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Thyroid function screening in pregnancy: Risk factor-based or universal?

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Outline

- Introduction
- Universal screening SHOULD be performed
- Universal screening SHOULD NOT be recommended
- ACOG practice bulletin summary

Introduction

Changes in Thyroid Function Test Results in Thyroid Disease

Maternal Status	TSH	Free T4
Overt hyperthyroidism	Decrease	Increase
Subclinical hyperthyroidism	Decrease	No change
Overt hypothyroidism	Increase	Decrease
Subclinical hypothyroidism	Increase	No change

Hyperthyroidism (1)

- Occurs in 0.2 to 0.7% of pregnancies
- Graves disease accounts for 95% of these cases
- Signs and symptoms
  - Nervousness, Tremors
  - Tachycardia, Frequent stools
  - Excessive sweating, heat intolerance
  - Weight loss, goiter
  - Insomnia, palpitations, and hypertension

Hyperthyroidism (2)

- Inadequately treated maternal thyrotoxicosis
  - Preeclampsia with severe features
  - Maternal heart failure
  - Thyroid storm
- Fetal and Neonatal Effects
  - Preterm deliveries
  - Low birth weight
  - Miscarriage
  - Stillbirth

Subclinical Hyperthyroidism

- Occurs in 0.8 to 1.7% of pregnant women
- Abnormally low serum TSH concentration with normal free T4 levels
- Treatment subclinical hyperthyroidism is **not** recommended
  - Because there is no demonstrated benefit to the mother or fetus
- There are theoretical risks to the fetus
  - Because antithyroid medications cross the placenta and may **adversely affect** fetal thyroid function.

Hypothyroidism (1)

- Complicates 0.5% pregnancies
- Hashimoto thyroiditis is the most common cause of hypothyroidism in pregnancy
- Can present with nonspecific clinical findings
  - Fatigue, constipation, cold intolerance, muscle cramps, and weight gain.
  - Other clinical findings : edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes

Hypothyroidism (2)

- Adverse perinatal outcomes
  - Spontaneous abortion, preterm birth
  - Abruptio placenta, and stillbirth
- Fetal and Neonatal Effects
  - Low birth weight
  - Impaired neuropsychologic development of the offspring
  - The prevalence of fetal hypothyroidism in the offspring of women with Hashimoto thyroiditis is estimated to be only 1 in 180,000 neonates

Subclinical Hypothyroidism

- Elevated serum TSH level in the presence of a normal free T4 level
- The prevalence in pregnancy has been estimated to be 3.47%
- Subclinical hypothyroidism is unlikely to progress to overt hypothyroidism during pregnancy in otherwise healthy women.

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Universal screening for thyroid disease during pregnancy should be performed

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Universal screening for thyroid disease during pregnancy should be performed

- Can identify patients with thyroid disease requiring treatment
- Ultimately decrease rates of complications
- Cost-effective and cost-saving in some healthcare systems

History of screening in pregnancy

- In 1970, gestational diabetes and Rh screening was implemented
- ACOG currently recommends that all women be offered aneuploidy screening with one or more of the non-invasive modalities
  - Maternal serum screening for Down Syndrome began in the 1980’
    - Including hCG、free bhCG, PAPP-A, unconjugated estriol (uE3), inhibin A, AFP and nuchal translucency by ultrasound
  - Chorionic villus sampling
  - Advances with noninvasive screening of the fetus through a maternal blood
    - Diagnose fetal aneuploidies for chromosomes 21, 13, 18, X and Y
  - Spinal muscular atrophy (SMA)（1 / 12,000 live births）and cystic fibrosis (CF)（1 /3000 live births）
    - The consequences of diagnosis are often severe and life-long for both parents and children

How does universal screening for thyroid disease during pregnancy fit in with the other universal prenatal screening?

Overt hyperthyroidism

- Maternal congestive heart failure
- Hypertensive disorders
- Miscarriage
- Stillbirth
- Preterm delivery
- Placental abruption
- Neonatal low birth weight
- Congenital abnormalities

Overt hyperthyroidism

- Treatment for hyperthyroidism in pregnancy is also effective
  - With antithyroid drug therapy
  - Decreased rates of low birth weight , miscarriage , stillbirth and preterm delivery
  - First trimester :Propylthiouracil (PTU) preferred
  - Second and third trimesters: methimazole (MMI, Tapazole)
- Side risk
  - PTU carries the risk of severe hepatotoxicity, agranulocytosis
  - MMI is teratogenic, agranulocytosis

Subclinical hyperthyroidism

- **No association** between subclinical hyperthyroidism and adverse pregnancy outcomes
- Subclinical hyperthyroidism need not be treated in pregnancy

Thyroid autoimmunity

- Miscarriage and preterm delivery
- Premature rupture of membranes (PROM)
- Low birth weight and childhood cognitive deficit
- ACOG **does not** recommend treatment for thyroid antibody positive, euthyroid women

Cost effectiveness of universal screening

- Most guidelines recommend targeted screening over universal screening
- While there is still debate regarding whether or not treating subclinical hypothyroidism decreases maternal/fetal adverse outcomes
- The cost-effective studies demonstrate that universal screening is **superior** to targeted screening even if one assumes no benefit for identifying and treating subclinical hypothyroidism

Society and national guidelines

- In 2017, the ATA reaffirmed that there was **insufficient evidence** to recommend for or against universal screening
- In 2020 the Practice Bulletin from ACOG recommended for **targeted** and against universal screening for pregnant women
- The 2012 statement from the American Society for Maternal Fetal Medicine also recommended **targeted**, not universal screening
- The Cochrane Database of Systematic Reviews 2015, based on available evidence, there was **no clear evidence** of benefit for improving maternal or infant health with universal screening of thyroid disease in pregnancy

This able reveal a **lack** of consensus on the issue of universal screening

Recommendations from national and international societies on screening for thyroid disease in pregnancy.

	Society	Timing	TSH	fT4	TPOAb	TgAb
Recommend Universal Screening	American Association of Clinical Endocrinologists (1999) [127]	Pre-Pregnancy	✓			
	American Association of Clinical Endocrinologists (2002) [128]	Pre-Pregnancy or 1st Trimester	✓	Consider	Consider	Consider
	Italian Thyroid Association & Italian Association of Clinical Endocrinologists (2011) [131]	1st Visit	✓	✓		
	Endocrine Society (Minority) (2012) [54]	1st Visit	✓		✗	✗
	Spanish Society of Endocrinology and Nutrition jointly with Spanish Society of Gynaecology and Obstetrics (2012) [132]	Pre-Pregnancy or 1st Trimester	✓	Reflex		
	European Thyroid Association (Majority) (2014) [133]	1st Trimester	✓	Reflex	Reflex	

Recommendations from national and international societies on screening for thyroid disease in pregnancy.

	Society	Timing	TSH	fT4	TPOAb	TgAb
Recommend Targeted Screening	Endocrine Society (2007) [129]		✓		✗	✗
	American Thyroid Association (2011) [30]		✓			
	Endocrine Society (Majority) (2012) [54]		✓			
	Society for Maternal-Fetal Medicine (2012) [136]		✓			
	American Association of Clinical Endocrinologists jointly with American Thyroid Association (2012) [130]		✓			Consider
	Brazilian Society of Endocrinology and Metabolism (2013) [134]		✓	✓	Consider	Consider
	Indian Ministry of Health and Family Welfare (2014) [135]		✓			
	American College of Obstetricians and Gynecologists (2015) [53]		✓	✓	✗	✗
	American Thyroid Association (2017) [31]		✓		Reflex	

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Targeted screening

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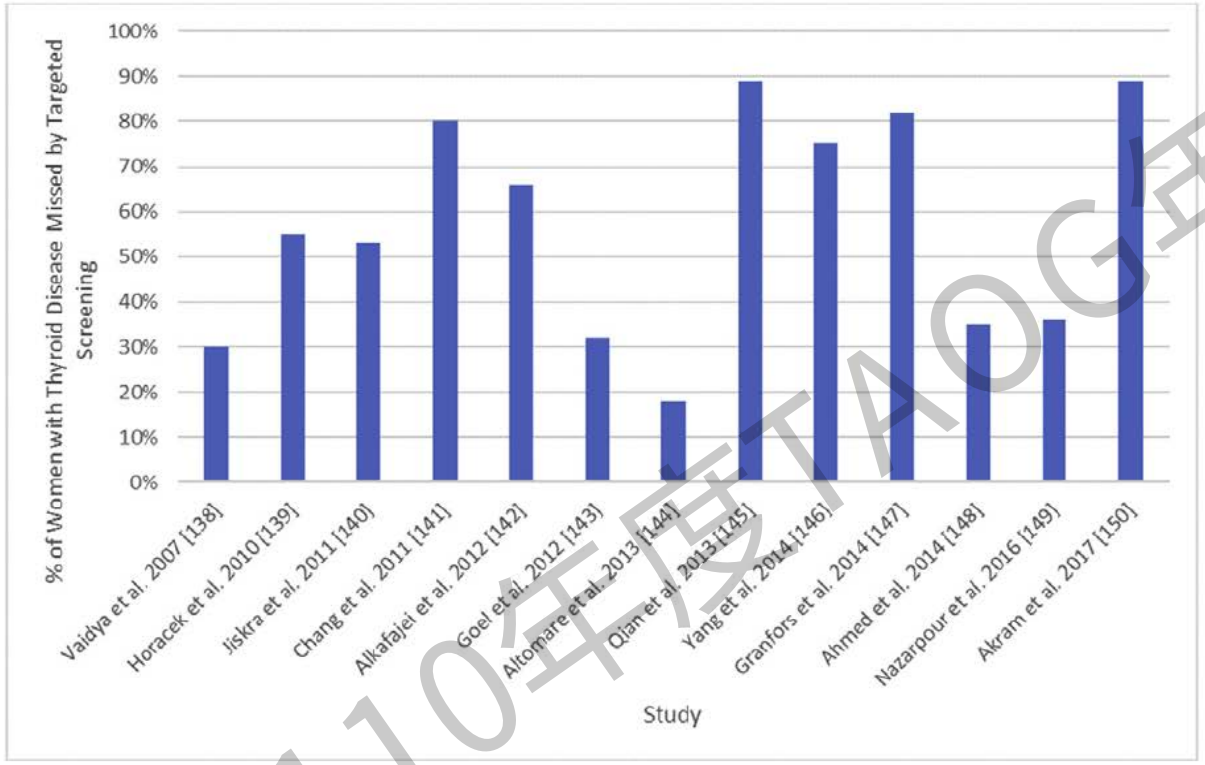
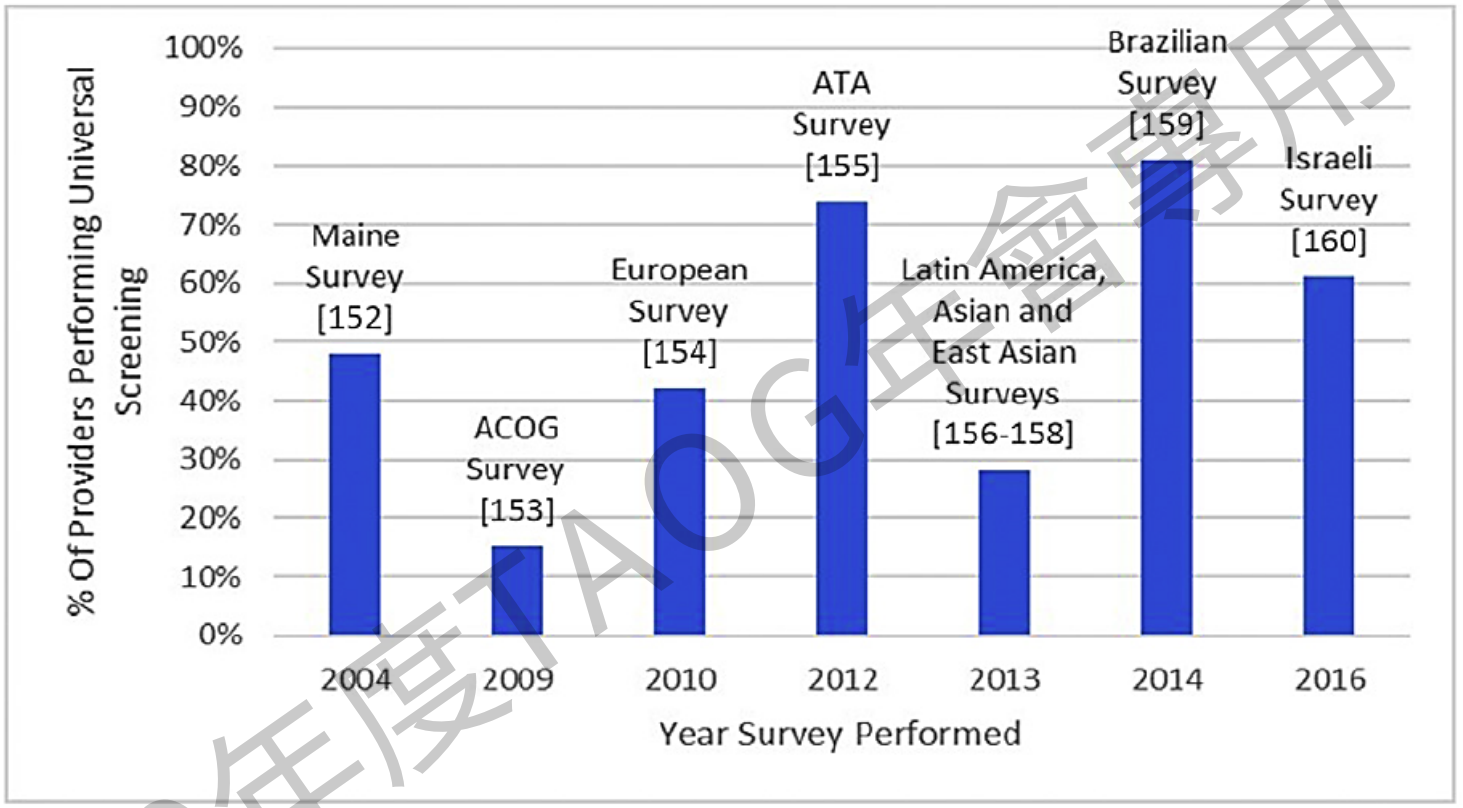


Women with overt and/or subclinical disease in pregnancy missed with targeted screening.

Targeted screening **Misses** between 18 and 89% of women with either overt or subclinical thyroid disease in pregnancy

Pop et al. concluded that even clinical symptoms are unable to predict or exclude thyroid dysfunction in pregnancy

Clin Endocrinol 2017;87:838e43



Rates of universal screening for thyroid disease in pregnancy among providers as reported by surveys.

Except for in Asia, the rate of adoption of universal screening is rising

Whether treatment of individuals identified with thyroid disease is beneficial or not

- Negro et al. found that **universal screening** and treatment resulted in a decreased number of overall adverse outcomes in women of low-risk status compared to untreated women at low-risk.

J Clin Endocrinol Metabol 2010;95:1699e707

- Similarly, Ma et al. reported that treatment of women identified with subclinical hypothyroidism by **universal screening** resulted in decreased rates of miscarriage compared to a control group that had serum frozen for analysis post partum

Matern Fetal Neonatal Med 2016;29:1391e4

Criteria for screening

The gold standard for evaluating a screening strategy are the "10 Principles" defined by Wilson and Junger in their 1968 World Health Organization publication. The 10 Principles are as follows :

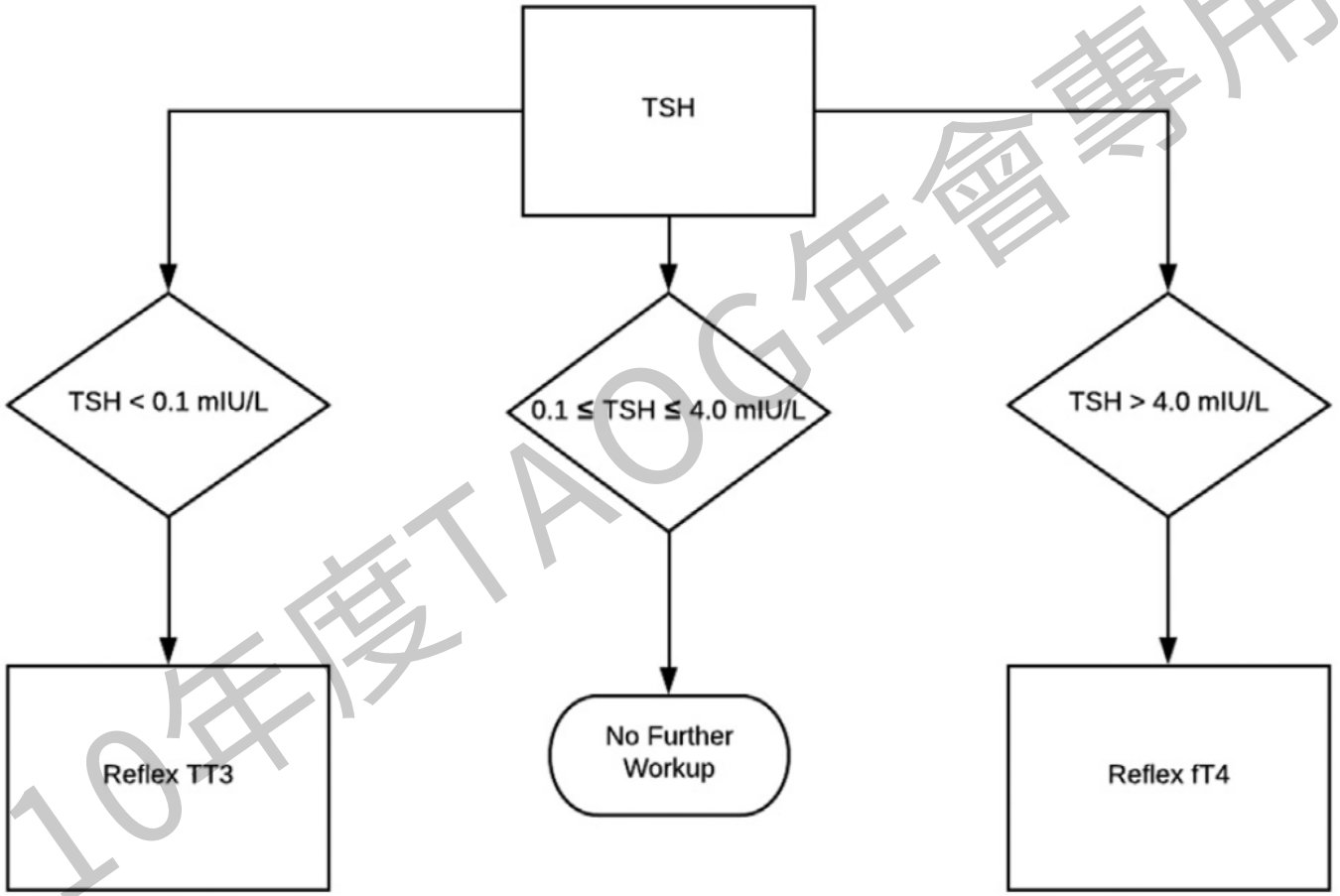
- The condition has a substantial health impact
- The condition has an effective treatment
- A mechanism exists by which screening can occur
- The condition has a period where it can be identified and before the negative effect of the condition occurs
- A screening test with a low false negative rate exists
- The test is low risk and acceptable to those screened
- The changes caused by the condition with time should be pathological and not just physiological
- Agreement should exist as to who to treat
- Identification and treatment of the condition is cost effective
- Case-finding is a comprehensive process.

The "10 Principles" by Wilson and Junger [24] for universal screening with respect to thyroid disease in pregnancy.

Principle	Overt Hypothyroidism	Subclinical Hypothyroidism	Isolated Hypothyroxinemia	Overt Hyperthyroidism	Subclinical Hyperthyroidism	Thyroid Autoimmunity
1. The condition should be an important health problem.	+	+/−	+/−	+	−	+
2. There should be an accepted treatment	+	+/−	+/−	+	−	+/−
3. Facilities for diagnosis and treatment should be available.	+	+	+	+	+	+
4. There should be a recognizable latent or early symptomatic stage.	+	+	+	+	+	+
5. There should be a suitable test or examination.	+	+	+	+	+	+
6. The test should be acceptable to the population.	+	+	+	+	+	+
7. The natural history of the condition should be adequately understood.	+	+/−	+/−	+	+/−	+/−
8. There should be an agreed policy on whom to treat as patients	+	+/−	+/−	+	+	+/−
9. The cost of case-finding should be economically balanced.	+	+/−	?	?	?	+
10. Case-finding should be a continuing process.	+	+	+	+	+	+

+, Evidence supports; −, Evidence does not support; +/−, Evidence is inconclusive; ?, No evidence.

Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Org; 1968.



Proposed universal screening algorithm for thyroid disease to be done prior to pregnancy or at the first prenatal visit.

Conclusion

- Universal screening for **overt hypothyroidism** meets all of the World Health Organization criteria
- The identification of women with **overt hyperthyroidism** will add **minimal cost** but will have a significant impact on decreasing the morbidity and mortality associated with overt hyperthyroidism
- Universal screening will identify **1.15%** women with overt thyroid disease who require treatment
- We therefore strongly recommend that **all women** should be screened either prior to pregnancy, or at the first prenatal visit

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Universal screening for thyroid disease SHOULD NOT be recommended before and during pregnancy

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Thyroid dysfunction in pregnancy is strongly associated with adverse maternal and foetal outcomes. The effects of treatment are less clear. There is ongoing discussion on whom to treat, when to treat and whether treatment is beneficial. Although universal screening for thyroid disease during pregnancy increases diagnosis and treatment of thyroid dysfunction, there is currently insufficient evidence demonstrating a positive effect of screening on maternal and foetal outcomes. We therefore, at present, recommend against universal screening for thyroid disease before and during pregnancy.

Universal screening for thyroid disease **should not** be recommended before and during pregnancy

- In order for a disease or condition to be eligible and suitable for universal screening, the WHO advocates the use of **screening criteria**
- Although there is a clear association between thyroid dysfunction and adverse pregnancy and fetal outcomes , the condition fails to meet a number of important screening criteria, making it unsuitable for universal screening
- At present there is insufficient evidence or consensus for thyroid dysfunction in pregnancy to meet several other key screening criteria.

Table 2
The "10 Principles" by Wilson and Junger [24] for universal screening with respect to thyroid disease in pregnancy.

Principle	Overt Hypothyroidism	Subclinical Hypothyroidism	Isolated Hypothyroxinemia	Overt Hyperthyroidism	Subclinical Hyperthyroidism	Thyroid Autoimmunity
1. The condition should be an important health problem.	+	+/−	+/−	+	−	+
2. There should be an accepted treatment	+	+/−	+/−	+	−	+/−
3. Facilities for diagnosis and treatment should be available.	+	+	+	+	+	+
4. There should be a recognizable latent or early symptomatic stage.	+	+	+	+	+	+
5. There should be a suitable test or examination.	+	+	+	+	+	+
6. The test should be acceptable to the population.	+	+	+	+	+	+
7. The natural history of the condition should be adequately understood.	+	+/−	+/−	+	+/−	+/−
8. There should be an agreed policy on whom to treat as patients	+	+/−	+/−	+	+	+/−
9. The cost of case-finding should be economically balanced.	+	+/−	?	?	?	+
10. Case-finding should be a continuing process.	+	+	+	+	+	+

+, Evidence supports; −, Evidence does not support; +/−, Evidence is inconclusive; ?, No evidence.

Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Org; 1968.

- In euthyroid women with TPO antibodies, treatment with levothyroxine
  - **Not shown** to reduce the risk of premature delivery
- The effects of treatment on miscarriage risk in this population
  - **Inconsistent**.
- Pregnant women with subclinical hypothyroidism, the effect of levothyroxine on pregnancy loss and preterm delivery
  - **Unclear**
- Universal screening for thyroid dysfunction in pregnancy
  - **Does not improve** neurocognitive outcome measures in children

Targeted screening

- Targeted screening operates on three principles:
  - Risk factors or clinical attributes can identify patients predisposed to the disease of interest
  - Screening individuals with these risk factors will identify the majority of patients with the disease of interest
  - The lower cost derived from targeted screening is worth the downside of false positives and false negatives.

Targeted screening

The 2017 ATA guidelines include a list of indicators which identify women “at risk” for thyroid disease in pregnancy and therefore constitute an indication for targeted screening. They include the following :

- History of or current signs of thyroid disease, known thyroid antibody positivity or goiter presence
- History of prior thyroid surgery or head or neck radiation
- Maternal age > 30 years
- History of type 1 diabetes or other autoimmune disorders
- History of pregnancy loss, preterm delivery or infertility
- > 2 prior pregnancies
- Family history of thyroid disease
- Morbid obesity
- Use of known thyrotoxic agents such as amiodarone, lithium or iodine contrast
- Residing in known areas of iodine insufficiency.

Conclusion

- Thyroid dysfunction and autoimmunity in pregnancy are strongly associated with adverse maternal and fetal outcomes.
- There is currently **no evidence** that treatment of maternal subclinical hypothyroidism or hypothyroxinaemia during pregnancy improves neurocognitive fetal outcomes.
- There is **insufficient evidence** to support universal screening for thyroid dysfunction in or before pregnancy
- **Only targeted screening** of pregnant women at increased risk for thyroid dysfunction is advised by the authors and current clinical guidelines.

Conclusion

- Although universal screening for thyroid disease during pregnancy increases diagnosis and treatment of thyroid dysfunction
- There is currently **insufficient evidence** of a positive effect of screening on maternal and fetal outcomes
- We therefore at present recommend **against universal screening** for thyroid disease before and during pregnancy.

Thyroid function screening in pregnancy: Risk factor-based or universal?

ACOG
The American College of Obstetricians and Gynecologists

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 223 *(Replaces Practice Bulletin Number 148, April 2015)*

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the Committee on Practice Bulletins—Obstetrics with the assistance of Brian M. Casey, MD and Torri D. Metz, MD, MS in collaboration with American Academy of Family Physicians liaison Jeff Quinlan, MD.

Thyroid Disease in Pregnancy

Both thyrotoxicosis and hypothyroidism are associated with adverse pregnancy outcomes. There also is concern about the effect of overt maternal thyroid disease on fetal development. In addition, medications that affect the maternal thyroid gland can cross the placenta and affect the fetal thyroid gland. This document reviews the thyroid-related pathophysiologic changes that occur during pregnancy and the effects of overt and subclinical maternal thyroid disease on maternal and fetal outcomes. This Practice Bulletin has been updated with information on the diagnosis and the management of thyroid disease in pregnant women and includes a new clinical algorithm on management of

- Obstet Gynecol. 2020 Jun;135(6):1496-1499.

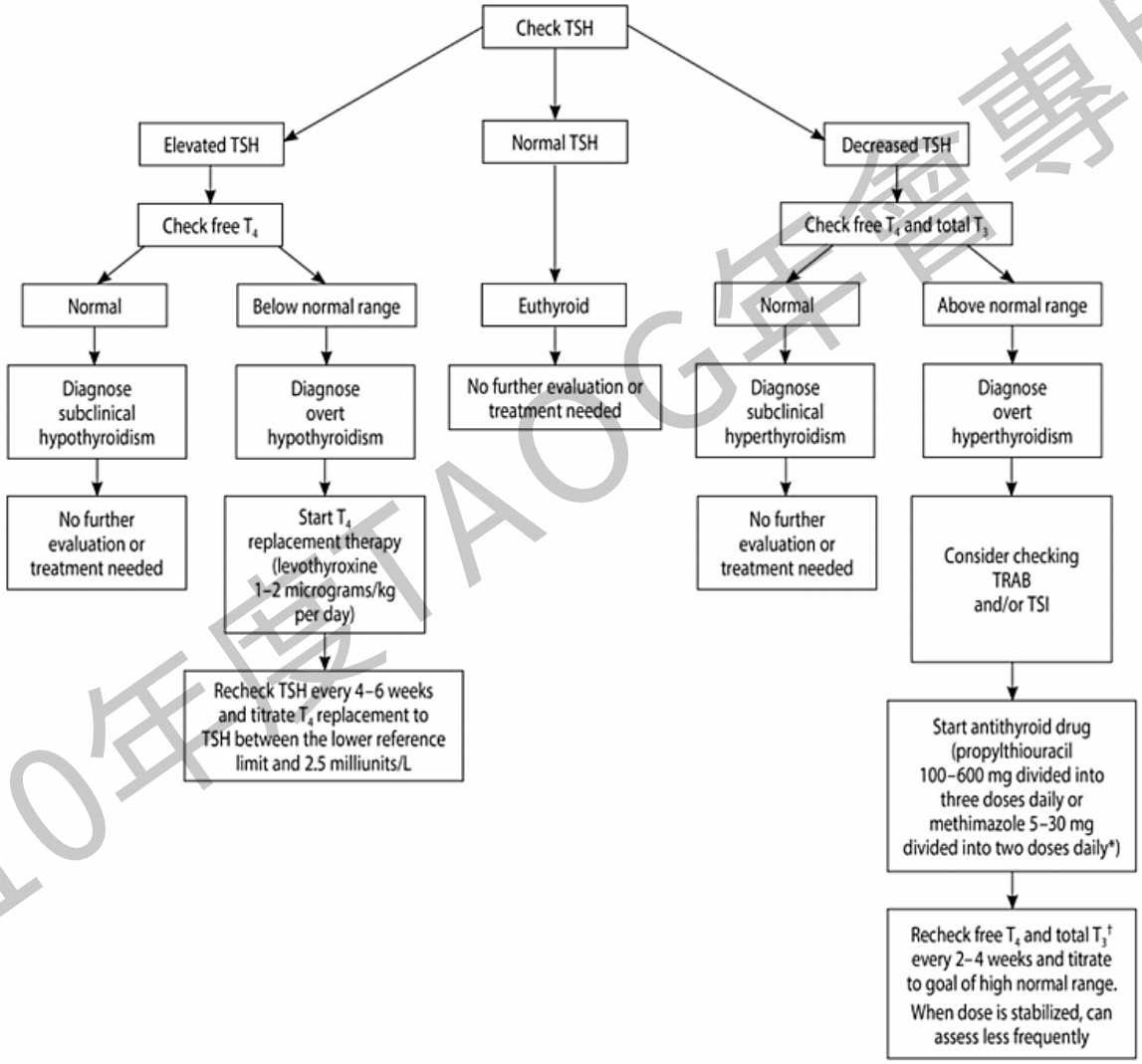
Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes and neurocognitive function in offspring.
- If indicated, the first-line screening test to assess thyroid status should be measurement of the TSH level.
- The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroid-stimulating hormone typically is evaluated every 4–6 weeks while adjusting medications.
- Pregnant women with overt hypothyroidism should be treated with adequate thyroid hormone replacement to minimize the risk of adverse outcomes.
- The level of free T_4 should be monitored in pregnant women being treated for hyperthyroidism, and the dose of antithyroid drug (thioamide) should be adjusted accordingly to achieve a free T_4 at the upper end of the normal pregnancy range. Among women who also have T_3 thyrotoxicosis, total T_3 should be monitored with a goal level at the upper end of normal pregnancy range.
- Pregnant women with overt hyperthyroidism should be treated with antithyroid drugs (thioamides).

Universal screening for thyroid disease in pregnancy is **not recommended** because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes and neurocognitive function in offspring.

Clinical Algorithm for Management of Thyroid Disease in Pregnancy



Thank you

Table 1
Wilson and Jungner criteria for screening (4).

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Table 2
Additional emerging screening criteria as proposed by Andermann et al. (5).

1. The screening programme should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The programme should ensure informed choice, confidentiality and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

- Data on the effect of levothyroxine treatment in euthyroid TPO+ women is inconsistent
- Has not been replicated in women with subclinical hypothyroidism
- A retrospective study even found an increased rate of preterm delivery and other pregnancy complications in women with subclinical hypothyroidism treated with levothyroxine
- At present there are no studies indicating an effect of treatment on child IQ
- There is therefore insufficient evidence at present to determine which group of patients, **besides** overt hypo-and hyperthyroidism, would benefit from treatment
- An agreed upon policy on **whom to treat** as patients is a fundamental requirement for universal screening.

- Besides **whom to treat** there is also insufficient evidence on **when to screen** and **start treatment**
- As the effects of screening for thyroid dysfunction before pregnancy are unknown, we feel that the potential harm of universal screening does not currently outweigh the benefits in this group.
- There is currently **no evidence** that treatment initiated early in the second trimester affects maternal and foetal outcomes including preterm delivery and child IQ
- Recent data **do not** justify universal screening of the entire pregnant population
- There is at present insufficient evidence of screening programme effectiveness

Effect of treatment with levothyroxine on adverse pregnancy outcomes

- Thyroid autoimmunity
  - Treatment of euthyroid TPO+ women with levothyroxine results in improved pregnancy outcomes
- Hypothyroidism
  - Should be treated with levothyroxine
- Subclinical hypothyroidism
  - There was **no statistically significance** difference in early pregnancy loss, premature delivery or other adverse pregnancy outcomes
- Isolated hypothyroxinaemia
  - **No data available**

Recommendations from national and international societies on screening for thyroid disease in pregnancy.

	Society	Timing	TSH	fT4	TPOAb	TgAb
Recommend Universal Screening	American Association of Clinical Endocrinologists (1999) [127]	Pre-Pregnancy	✓			
	American Association of Clinical Endocrinologists (2002) [128]	Pre-Pregnancy or 1st Trimester	✓	Consider	Consider	Consider
	Italian Thyroid Association & Italian Association of Clinical Endocrinologists (2011) [131]	1st Visit	✓	✓		
	Endocrine Society (Minority) (2012) [54]	1st Visit	✓		✗	✗
	Spanish Society of Endocrinology and Nutrition jointly with Spanish Society of Gynaecology and Obstetrics (2012) [132]	Pre-Pregnancy or 1st Trimester	✓	Reflex		
	European Thyroid Association (Majority) (2014) [133]	1st Trimester	✓	Reflex	Reflex	

Table 1
Recommendations from national and international societies on screening for thyroid disease in pregnancy.

	Society	Timing	TSH	fT4	TPOAb	TgAb
Recommend Targeted Screening	Endocrine Society (2007) [129]		✓		✗	✗
	American Thyroid Association (2011) [30]		✓			
	Endocrine Society (Majority) (2012) [54]		✓			
	Society for Maternal-Fetal Medicine (2012) [136]		✓			
	American Association of Clinical Endocrinologists jointly with American Thyroid Association (2012) [130]		✓			Consider
	Brazilian Society of Endocrinology and Metabolism (2013) [134]		✓	✓	Consider	Consider
	Indian Ministry of Health and Family Welfare (2014) [135]		✓			
	American College of Obstetricians and Gynecologists (2015) [53]		✓	✓	✗	✗
	American Thyroid Association (2017) [31]		✓		Reflex	