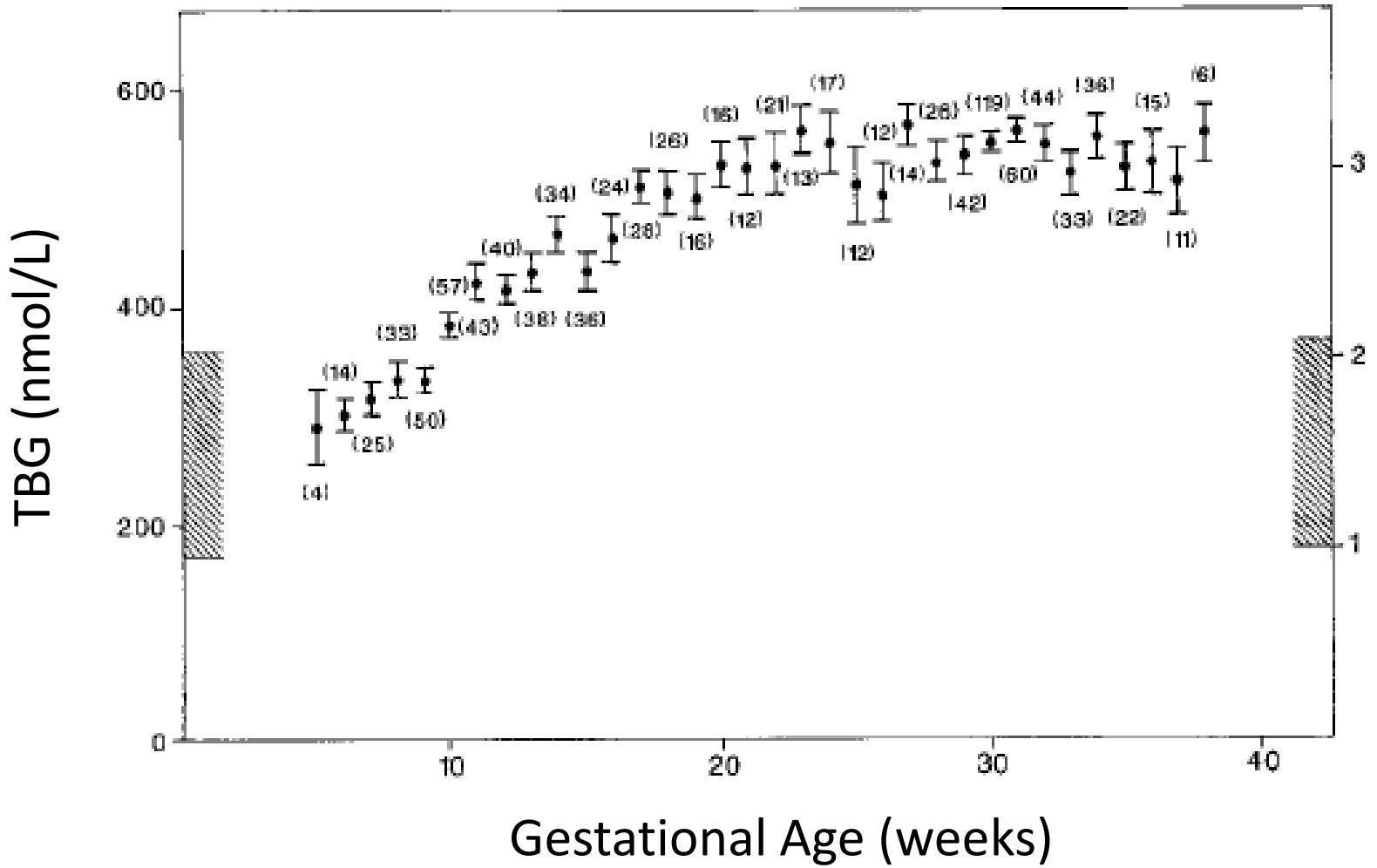


Larsen PR, Zavacki AM. The role of the iodothyronine deiodinases in the physiology and pathophysiology of thyroid hormone action. Eur Thyroid J 2012;1(4):232-242.

Most Circulating Thyroid Hormone is Protein-Bound

	% Distributions of Bound TH	% Free TH
T4-TBG	75	
T4-Albumin	10	0.03
T4-Transthyretin	15	
T3-TBG	75	0.30
T3-Albumin	25	

Serum Thyroid Binding Globulin (TBG) Doubles During Pregnancy



Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997 Jun;18(3):404-33.

Reasons for Increased Maternal Thyroid Hormone Needs in Pregnancy

- Increased TBG concentrations (due to increased E_2)
    - Glycosylation leads to ↓ hepatic clearance
- Increased T3 and T4 inactivation by placental, fetal, and uterine D3
- Increased plasma volume of T4 distribution
- Placental transfer of T4 to the fetus (minimal amount)

Chen AX, Leung AM, Korevaar TIM. Thyroid Function and Conception. N Engl J Med. 2019 Jul 11;381(2):178-181.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Thyroid Function and Conception

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Woman Trying to Conceive

Angela X. Chen, M.B., B.S., M.P.H.

Ms. Thompson is a 31-year-old woman who has been trying to conceive for the past 12 months and comes to see you, her primary care physician. One month ago, she had a miscarriage at 7 weeks of gestation. She has not had any other pregnancies.

Ms. Thompson has always been healthy; she has no significant medical history. Her only regular medication is a prenatal multivitamin, which she has been taking regularly for the past 12 months. Before that, she had used the combined estrogen–progesterone oral contraceptive pill for several years. Since she discontinued the contraceptive pill, her menses have been regular, with a 28-day cycle.

Her family history is significant for autoim-

0.5 to 4.0) and the free thyroxine (T_4) concentration is 1.1 ng per deciliter (14 pmol per liter; normal range, 0.86 to 1.9 ng per deciliter [11 to 24 pmol per liter]). However, the test for thyroid peroxidase antibodies is positive (78 IU per milliliter [normal range, <35)

Ms. Thompson has read that changes in thyroid function can affect a woman's chances of having a successful pregnancy. Given the results of her tests, she is interested in your recommendation as to whether she should begin treatment with levothyroxine to increase her chances of conceiving.

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, published guidelines, and other information sources.

A Case

- 31 year old woman, trying to conceive for the past year
- No significant medical history
- Only medication is a prenatal multivitamin
- One month ago:
  - Miscarriage at 7 weeks gestation
  - No prior pregnancies
- Family history significant for autoimmune disease
  - Brother: T1DM
  - Maternal uncle: Hashimoto's thyroiditis
- Serum TSH **3.2** (reference, 0.5-4.0), free T4 1.1 (reference, 0.86-1.9)
- Serum TPO Ab **78** IU/mL (normal, <35)

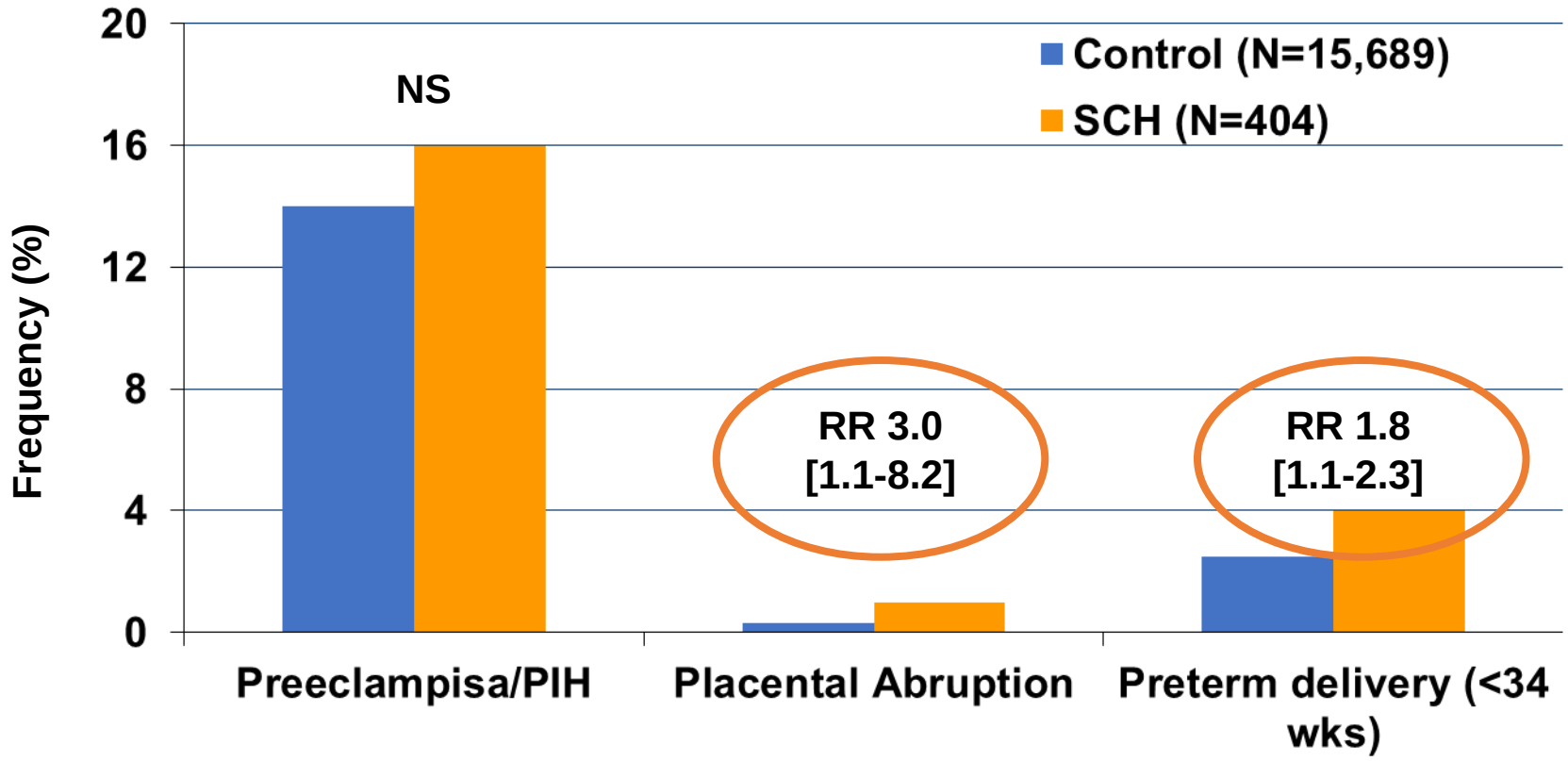
Would you recommend starting levothyroxine?

Chen AX, Leung AM, Korevaar TIM. Thyroid Function and Conception. N Engl J Med. 2019 Jul 11;381(2):178-181.

How Common is Hypothyroidism in Pregnancy?

Region	Prevalence	n	TSH threshold	Reference
Maine, USA	2.2%	9,403	>6 mIU/L	Allan et al. *J Med Screen* 2000
Texas, USA	2.3%	25,756	>97.5 th percentile	Casey et al. *Obstet Gynecol* 2005
China	4.6%	8,012	Trimester-specific TSH result	Chen et al. *PLoS One* 2014
Spain	16.6%	2,509	Trimester-specific TSH result	Diguez et al. *Clin Endocrinol (Oxf)* 2014

Subclinical Hypothyroidism (SCH) and Adverse Pregnancy Outcomes



Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005 Feb;105(2):239-45.

Consequences of Maternal Hypothyroidism During Pregnancy

Obstetric Complications

- Miscarriage
- Placental abruption
- Preterm delivery

Neonatal Complications

- Low birth weight / small for gestational age (SGA)
- Neonatal admissions to the NICU
- Neonatal respiratory distress syndrome
- Infant neurocognition

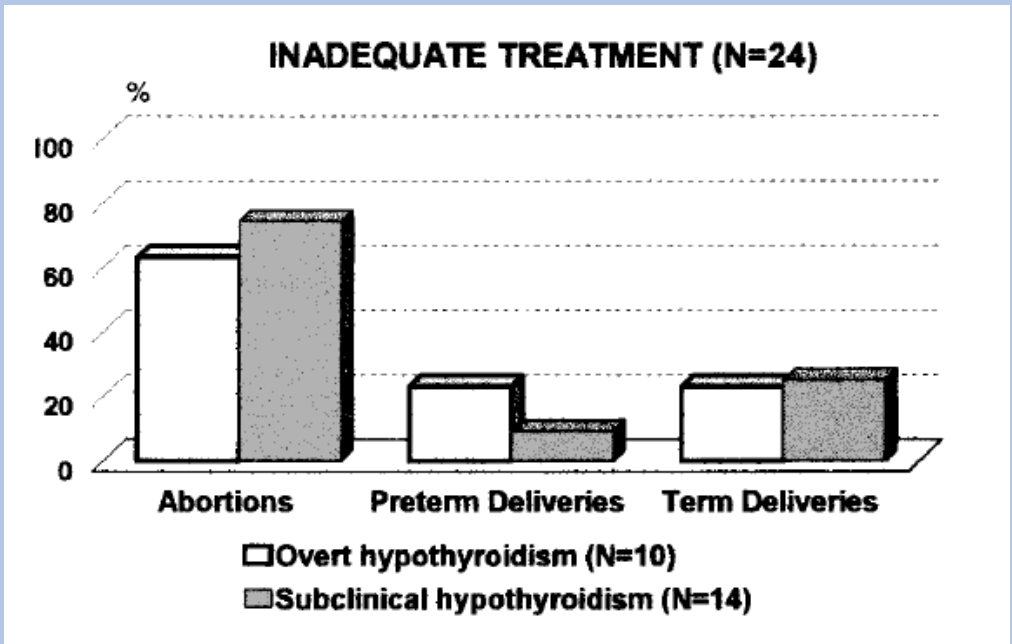
  - Verbal and nonverbal cognitive delays at 18-30 months

  - Decreased IQ at 7-9 years

Created by Oksana Latysheva from the Noun Project

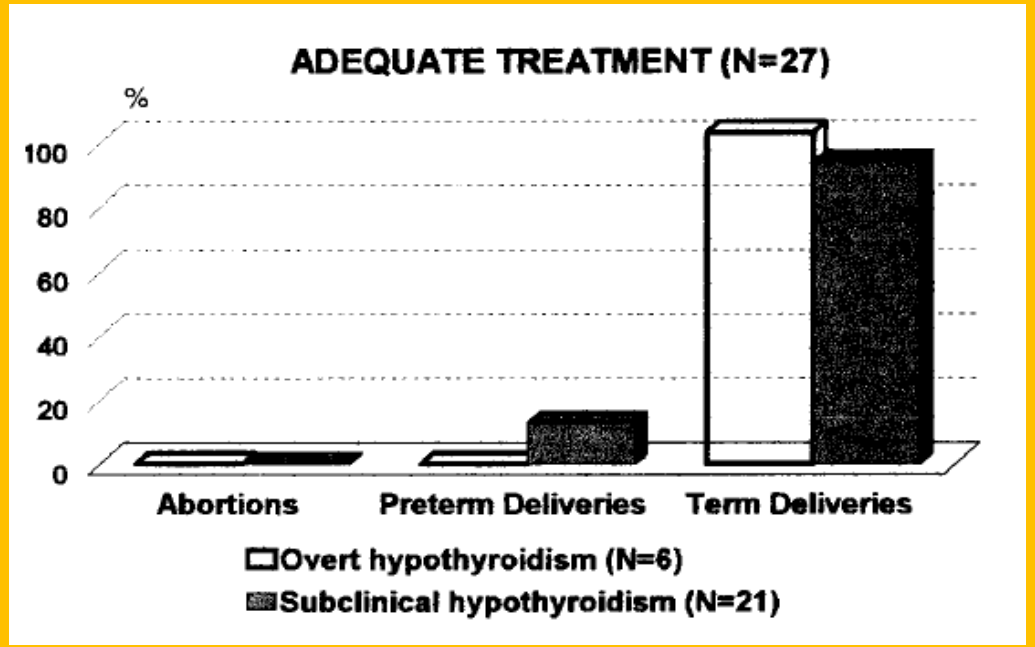
Haddow JE et al. *J Clin Endocrinol Metab* 1999
Casey B et al. *Obstet Gynecol* 2005
Negro R et al. *J Clin Endocrinol Metab* 2010
Heinrechs J et al. *J Clin Endocrinol Metab* 2010
Medici M et al. *J Clin Endocrinol Metab* 2012

Obstetric Benefits of Treating Maternal Hypothyroidism



Untreated maternal hypothyroidism:

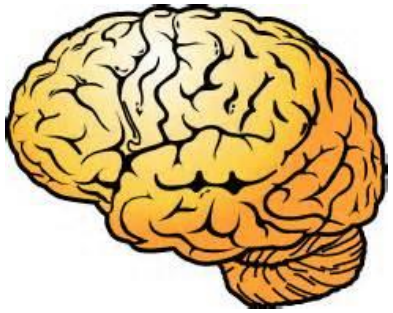
- Relatively high rate of abortions and preterm deliveries
- Relatively low rate of term deliveries



Correction of maternal hypothyroidism:

- Decreases prevalence spontaneous abortions and preterm deliveries
- Increases prevalence of term deliveries

Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002 Jan;12(1):63-8.



Importance of Normal Thyroid Function for Brain Development

Prenatal neocortical neurogenesis [1]
Growth of subventricular and subgranular zones [2-5]
Cell migration in cerebral cortex, hippocampus, cerebellum [6]
Axonal myelination [7]
Axon and dendrite formation [1]
Granule and other cerebellar cell proliferation; granule cell migration to intergeniculate leaflet; Purkinje cell maturation [8]
Postnatal neurogenesis [9]

[1] Stenzel D et al. *Front Neuroanat* 2013
[2] DeSouza LA et al. *Mol Cell Neurosci* 2005
[3] Ambrogini P et al. *Neuroendocrinology* 2005
[4] Montero-Pedrazuela A et al. *Mol Psychiatry* 2006
[5] Lemkine GF et al. *FASEB J* 2005
[6] Auso E et al. *Endocrinology* 2004
[7] Noguchi T et al. *Neurochem* 1984
[8] Zoeller RT et al. *J Neuroendocrinol* 2004
[9] Ahmed OM et al. *Int J Dev Neurosci* 2008

Haddow Study:
Maternal Hypothyroidism and Childhood IQ

- Study cohort: >25,000 women with available banked sera
- There were 62 samples with maternal TSH >98%ile (~8-100 mIU/L), compared with 125 matched euthyroid controls
- Mother's offspring (7-9 yrs old) tested for 15 areas of intelligence, reading, attention, language, others

Conclusion: Children of hypothyroid mothers had **lower IQ (-4 points)** than controls

- The 48 children of <u>untreated</u> hypothyroid women had even lower IQ (-7 points) lower than controls

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999 Aug 19;341(8):549-55.

Professional Society Recommendations for Thyroid Function Screening During Pregnancy

- Insufficient evidence for routine screening in pregnancy (ACOG, 2015)
- Universal screening in pregnancy (including in assisted reproduction) not recommended (AACE, 2012)
- Case-finding recommended only in high-risk pregnant women (Endocrine Society, 2012)
- Insufficient evidence to universal screening in preconception or pregnancy (ATA, 2017)
  - Exception is presence of risk factors

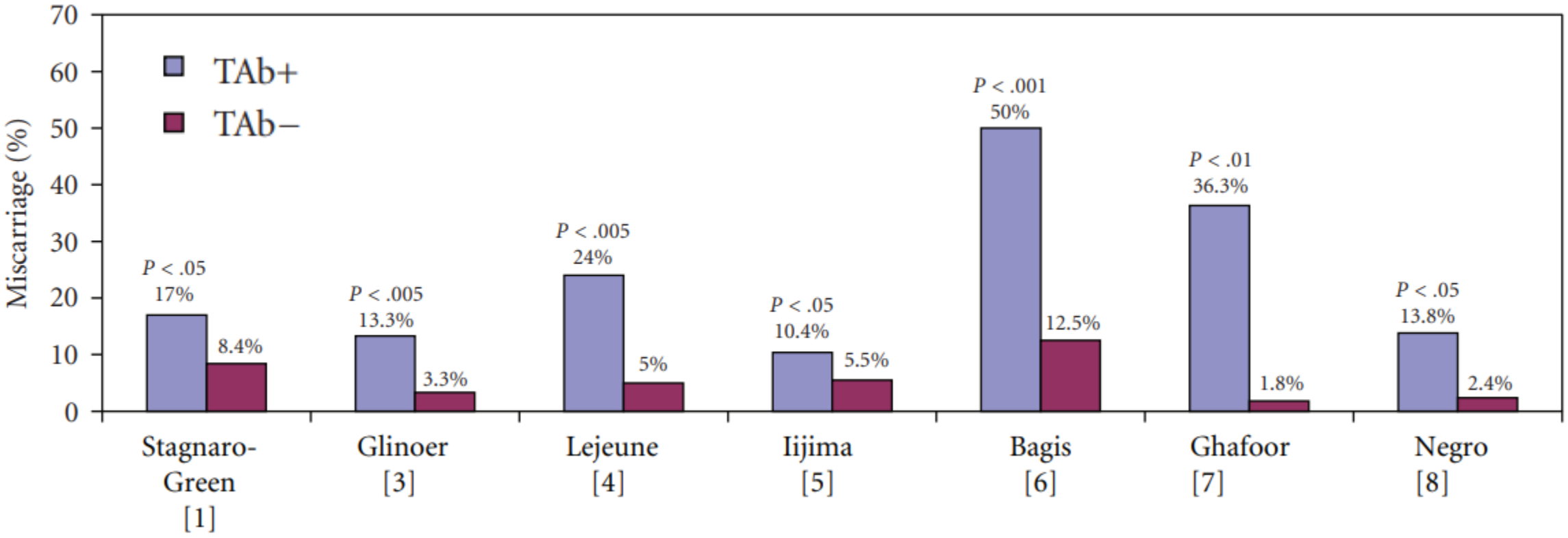
ACOG The American College of Obstetricians and Gynecologists
Women's Health Care Physicians

AACE

The Endocrine Society

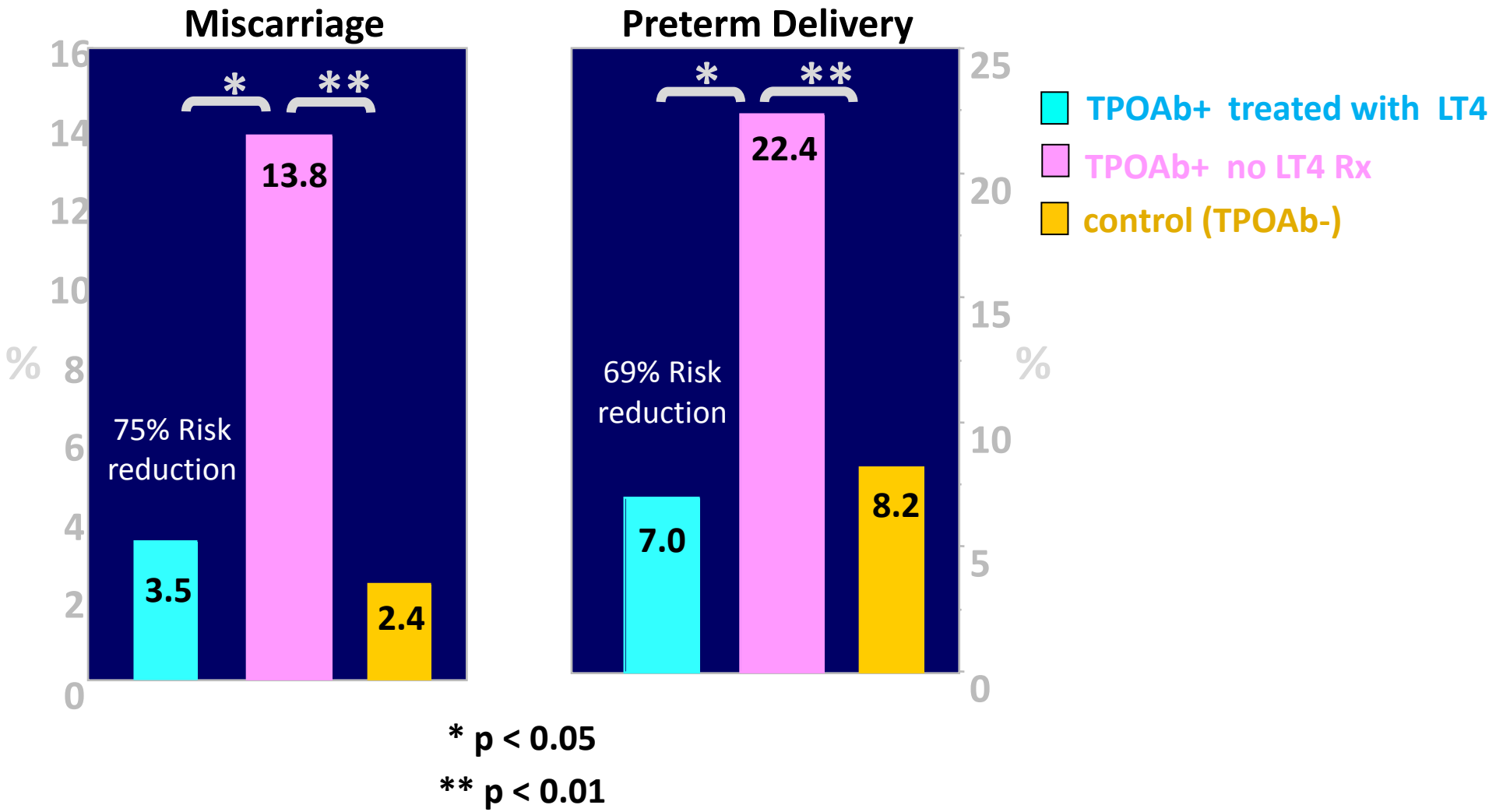
American Thyroid Association
ATA | Founded 1923

Maternal Thyroid Antibodies and Spontaneous Miscarriage



Stagnaro-Green A. Thyroid antibodies and miscarriage: where are we at a generation later? J Thyroid Res. 2011;2011:841949.

LT4 Benefits in Euthyroid TPOAb+ Pregnant Women



*** p < 0.05**

**** p < 0.01**

Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006 Jul;91(7):2587-91.

TABLET Trial: Levothyroxine for Euthyroid TPO Ab(+) Women

- Double-blind placebo-controlled trial, 49 centers in the U.K.
- 50 mcg LT4 (n=952) versus placebo (n=476)

	LT4	Placebo	RR (95% CI)
Live birth ≥34 weeks GA	37.4%	37.9%	0.97 (0.83-1.14)
Pregnancy at 7 weeks GA	89.1%	90.5%	0.98 (0.93-1.04)
Miscarriage	28.2%	29.6%	0.95 (0.73-1.23)

Conclusion: Levothyroxine treatment in euthyroid TPO Ab(+) pregnant women did not improve birth rates and pregnancy outcomes compared to placebo

Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, Bender-Atik R, Agrawal R, Bhatia K, Edi-Osagie E, Ghobara T, Gupta P, Jurkovic D, Khalaf Y, MacLean M, McCabe C, Mulbagal K, Nunes N, Overton C, Quenby S, Rai R, Raine-Fenning N, Robinson L, Ross J, Sizer A, Small R, Tan A, Underwood M, Kilby MD, Boelaert K, Daniels J, Thangaratinam S, Chan SY, Coomarasamy A. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. N Engl J Med. 2019 Apr 4;380(14):1316-1325.

CATS (Controlled Antenatal Thyroid Screening Study)

- Randomized trial of TFT screening in pregnant women before 15 weeks gestation
- Nearly 22,000 women in U.K. and Italy studied:
  - Sera either screened immediately or stored until after delivery
  - For abnormal screened results, LT4 initiated
- Childhood cognition tested at 3 years age

Conclusion: No difference in childhood IQ between screened and unscreened pregnant women

Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012 Feb 9;366(6):493-501.

When to Treat Hypothyroid Pregnant Women

- Treatment of **overt hypothyroidism** is recommended during pregnancy.
- Pregnant women with **TSH concentrations >2.5 mU/L** should be evaluated for TPO Ab status:

TPO Ab	TSH	Recommendation
TPO (+)	> 4.0 (1st trimester) or > 5.0 (2nd/3rd trimesters)	Treat
TPO (-)	>10	Treat

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

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TPO Ab	TSH	Recommendation
TPO (+)	> 4.0 (1st trimester) or > 5.0 (2nd/3rd trimesters)	Treat
TPO (-)	>10	Treat
TPO (+)	2.5-4.0 (1st trimester) or 2.5-5.0 (2nd/3rd trimesters)	Consider treatment
TPO (-)	4.0-10.0	Consider treatment
TPO (-)	< 4.0	No treatment

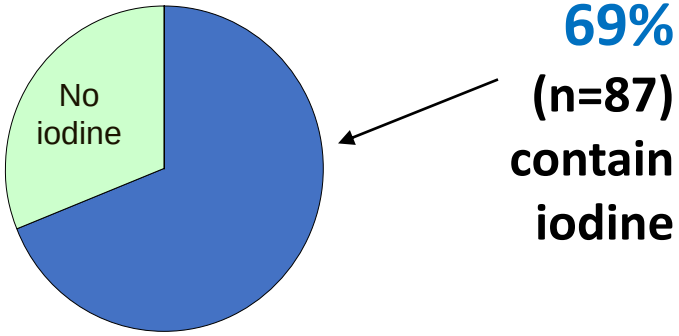
Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

Thyroid Hormone Replacement in Pregnancy

- The recommended treatment of maternal hypothyroidism is administration of **oral levothyroxine (LT4)**.
- Avoid any T3-containing preparations such as synthetic T3 or desiccated thyroid extract.
- Women with overt and subclinical hypothyroidism (treated or untreated) or those at risk for hypothyroidism:
  - Euthyroid but TPOAb-positive or TgAb-positive
  - Post-hemithyroidectomy
  - History of RAI receipt
- Monitor with serum TSH **every 4 weeks until midgestation** and **at least once near 30 weeks gestation.**

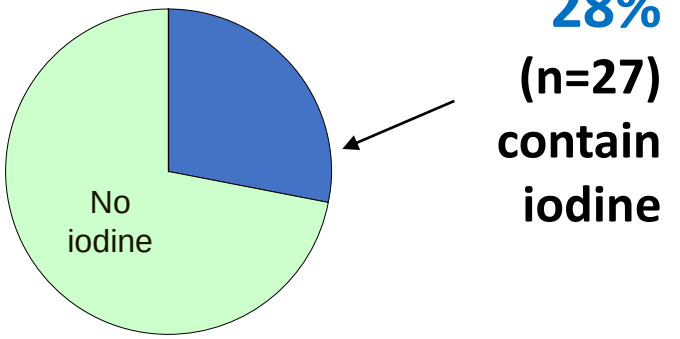
Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

Proportion of U.S. Prenatal Multivitamins Containing Iodine



69%
(n=87)
contain
iodine

Non-prescription prenatal multivitamins (n = 127)



28%
(n=27)
contain
iodine

Prescription prenatal multivitamins (n = 96)

Leung AM, Pearce EN, Braverman LE. Iodine content of prenatal multivitamins in the United States. N Engl J Med. 2009 Feb 26;360(9):939-40.

American Thyroid Association Recommendations for Iodine Intake during Preconception, Pregnancy, and Lactation

- All women during the preconception period, pregnancy, and lactation are advised to take an iodine-containing **prenatal MVI of 150 mcg daily**, preferably those derived from potassium iodide

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

Outline

- Maternal hypothyroidism
- Maternal thyroid autoimmunity
- **Maternal hyperthyroidism**
- Thyroid nodules and thyroid cancer in pregnancy

Goal Serum TSH Levels in Pregnancy

First trimester:

bHCG

Lower limit	0.4 mIU/L lower than the lab's normal range
Upper limit	4.0 mIU/L if TPO (-) 2.5 mIU/L if TPO (+)

Second and third trimesters:

Lower limit	Lab's normal range
Upper limit	Lab's normal range

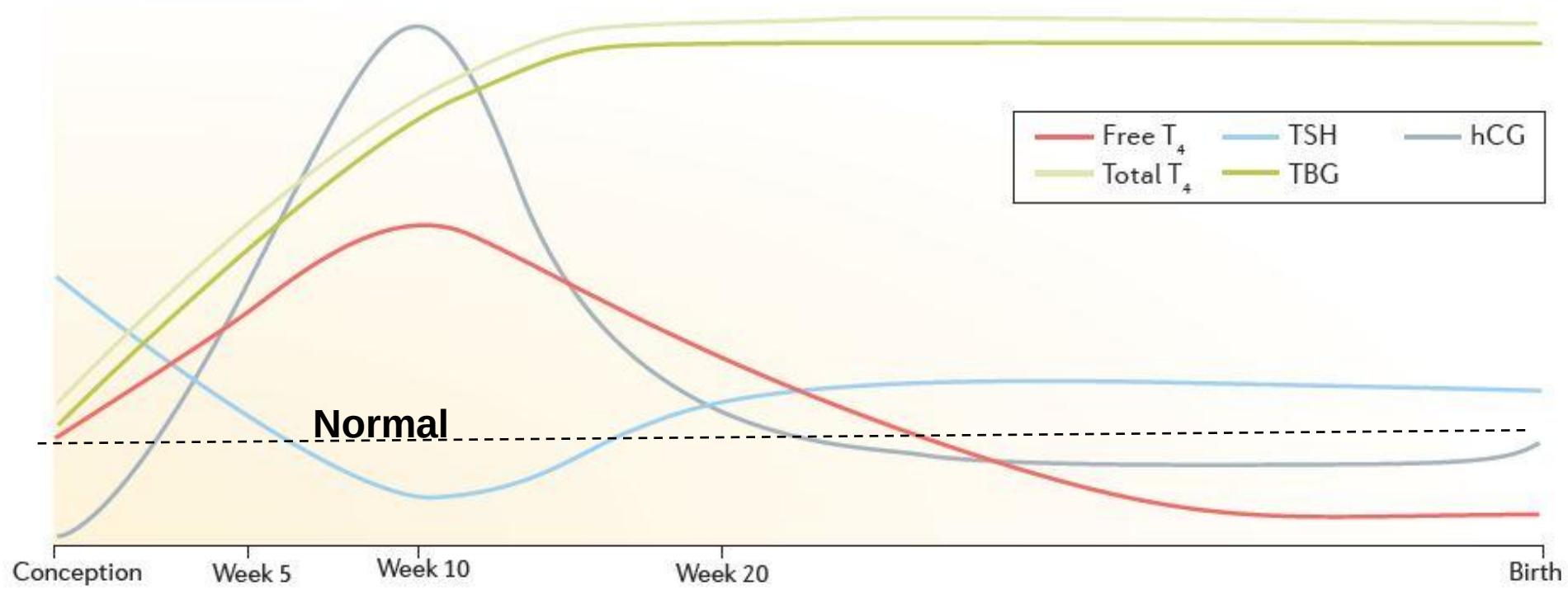
Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

Challenges of a Decreased TSH in Early Pregnancy

- Medical history and physical examination are key
- Differential diagnosis:
  - Gestational thyrotoxicosis
  - New onset hyperthyroidism
- Radioiodine uptake are unable to be performed in pregnancy

Labadzhyan A, Brent GA, Hershman JM, Leung AM. Thyrotoxicosis of Pregnancy. J Clin Transl Endocrinol. 2014 Dec 1;1(4):140-144.

Serum Thyroid Function Tests During Pregnancy



- bhCG has a mild stimulatory effect on the TSH receptor in thyroid tissues
- Thus in the first trimester:
  - Mild increase of serum FT4 levels
  - TSH is inverse related to rising hCG levels

Adapted from Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nature Reviews Endocrinology* 2017;13:610-622.

Persistent Risks of Treated Graves' Disease

Circulating TSI antibodies can remain positive several years later

(remember in your pregnant patient)

Slide courtesy of Lewis E. Braverman

Anti-Thyroid Drug Associated Embryopathies

First identified in 1972 as choanal atresia (blockage of the rear nasal passage due to abnormal bony recanalization)

Hypothelia (absence of breast/nipples)

Broad nasal bridge
Prominent epicanthic folds
Short upslanting palpebral fissures
Hypoplastic alae nasi (lateral nose atrophy)

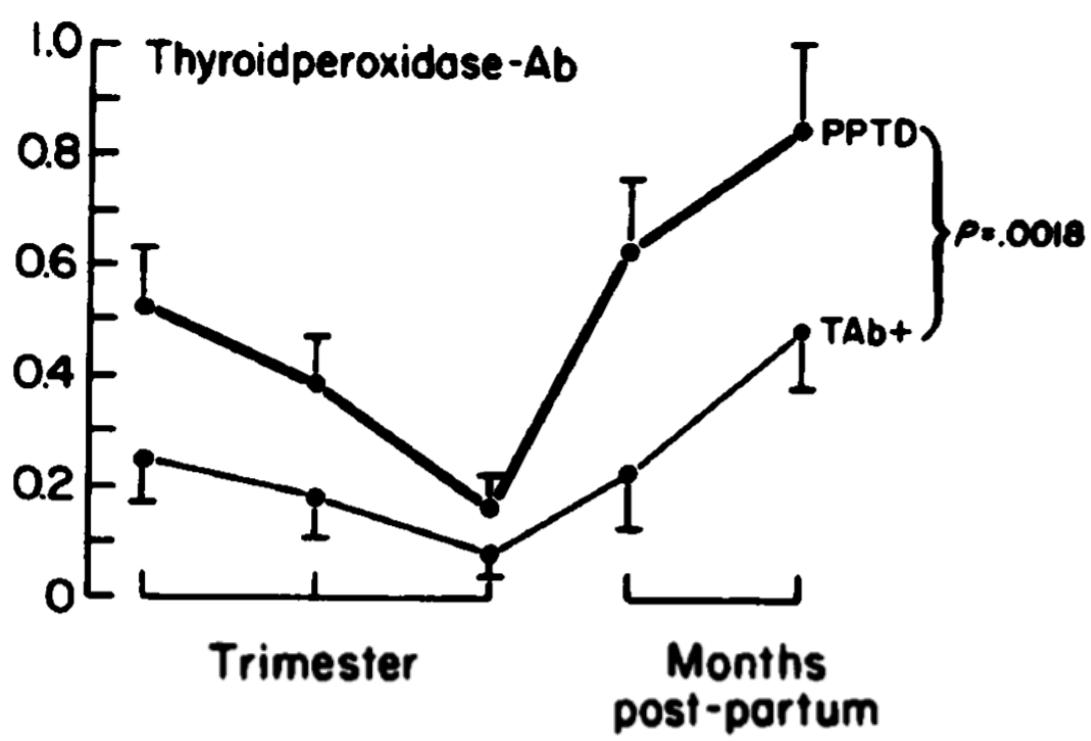
High, broad nasal bridge
Upward slanting palpebral fissures
Micrognathia (mandibular hypoplasia)

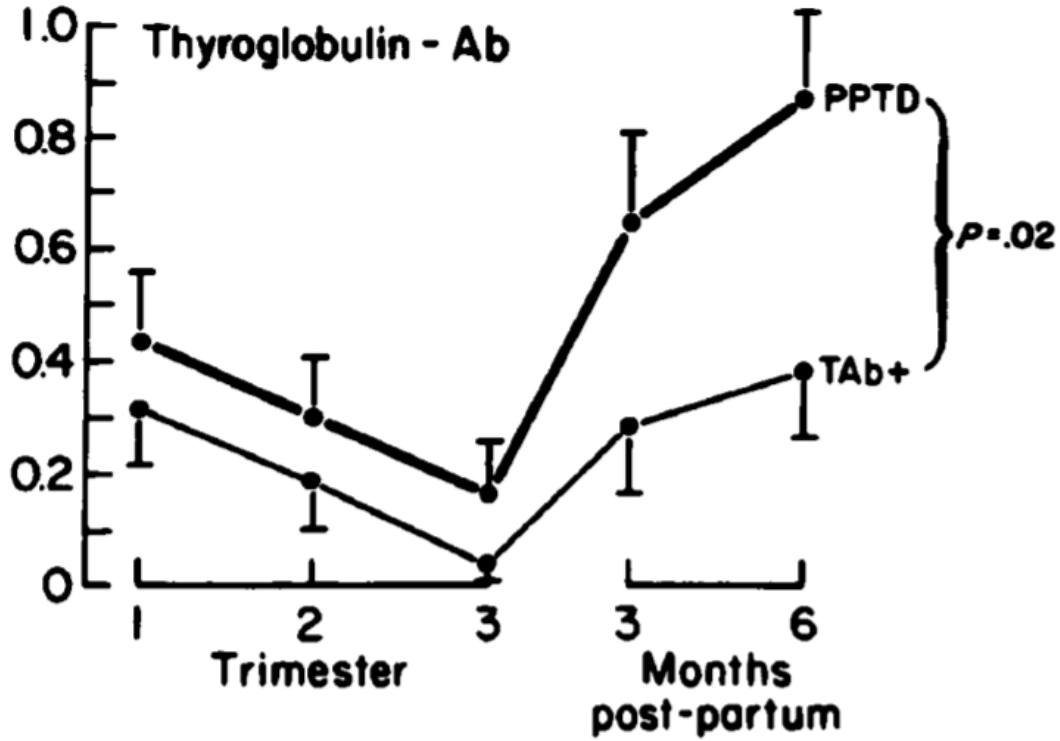
Aplasia cutis (localized absence of skin)

Radioulnar synostosis
(fusing of adjacent bones)

Wolf D et al. *Arch Otolaryngol Head Neck Surg* 2006;132(9):1009-1011.
Abulezz TA, Shalkamy MA. *Indian J Plast Surg* 2009;42(2):261-264.
Laurberg P, Andersen SL. *Thyroid* 2015;25(11):1185-1190.

Autoimmunity Rebounds in the Postpartum Period





PPTD=Postpartum thyroid dysfunction

Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Wallenstein S, Davies TF. A prospective study of lymphocyte-initiated immunosuppression in normal pregnancy: evidence of a T-cell etiology for postpartum thyroid dysfunction. J Clin Endocrinol Metab. 1992 Mar;74(3):645-53.

Transfer of Thionamides to Infants via Breastmilk

	Propylthiouracil (PTU)	Methimazole (MMI) or Carbimazole (CM)
Amount transferred into breastmilk	0.025%	0.10-0.17% **(4-7x higher than PTU)**
Example	PTU 200 mg TID transfers ~0.149 mg daily to infant	Single MMI 40 mg dose transfers ~0.07 mg to infant
No known infant risks	Maternal doses <750 mg/day	Maternal doses <20 mg/day

Kampmann JP et al. *Lancet* 1980;1:736-737.
Johansen K et al. *Eur J Clin Pharmacol* 1982;23:339-341.
Hudzik B, Zubelewicz-Szkodzinska B. *Clin Endocrinol (Oxf)* 2016;85(6):827-830.

Outline

- Maternal hypothyroidism
- Maternal thyroid autoimmunity
- Maternal hyperthyroidism
- **Thyroid nodules and thyroid cancer in pregnancy**

Thyroid Nodules are Common in Pregnancy

- Overall thyroid nodule prevalence in pregnancy varies from **3-21%**
- At least 1/3 of all thyroid cancer patients are age <45 years (75% women)
- 11-20% of women with a nodule detected in the first trimester of pregnancy develop a second nodule in later pregnancy
- Thyroid nodule prevalence increases with parity:
  - 9.4% without prior pregnancy
  - 20.7% with one prior pregnancy
  - 20.7% with two prior pregnancies
  - 33.9% with ≥three prior pregnancies
- Positive association between increasing age & thyroid nodule prevalence during pregnancy

U.S. Surveillance, Epidemiology, and End Results (SEER) Program

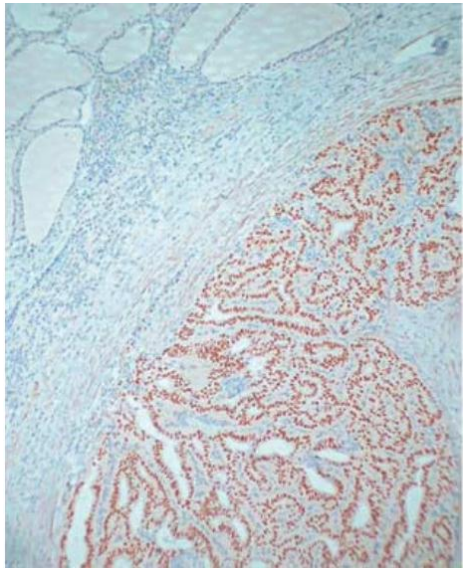
Glinoer D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, Kinthaert J, Robijn C, Grun JP, de Nayer P. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab*. 1991 Aug;73(2):421-7.

Struve CW, Haupt S, Ohlen S. Influence of frequency of previous pregnancies on the prevalence of thyroid nodules in women without clinical evidence of thyroid disease. *Thyroid*. 1993 Spring;3(1):7-9.

Potential Reasons for Pregnancy as a Thyroid Cancer Risk Factor

- Higher frequency of ERα(+) tumors in pregnancy, compared to post-partum
- Thyroid cancer can be stimulated by:
  - Estrogen-mediated growth
  - Stimulation of the MAPK pathway
  - Increased thyroglobulin expression
- hCG can mediate increased thyroid hormone and thyroglobulin levels

Section of PTC Diagnosed During Pregnancy:

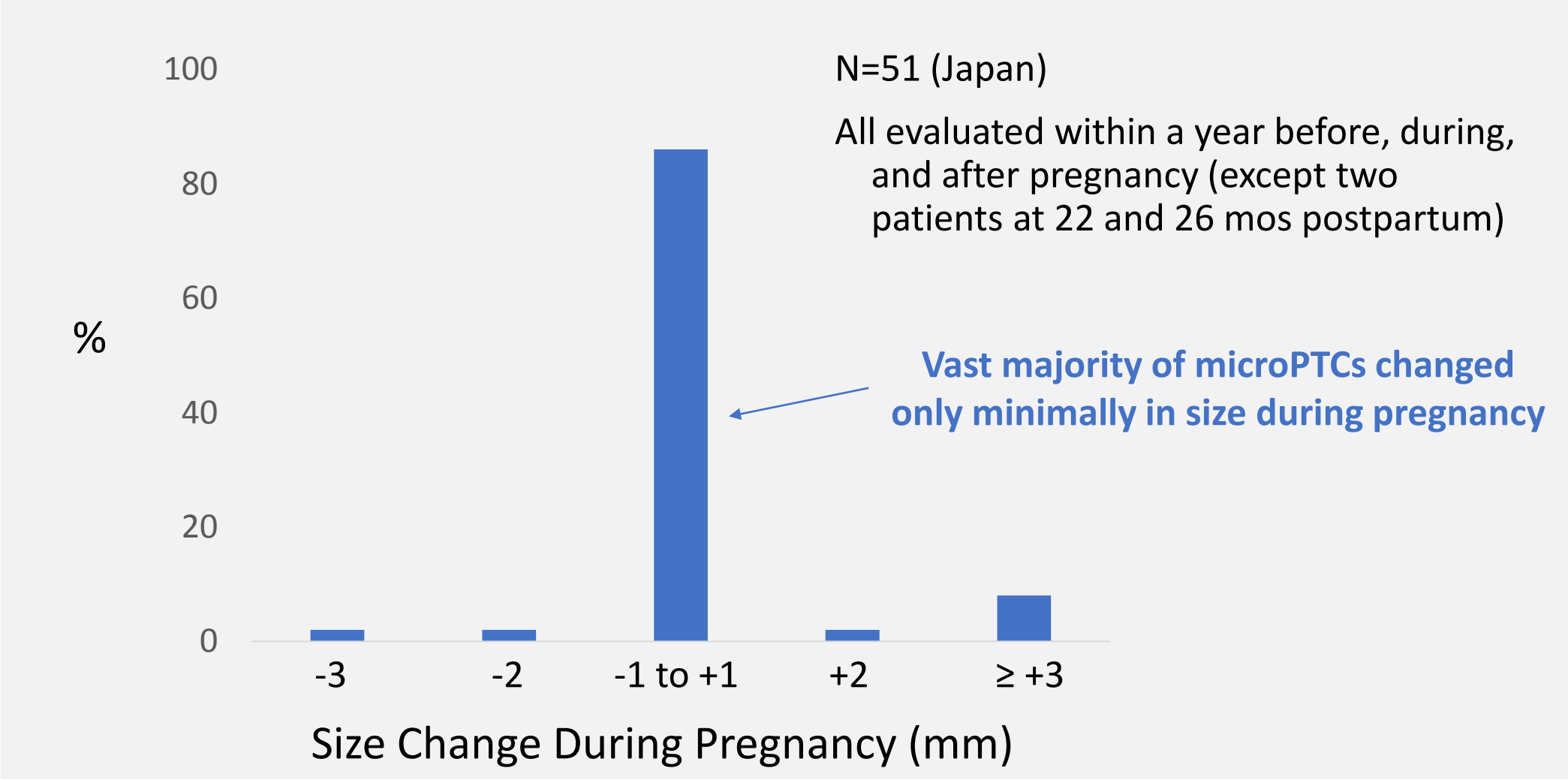


Positive immunohistochemistry for estrogen receptor α

Vannucchi G, Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, Beck-Peccoz P, Fugazzola L. Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol*. 2010 Jan;162(1):145-51.

Messuti I, Corvisieri S, Bardesono F, Rapa I, Giorcelli J, Pellerito R, Volante M, Orlandi F. Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features. *Eur J Endocrinol*. 2014 Apr 10;170(5):659-66.

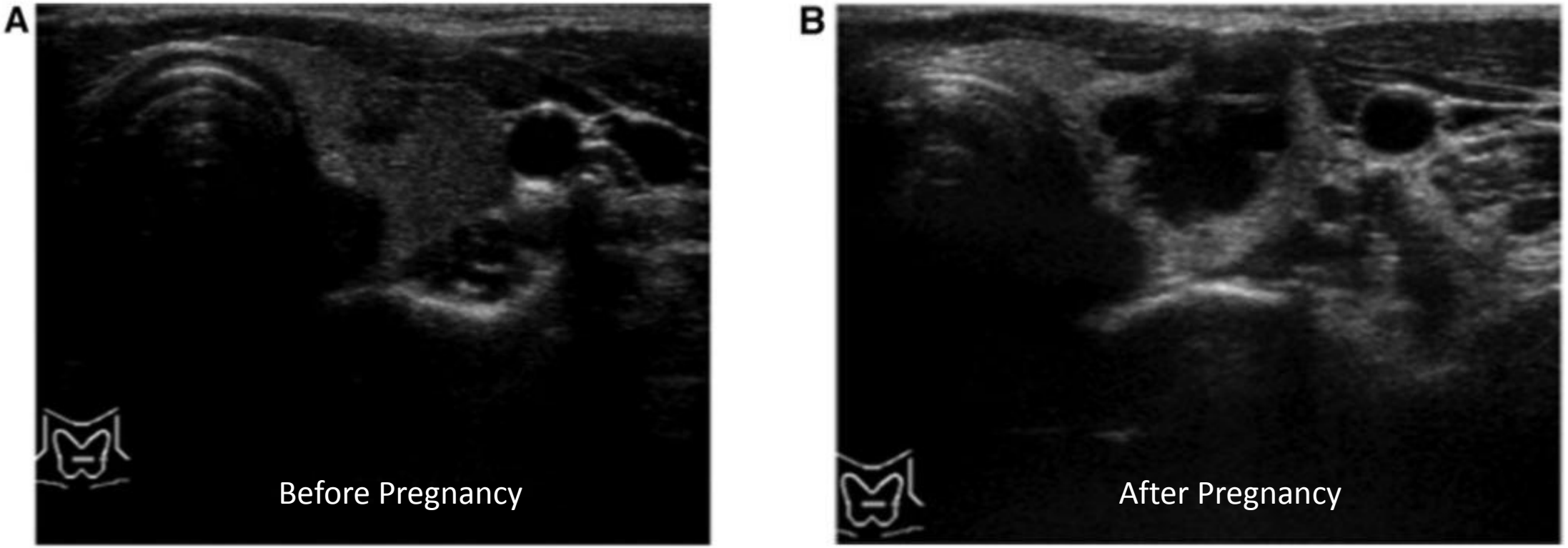
Observation of Micropapillary Thyroid Cancers During Pregnancy



Ito Y, Miyauchi A, Kudo T, Ota H, Yoshioka K, Oda H, Sasai H, Nakayama A, Yabuta T, Masuoka H, Fukushima M, Higashiyama T, Kihara M, Kobayashi K, Miya A. Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital. *Thyroid*. 2016 Jan;26(1):156-60.

Observation of Micropapillary Thyroid Cancers During Pregnancy

Patient #2

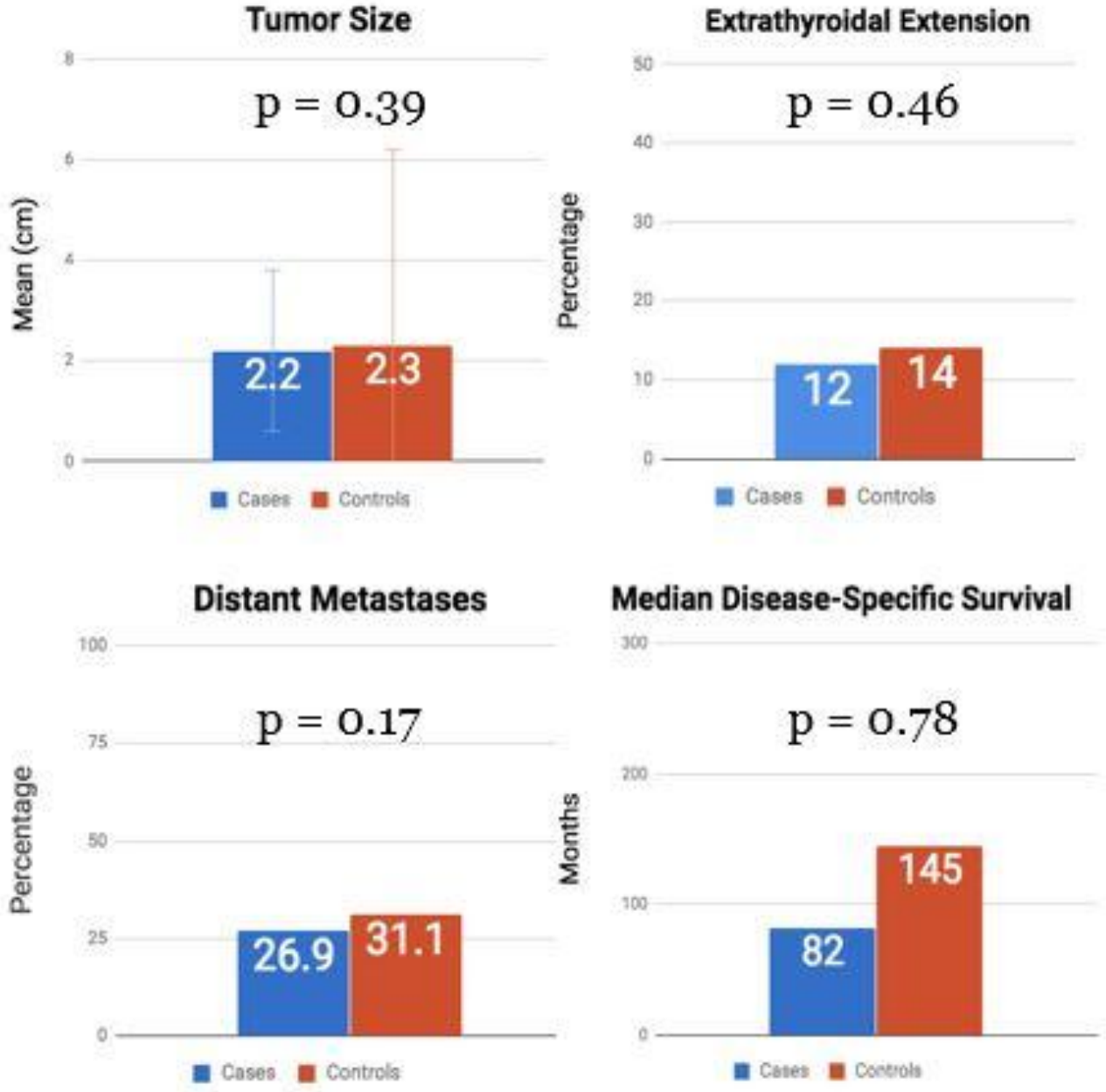


Ito Y, Miyauchi A, Kudo T, Ota H, Yoshioka K, Oda H, Sasai H, Nakayama A, Yabuta T, Masuoka H, Fukushima M, Higashiyama T, Kihara M, Kobayashi K, Miya A. Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital. Thyroid. 2016 Jan;26(1):156-60.

History of Pregnancy is Not Associated with High-Risk Thyroid Cancer Features

N=1,204

California Cancer Registry (1999-2012)



Chen AC, Livhits MJ, Du L, Wu JX, Kuo EJ, Yeh MW, Leung AM. Recent Pregnancy Is Not Associated with High-Risk Pathological Features of Well-Differentiated Thyroid Cancer. *Thyroid*. 2018 Jan;28(1):68-71.

2017 American Thyroid Association Pregnancy Recommendations

"Pregnancy ***does not*** appear to pose a risk for tumor recurrence in women without structural or biochemical disease present prior to pregnancy."

"However, for those who have a known structural or biochemical disease present at the time of conception, ***pregnancy may represent a stimulus to thyroid cancer growth*** and requires monitoring."

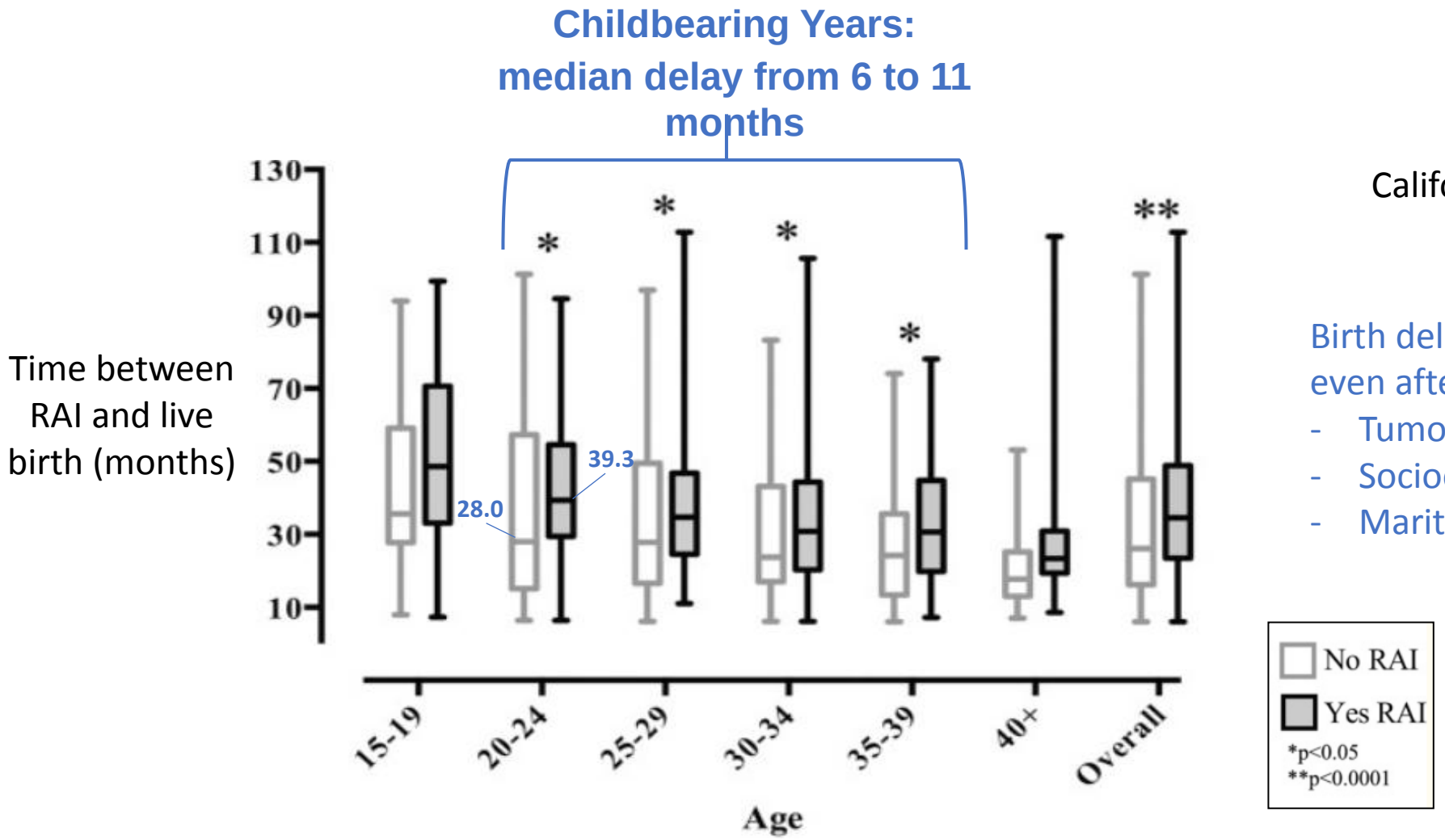
Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389.

Risks vs. Benefits of TSH Suppression for DTC During Pregnancy

- Whether or not to suppress TSH (and target TSH level) **should be similar** to that of non-pregnant, non-lactating patients.
- Caution levothyroxine **overtreatment**.
- Lower TSH and/or higher FT4 levels in pregnancy have been associated with:
  - Preeclampsia
  - Small for gestational age newborns
  - Lower childhood IQ scores
  - Lower amount of cerebral gray mass in infants
- Possible benefits of TSH suppression (in lieu of immediate surgery during pregnancy) are unknown.

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017 Mar;27(3):315-389.

RAI Ablation in Women is Associated with Delayed Childbirth



N=18,850

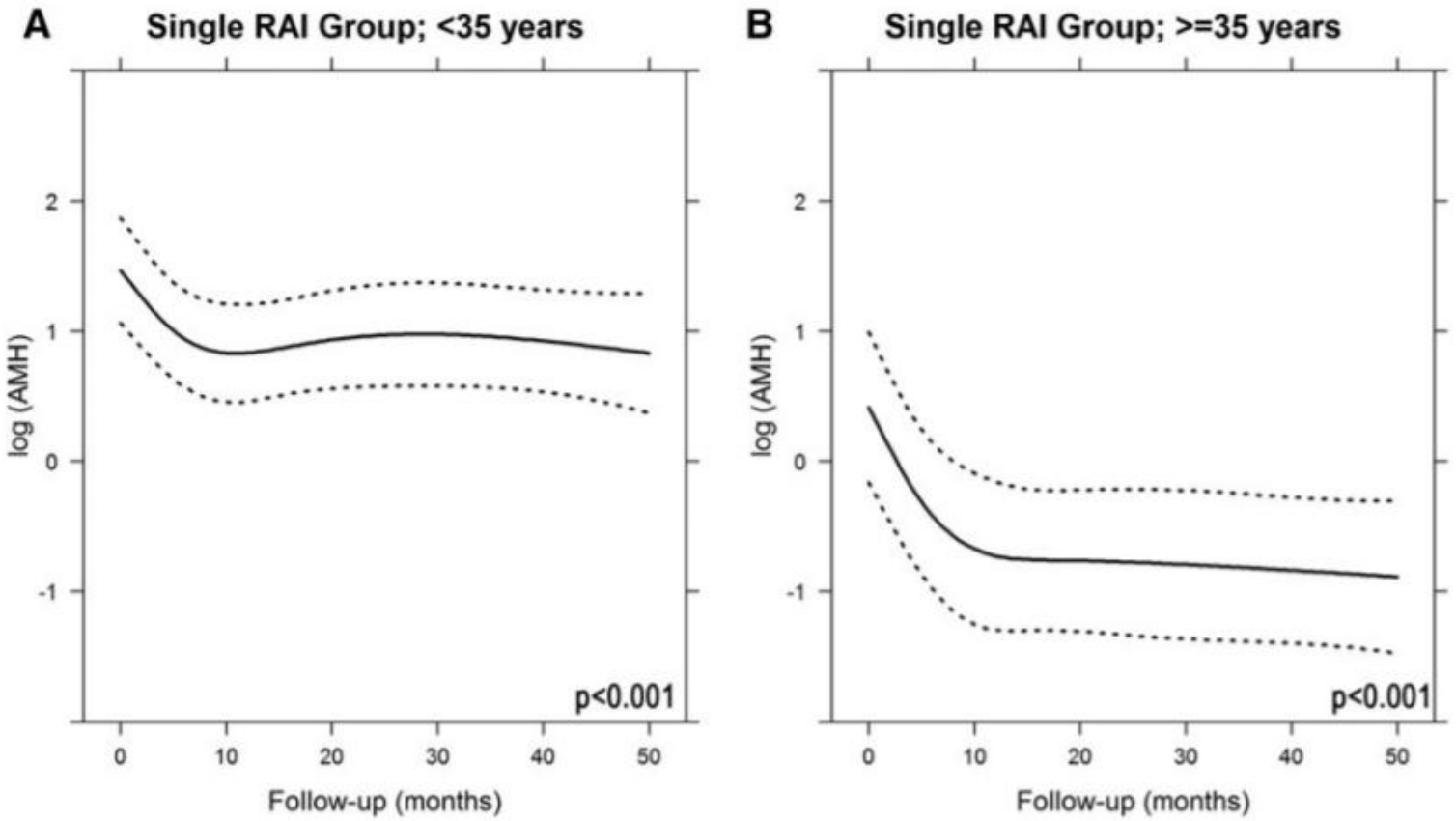
California Cancer Registry (1999-2008)

Birth delays remained significant even after adjustment for:

- Tumor characteristics
- Socioeconomic status
- Marital status

Wu JX, Young S, Ro K, Li N, Leung AM, Chiu HK, Harari A, Yeh MW. Reproductive outcomes and nononcologic complications after radioactive iodine ablation for well-differentiated thyroid cancer. *Thyroid*. 2015 Jan;25(1):133-8.

Faster Decline of Ovarian Reserve After ^{131}I in Older Women



- **Median elapsed time between RAI and final AMH measurement: 34 mos**
- **Median of 5 AMH levels obtained per woman**

van Velsen EFS, Visser WE, van den Berg SAA, Kam BLR, van Ginhoven TM, Massolt ET, Peeters RP. Longitudinal Analysis of the Effect of Radioiodine Therapy on Ovarian Reserve in Females with Differentiated Thyroid Cancer. *Thyroid*. 2020 Apr;30(4):580-587.

Medullary Thyroid Cancers During Pregnancy

- **No available data** regarding:
  - Relative benefits of immediate vs delayed (post-delivery) surgery for MTC
  - Rate of MTC progression/recurrence during pregnancy in women with MTC
- If surgery is deferred, can consider **following MTC biomarkers**
  - Caveat: Calcitonin levels can rise 2-3 fold during pregnancy in post-thyroidectomy women, and remain high during breastfeeding
  - CEA levels not affected by pregnancy
- Both American and British guidelines **recommend surgery for WTC** during pregnancy, given the aggressiveness of these tumors

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017 Mar;27(3):315-389.

Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR, British Thyroid A. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)* 2014; 81 Suppl 1:1-122.

Anaplastic Thyroid Cancers During Pregnancy

- Lack of any human studies on ATC progression during pregnancy.
- Risks of ATC progression are likely outweighed by surgical risks.
- The ATA advises that **surgery for ATC should not be delayed until after delivery**.
- TKIs can be considered given the high morbidity/mortality of ATC.

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017 Mar;27(3):315-389.

TKIs in Pregnancy are Class D

- Animal studies show associated teratogenicity and embryo toxicity.
- Case series have not reported any major obstetric complications and/or fetal anomalies.
- Currently TKIs are U.S. Food and Drug Administration Class D drugs
  - Possible human fetal risk
  - Potential benefits may warrant use of the drug in pregnant women despite potential risks

Key Takeaway Points

- Thyroid hormone **requirements increase** in pregnancy
- Serum thyroid function and antibody **screening** during pregnancy is controversial
- Mild maternal hypothyroidism and/or positive thyroid antibodies may be associated with **adverse obstetric and childhood outcomes**
- **Trimester-specific TSH goals** should be targeted
- Graves' disease in pregnancy and lactation should be managed as conservatively as possible
- Pregnancy is **likely not a risk factor** for thyroid cancer development/progression but should be closely monitored


Thank You
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