# V Corso Aggiornamento Ame in Endocrinologia Clinica



Aggiornamenti su TIREOPATIE e GRAVIDANZA

Francesco Vermiglio

AGRIGENTO 20/22 MARZO 2014



#### CLINICAL PRACTICE GUIDELINE

Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

Marcos Abalovich, Nobuyuki Amino, Linda A. Barbour, Rhoda H. Cobin, Leslie J. De Groot, Daniel Glinoer, Susan J. Mandel, and Alex Stagnaro-Green

2007

THYROID Volume 21, Number 10, 2011

# It remains uncertain as to what extent clinicians follow these guidelines in their routine clinical practice

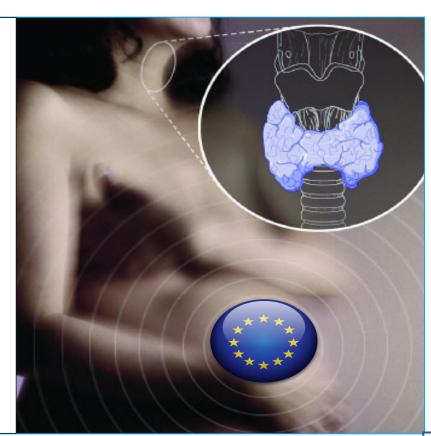
Noberto Negro, Angelita Nizon, Elizabeti N. Fearce, Olife F. Soldin, Soott Sullivan, 10 and Wilmar Wiersinga<sup>11</sup>

#### Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

Leslie De Groot, Marcos Abalovich, Erik K. Alexander, Nobuyuki Amino, Linda Barbour, Rhoda H. Cobin, Creswell J. Eastman, John H. Lazarus, Dominique Luton, Susan J. Mandel, Jorge Mestman, Joanne Rovet, and Scott Sullivan

2012

## Thyroid and Pregnancy: Results of a survey among ETA members

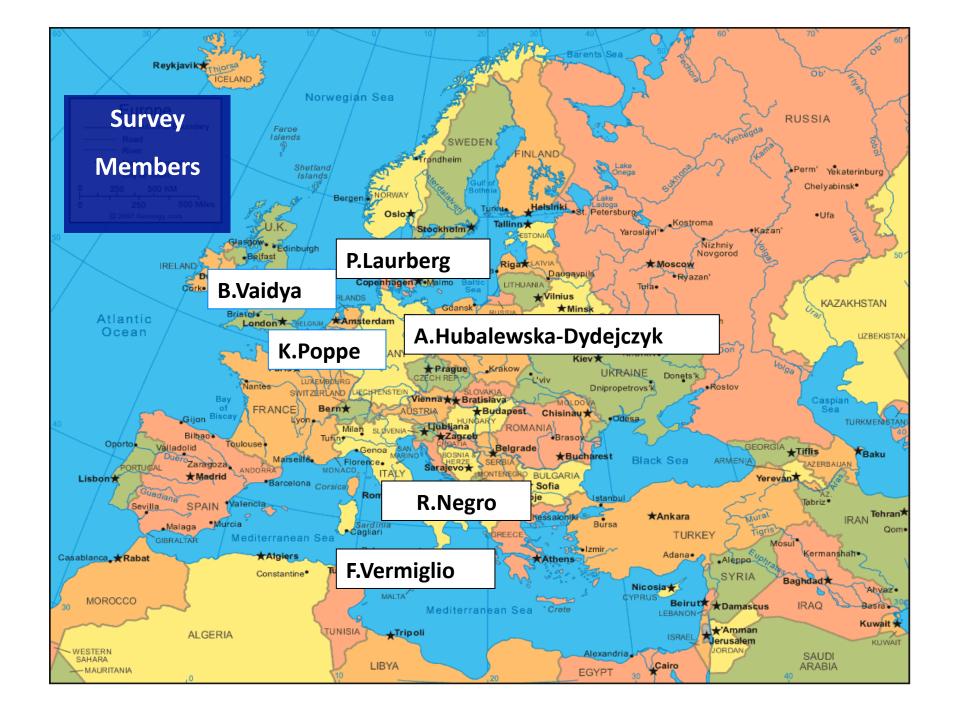






Kris Poppe on behalf of the Survey members







Alta % di tireopatie misconosciute 750 milioni esposti a iodocarenza

## Complicanze ostetriche e fetali malattie funzionali tiroidee

Abortività
Parto pretermine
Preeclampsia
Distacco intempestivo
di placenta
Emorragia post-partum
Mortalità perinatale
Basso peso alla nascita

IUGR
Sindrome da distress
respiratorio
Alterato sviluppo
neuro-intellettivo

## **Sommario**

## Screening tireopatie in gravidanza

Eutiroidismo Ipertiroidismo Ipotiroidismo

#### CLINICAL PRACTICE GUIDELINE

**Management of Thyroid Dysfunction during Pregnancy** and Postpartum: An Endocrine Society Clinical Practice Guideline

Marcos Abalovich, Nobuyuki Amino, Linda A. Barbour, Rhoda H. Cobin, Leslie J. De Groot, Daniel Glinoer, Susan J. Mandel, and Alex Stagnaro-Green

### 2007

#### SECTION 8. SCREENING FOR THYROID DYSFUNCTION DURING PREGNANCY

#### 8.4. RECOMMENDATIONS

Although the benefits of universal screening for hypothyroidism may not be justified by current evidence, as presented in Sections 1–7, we recommend case finding among the following groups of women at high risk for thyroid dysfunction:

- 1. Women with a history of hyperthyroid or hypothyroid disease, PPT, or thyroid lobectomy
- - 3. Women with a goiter
- 5. Women with symptoms or clini thyroid underfunction or overfuncti elevated cholesterol, and hyponatren

It should 2. Women with a family history of also be noted that women living in iodine-deficient areas have a high risk for thyroid disease. In those areas, rather 4. Women with thyroid antibodies than general screening for hypothyroidism, efforts should be made to supplement women's diet with iodine before and during pregnancy (see Section 6).

- 6. Women with type I diabetes
- 7. Women with other autoimmune disorders
- 8. Women with infertility should have screening with TSH as part of their infertility work-up.
  - 9. Women with prior therapeutic head or neck irradiation.
- 10. Women with a prior history of miscarriage or preterm delivery

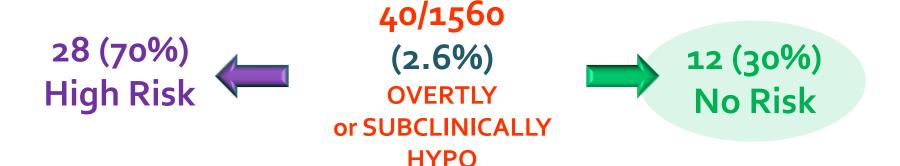
The USPSTF recommendation level is B; evidence is fair (GRADE 1|₩₩00).

### Detection of Thyroid Dysfunction in Early Pregnancy: Universal Screening or Targeted High-Risk Case Finding?

Bijay Vaidya, Sony Anthony, Mary Bilous, Beverley Shields, John Drury, Stewart Hutchison, and Rudy Bilous

Department of Endocrinology (B.V., B.S.), Peninsula Medical School, Royal Devon & Exeter Hospital, Exeter EX2 5DW, United Kingdom; and Departments of Endocrinology (S.A., M.B., R.B.), Clinical Biochemistry (J.D.), and Obstetrics (S.H.), James Cook University Hospital, Middlesbrough TS4 3BW, United Kingdom

## 1560 consecutive pregnant women FT4+TSH (1st trimester)



Conclusion: Targeted thyroid function testing of only the high-risk group would miss about one third of pregnant women with overt/ subclinical hypothyroidism. (J Clin Endocrinol Metab 92: 203–207, 2007)

THYROID Volume 21, Number 10, 2011 Mary Ann Liebert, Inc.

#### Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum

Alex Stagnaro-Green (Chair), Maroos Abalovich, Erik Alexander, Fereidoun Azizi, Jorge Mestman, Roberto Negro, Angelita Nixon, Elizabeth N. Pearoe, Offie P. Soldin, Scott Sullivan,10 and Wilmar Wiersingat

#### 2011

#### Thyroid Function Screening in Pregnancy

Question 83: Should all pregnant women be screened for serum TSH level in the first trimes ■ RECOMMENDATION 76

#### RECOMMENDATION 72

There is insufficient evidence to re against universal TSH screening at the f Level I-USPSTF

Question 84: Should serum TSH test out in a targeted population of pregi

Serum TSH values should be obtained early in pregnancy in the following women at high risk for overt hypothyroidism:

History of thyroid dysfunction or prior thyroid surgery

Age >30 years

Symptoms of thyroid dysfunction or the presence of goiter TPOAb positivity

Type 1 diabetes or other autoimmune disorders

History of miscarriage or preterm delivery

History of head or neck radiation

Family history of thyroid dysfunction

Morbid obesity (BMI ≥40 kg/m²)

Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast

Infertility

Residing in an area of known moderate to severe iodine insufficiency Level B-USPSTF

#### Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

2012

Leslie De Groot, Marcos Abalovich, Erik K. Alexander, Nobuyuki Amino, Linda Barbour, Rhoda H. Cobin, Creswell J. Eastman, John H. Lazarus, Dominique Luton, Susan J. Mandel, Jorge Mestman, Joanne Rovet, and Scott Sullivan

## 8.0. Screening for thyroid dysfunction during pregnancy

TABLE 1. Recommended patient profiles for targeted ▶thyroid disease case finding in women seeking pregnancy or newly pregnant

•Women over age 30 yr

Women with a family history or autoimmune thyroid disease or hypothyroidism

Women with a goiter

Women with thyroid antibodies, primarily thyroid peroxidase antibodies

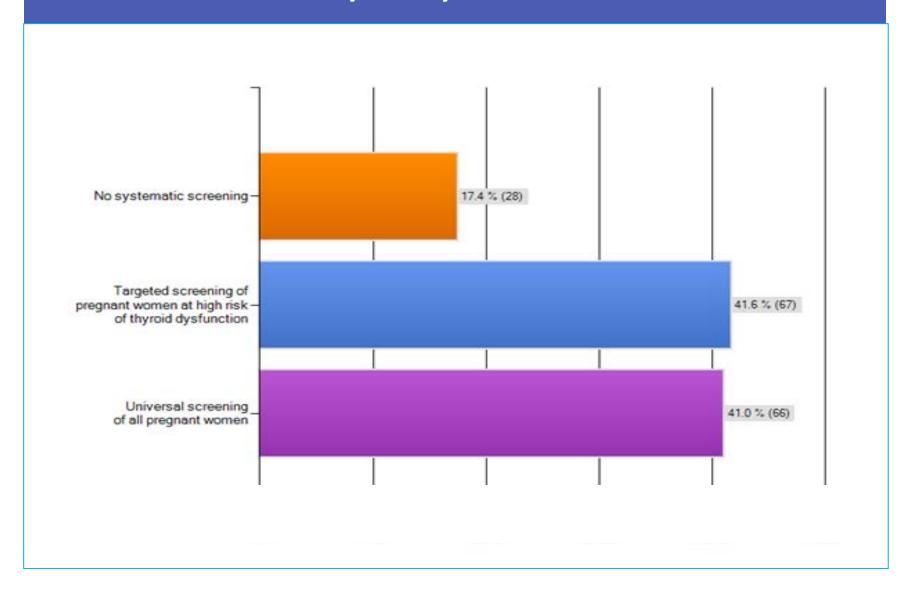
Women with symptoms or clinical signs suggestive of thyroid hypofunction

Women with type 1 DM or other autoimmune disorders. Women with infertility

Women with a prior history of miscarriage or preterm delivery Women with prior therapeutic head or neck irradiation or prior thyroid surgery

Women currently receiving levothyroxine replacement
Women living in a region with presumed iodine deficiency

## Do you (or your institution) screen pregnant women for thyroid dysfunction?

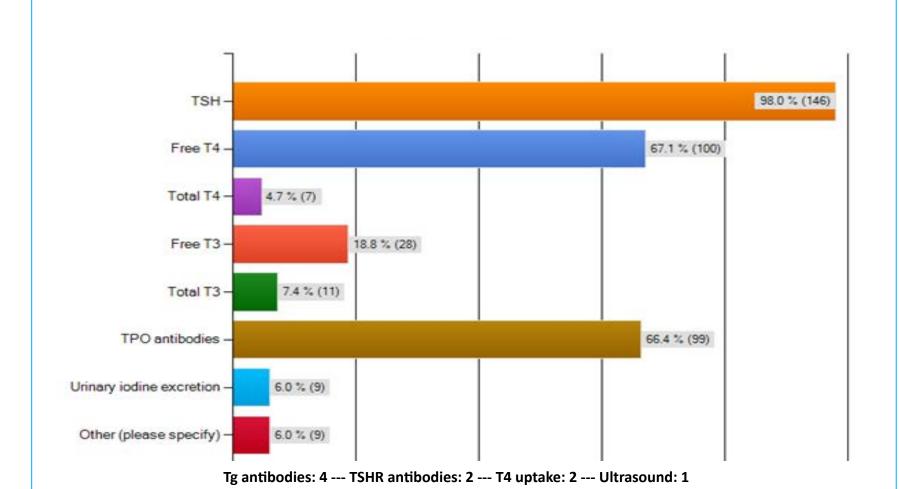


#### Stagnaro-Green et al. Thyroid 2011

First trimester screen hypothyroid algorithm

> TSH with reflex FT<sub>4</sub> if TSH <0.1 or TSH >2.5

## If you screen pregnant women for thyroid dysfunction, which tests do you use? (all answers possible)



## **Combined answers**

• TSH, FT4, TPO	41(27.5%)
• TSH	23 (15.4%)
<ul> <li>TSH, FT4, FT3, TPO</li> </ul>	18 (12.1%)
• TSH, TPO	18 (12.1%)
• TSH, FT <sub>4</sub>	16 (10.7%)

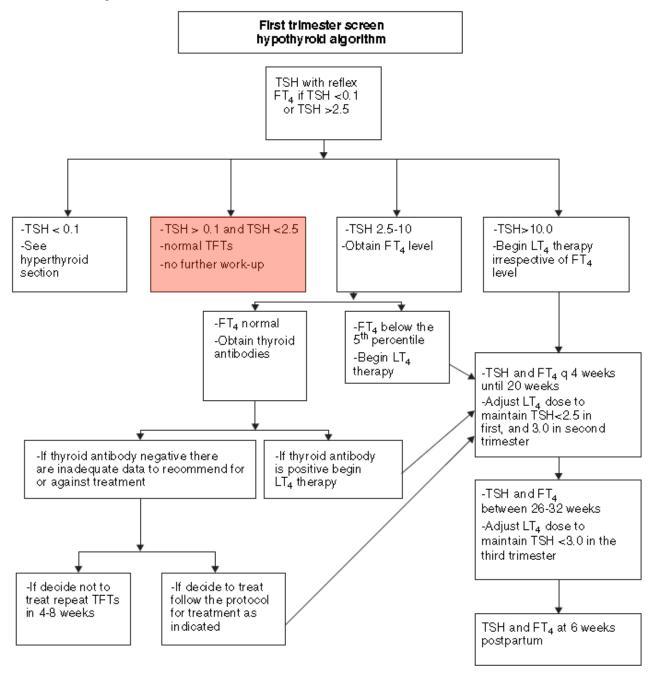
<ul> <li>TSH, FT4, TT3, TPO</li> </ul>	6 (4%)
<ul> <li>TSH, FT<sub>4</sub>, FT<sub>3</sub></li> </ul>	3 (2%)
<ul> <li>TSH, FT4, UI</li> </ul>	3 (2%)
<ul> <li>TSH, FT<sub>4</sub>, TPO, UI</li> </ul>	2 (1.3%)
<ul> <li>TSH, FT<sub>4</sub>, FT<sub>3</sub>, TPO, UI</li> </ul>	2(1.3%)
TSH, TPO, TG	2(1.2%)

## Sommario

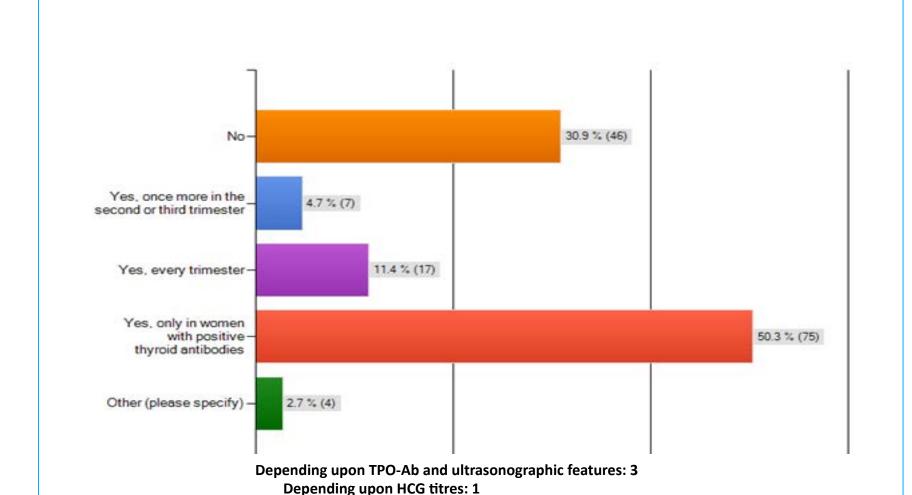
## Screening tireopatie in gravidanza

**Euti**roidismo Ipertiroidismo Ipotiroidismo

#### Stagnaro-Green et al. Thyroid 2011



If you screen pregnant women in the first trimester for thyroid dysfunction and if the initial screening test shows a TSH of 1.5 mIU/L, would you routinely test thyroid function again during the pregnancy?

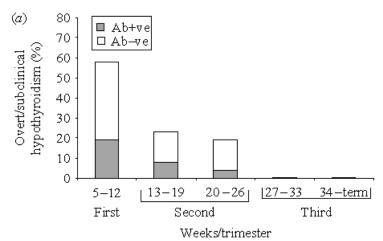


#### CLINICAL STUDY

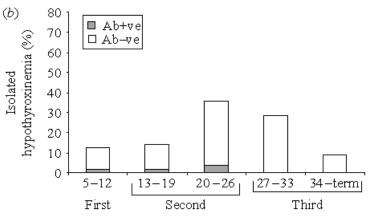
#### Gestational thyroid function abnormalities in conditions of mild iodine deficiency: early screening versus continuous monitoring of maternal thyroid status

Mariacarla Moleti<sup>1</sup>, Vincenzo Pio Lo Presti<sup>1</sup>, Filiberto Mattina<sup>1</sup>, Alfredo Mancuso<sup>2</sup>, Antonio De Vivo<sup>2</sup>, Grazia Giorgianni<sup>3</sup>, Beatrice Di Bella<sup>1</sup>, Francesco Trimarchi<sup>1</sup> and Francesco Vermiglio<sup>1</sup>

<sup>1</sup>Dipartimento Clinico-Sperimentale di Medicina e Farmacologia-Sezione di Endocrinologia, <sup>2</sup>Dipartimento di Scienze della Riproduzione, Sezione di Patologia Ostetrica and <sup>3</sup>Dipartimento di Scienze Biochimiche, Fisiologiche e della Nutrizione-Servizio di Biochimica Clinica, University of Messina, 0.8335 Macdina Italia.



>40% hypothyroid women would not have been diagnosed, if we had limited our observation to early thyroid function tests alone



Weeks/trimester

IH became progressively more common from the end of the first trimester onwards, peaking between weeks 20 and 26

## Sommario

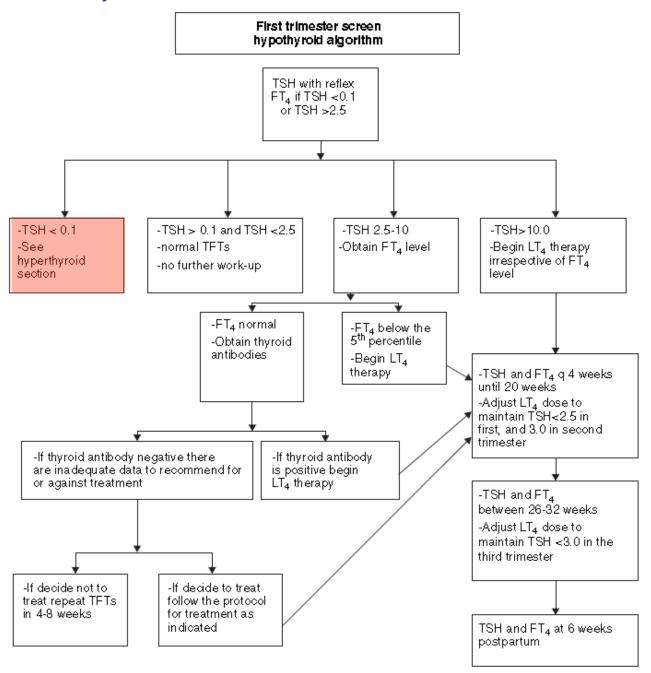
## Screening tireopatie in gravidanza

**Euti**roidismo

Ipertiroidismo

Ipotiroidismo

#### Stagnaro-Green et al. Thyroid 2011



## IPERTIROIDISMO IN GRAVIDANZA



1-3 casi/1000 gravidanze

## Sospetto clinico

Soggettività: astenia, palpitazioni, ansia, intolleranza al caldo, diaforesi, perdita di peso/non incremento ponderale con ↑ apporto calorico; iperemesi; prurito;

Anamnesi: pregressa storia di ipertiroidismo e/o familiarità per tireopatie autoimmuni; pregressa storia di iperemesi gravidica

Obiettività: iperplasia tiroidea, f.c.>100 b/min, segni di orbitopatia e/o mixedema pretibiale

## IPERTIROIDISMO IN GRAVIDANZA



TSH <0.1 μUI/mL + FT4 † ↑

Ipertiroidismo Gestazionale transitorio solo in gravidanza; non autoimmune; spesso associato a iperemesi gravidica

Malattia di Graves
 esordio in gravidanza RARO; autoimmune

Elevati livelli sierici di FT4 (FT3), TSH soppresso, AbTPO e TrAb negativi;

Esordio poco prima del termine del I trimestre

Tendenza alla risoluzione spontanea nel corso del II trimestre

Possibile recidiva nella(e) gravidanza(e) successiva(e)

Prevalenza variabile nelle diverse parti del mondo (% di tutte le gravidanze)

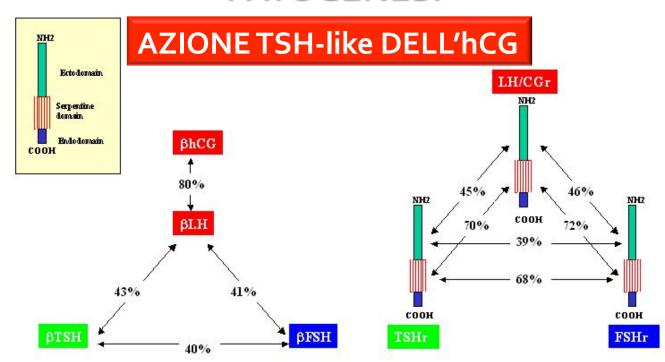
-Europa: 2-3% →10 volte più frequente del Graves

-Giappone: 0,3%

-Hong Kong: 11%

### **PATOGENESI**

Elevati variant

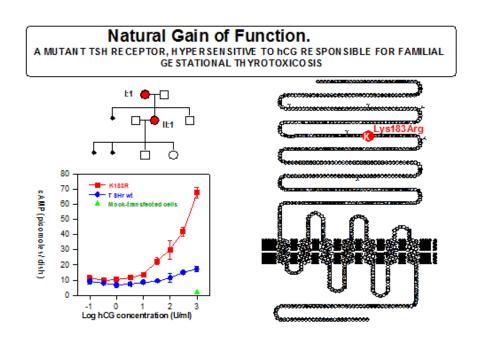


Livelli/anda normali ł 7

#### **PATOGENESI**

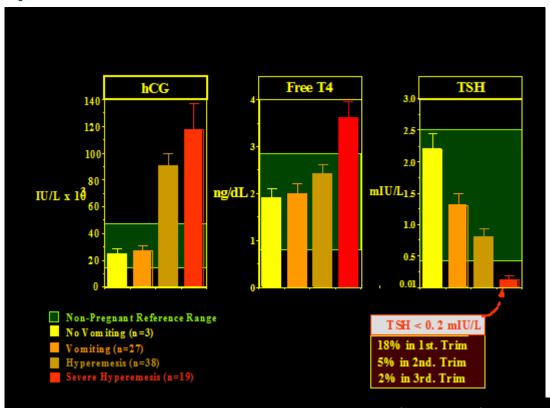
#### Mutazione del recettore del TSH

Descritta una singola mutazione nel dominio extracellulare del recettore del TSH che rende il recettore mutato altamente sensibile all' hCG



### Quando sospettarlo?

- Segni clinici di ipertiroidismo (rari)
- Iperemesi (frequente)



### Attendere il fisiologico decremento dell'hCG

### Monitoraggio della funzione tiroidea (FT4+TSH)

#### RECOMMENDATION 25

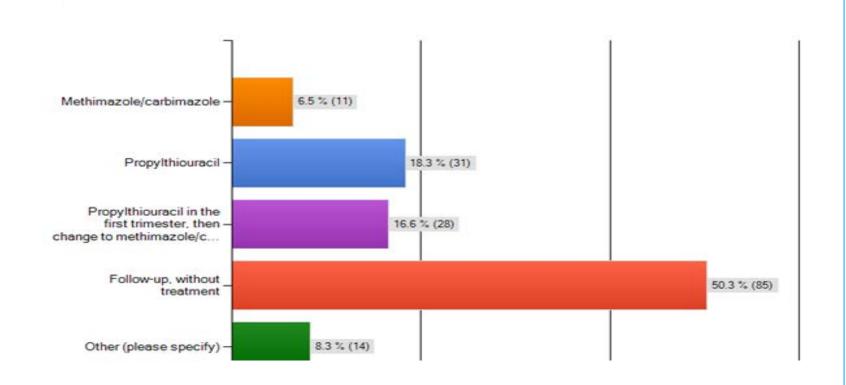
The appropriate management of women with gestational hyperthyroidism and hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. Level A-USPSTF

Stagnaro-Green et al. Thyroid 2011

3.2. Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free  $T_4$  do not require ATD treatment. USPSTF recommendation level: A; evidence, good ( $1 \oplus \oplus \oplus \oplus$ ). Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total  $T_3$  values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement. USPSTF recommendation level: B; evidence, poor ( $2 \oplus \oplus \oplus \oplus$ ).

De Groot et al. J Clin Endocrinol Metab, August 2012

## A 24 year old woman is 8 weeks pregnant. She has severe nausea and vomiting, weight loss and palpitation. Thyroid function tests showed hyperthyroidism, without thyroid antibodies



Beta blocker: 6 -- Miscellaneous: 8

## IPERTIROIDISMO IN GRAVIDANZA



TSH <0.1 μUI/mL + FT4 † ↑

Ipertiroidismo Gestazionale transitorio solo in gravidanza; non autoimmune; spesso associato a iperemesi gravidica

Malattia di Graves

esordio in gravidanza RARO; autoimmune

## TOLLERANZA IMMUNOLOGICA IN GRAVIDANZA



#### **PROGESTERONE- Cortisolo**

Riduzione generalizzata risposta immune materna

#### FATTORI UMORALI DI ORIGINE TROFOBLASTICA

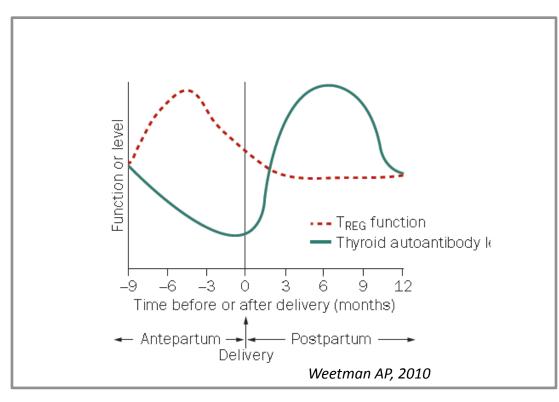
Soppressione della risposta immune a livello dell'interfaccia tra madre e placenta

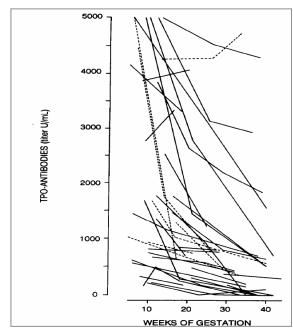
#### PRODUZIONE LINFOCITI Treg MATERNI

Induzione e mantenimento teleranza verso alloantigeni fetali

MIGLIORAMENTO MALATTIE AUTOIMMUNI IN GRAVIDANZA

## DECORSO TIREOPATIE AUTOIMMUNI IN GRAVIDANZA E NEL POST-PARTUM





↓ 50-60% titolo anticorpale

Glinoer D, 1994

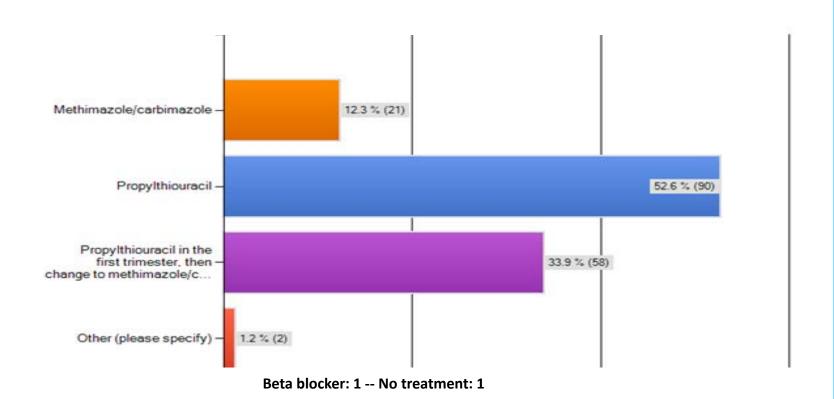
## IPERTIROIDISMO IN GRAVIDANZA

## Malattia di Graves

Rischio di complicanze materno-fetali direttamente correlato con la severità e la durata dell'ipertiroidismo

Pregnancy complications	Late or poor control of thyrotoxicosis (%)	Adequate control of thyrotoxicosis (%)
Spontaneous abortion	26	13
Congestive heart failure	25	3
Thyroid storm	21	<2
Preeclampsia	21	6
	11	2
Premature delivery	15	10
tection and excellent elementation of the Control o	18	3
Low birth weight 2	23	10 (P = 0.04)
	27	6
Stillbirth	25	0

# A 24 year old woman is 8 weeks pregnant. She is newly diagnosed with Graves' disease. How would you treat her thyrotoxicosis?



Commentary

#### **Putting Propylthiouracil in Perspective**

David S. Cooper and Scott A. Rivkees

### PTU-related hepatotoxicity vs MMI-related birth defects

➤ 33 published reports of severe PTU-related liver failure in adults

➤ Odds ratio of 18 (95% CI 3–121) for choanal atresia among infants

ure

be

าtal

- ... it is reasonable to recommend that pregnant hyperthyroid women be treated with PTU during the first trimester rather than with MMI. The risk of PTU for expectant mothers can be reduced by limiting PTU use to the first trimester and then changing to MMI
- **▶2** reports of serious maternal liver injury due to PTU during pregnancy and 2 reports of liver injury in fetuses whose mothers took PTU

The risk of aplasia cutis associated with prenatal MMI use is estimated in about 0.03%, not above background

3

4

## **TABLE 9.** Guidelines for the medical treatment of GD in pregnancy

Monitor clinical signs (heart rate, weight gain, thyroid size, etc.) and serum FT<sub>4</sub> and FT<sub>3</sub>, TSH every 2–4 wk.

Use the lowest dose of ATD to maintain the patient in a euthyroid or mildly hyperthyroid state. ATD dosage can usually be lowered after the first trimester and often discontinued during the last trimester. To avoid fetal hypothyroidism, it is advised to maintain maternal serum FT<sub>4</sub> concentrations at or slightly above (<10%) the upper limit of the normal nonpregnant reference range (~1.9 ng/dl or ~24.5 pmol/liter).

Do not attempt to normalize serum TSH. Serum TSH concentrations between 0.1 and 0.4 mlU/ liter are appropriate. Lower or undetectable TSH levels are acceptable if the patient's clinical condition remains satisfactory.

Concerning the choice of ATD, the use of PTU is

Evitare l'associazione ATD-LT4 permeabilità placentare ATD>>L-T4

Monitoraggio ogni 2-4 settimane

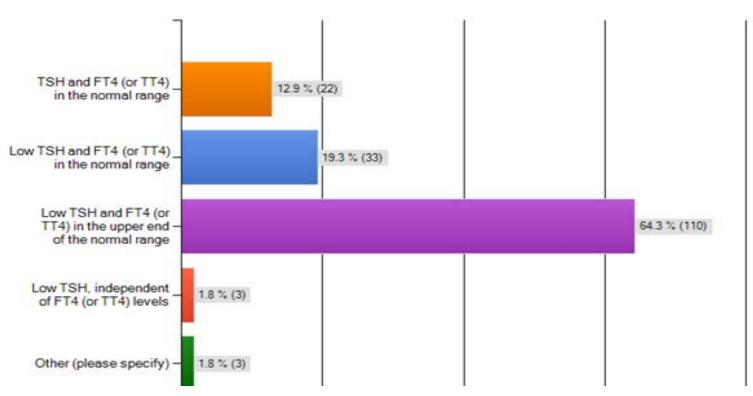
Utilizzare basse dosi MMI o PTU

Mantenere FT4 ai limiti alti della norma, TSH basso/indosabile

PTU 1° trim.

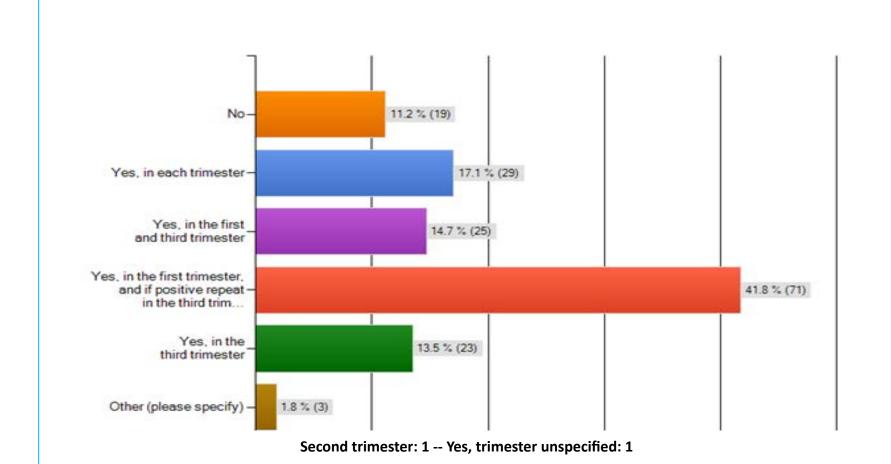
MMI 2° trim-termine

## What are the target thyroid test results you aim to achieve with antithyroid drugs in pregnancy?

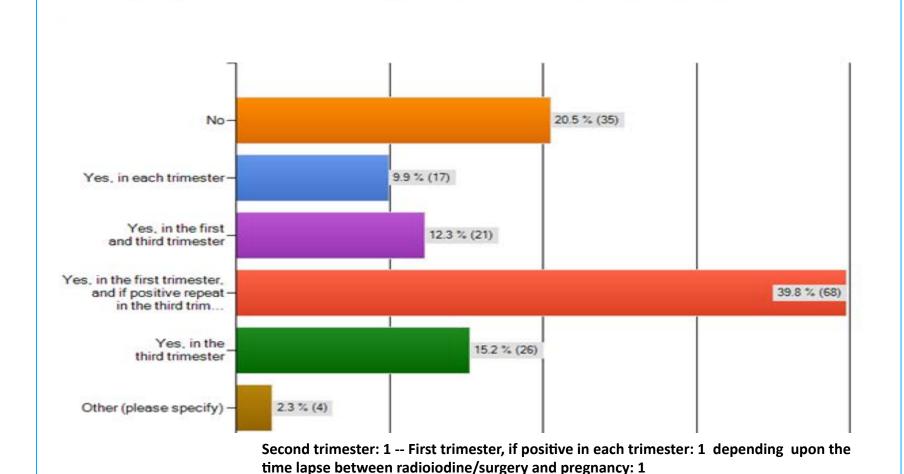


Low TSH and high normal FT4: 1 -- Depending upon TSHR antibody titre:1

## In a pregnant woman with Graves' disease treated with antithyroid drug, do you routinely check TSH receptor antibodies?



In a euthyroid pregnant woman previously treated with radioiodine or total thyroidectomy for Graves' disease, do you routinely check TSH receptor antibodies?



Question 34: What is the value of TRAb measurement in the evaluation of a pregnant woman with Graves' hyperthyroidism?

#### ■ RECOMMENDATION 32

If the patient has a past or present history of Graves' disease, a maternal serum determination of TRAb should be obtained at 20–24 weeks gestation. Level B-USPSTF

Stagnaro-Green et al. Thyroid 2011

2.2.1. Because thyroid receptor antibodies (thyroid receptor stimulating, binding, or inhibiting antibodies) freely cross the placenta and can stimulate the fetal thyroid, these antibodies should be measured by 22 wk gestational age in mothers with: 1) current Graves' disease; or 2) a history of Graves' disease and treatment with <sup>131</sup>I or thyroidectomy before pregnancy; or 3) a previous neonate with Graves' disease; or 4) previously elevated TRAb. Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction. USPSTF recommendation level: B; evidence, fair (1)

De Groot et al. J Clin Endocrinol Metab, August 2012

### Sommario

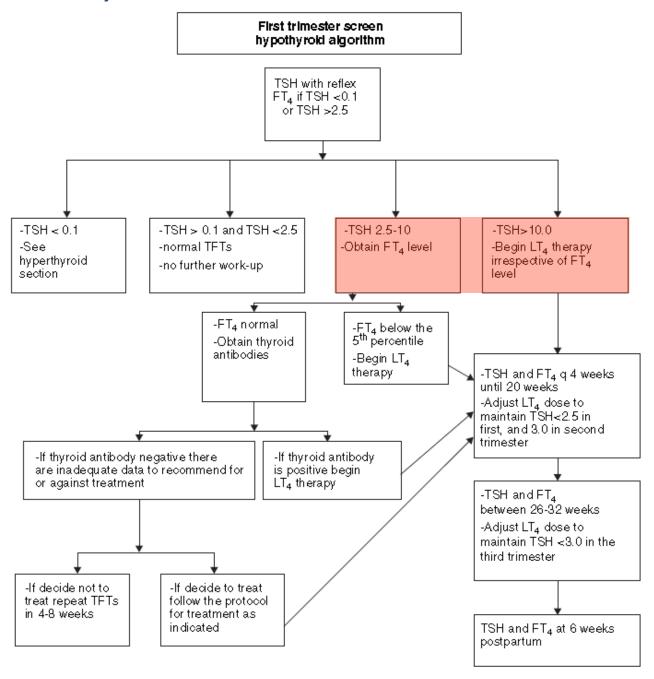
### Screening tireopatie in gravidanza

**Euti**roidismo

Ipertiroidismo

*Ipotiroidismo* 

#### Stagnaro-Green et al. Thyroid 2011



### IPOTIROIDISMO IN GRAVIDANZA



### Cause più frequenti (Europa)

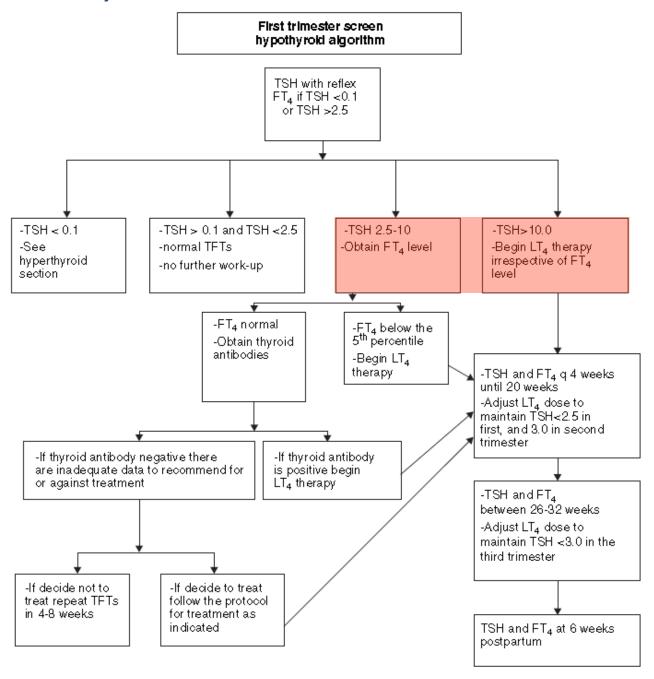
**INADEGUATO APPORTO IODICO** 

**TIROIDITE DI HASHIMOTO** 

PREGRESSA ABLAZIONE
CHIRURGICA/RADIOMETABOLICA



#### Stagnaro-Green et al. Thyroid 2011



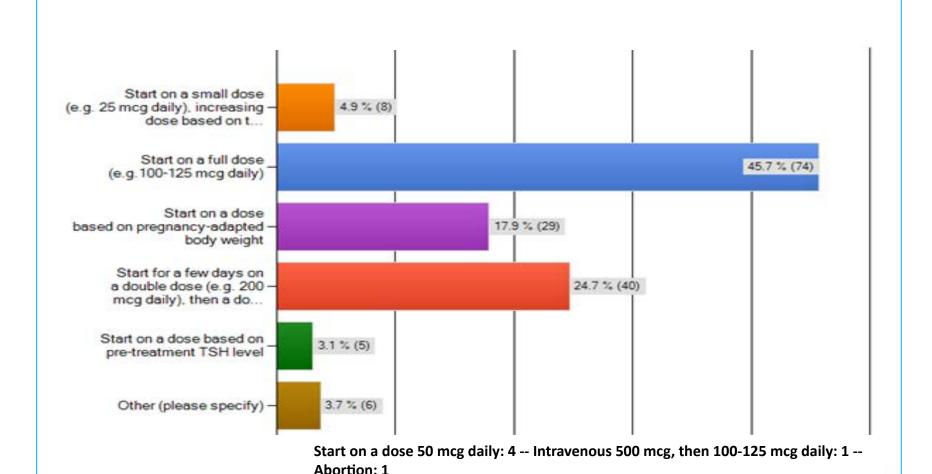
### 1.0. Management of hypothyroidism during pregnancy: maternal and fetal aspects

1.2.2. SCH (serum TSH concentration above the upper				
limit of the trimester-specific reference range with a nor-				
mal free T <sub>4</sub> ) may be associated with an adverse outcome				
for both the mother and offspring.				
the panel				
recommends T <sub>4</sub> replacement in women with SCH. For				

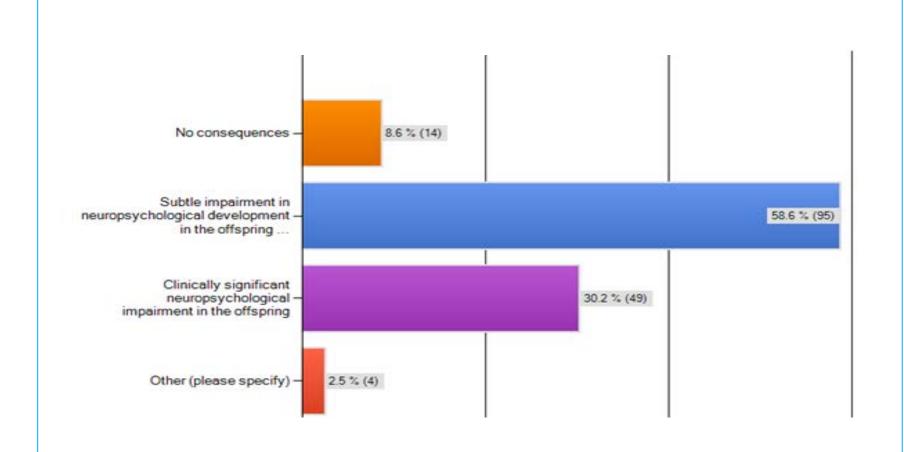
### De Groot et al. J Clin Endocrinol Metab, August 2012

- 1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T<sub>4</sub> dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter.
- 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  $(1|\oplus\oplus\oplus)$  (12-15).
- 1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T<sub>4</sub> 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.

## A 24 year old woman is 12 weeks pregnant and just been diagnosed with overt primary hypothyroidism (TSH 86 mIU/I) What dose of L-thyroxine would you initially start?

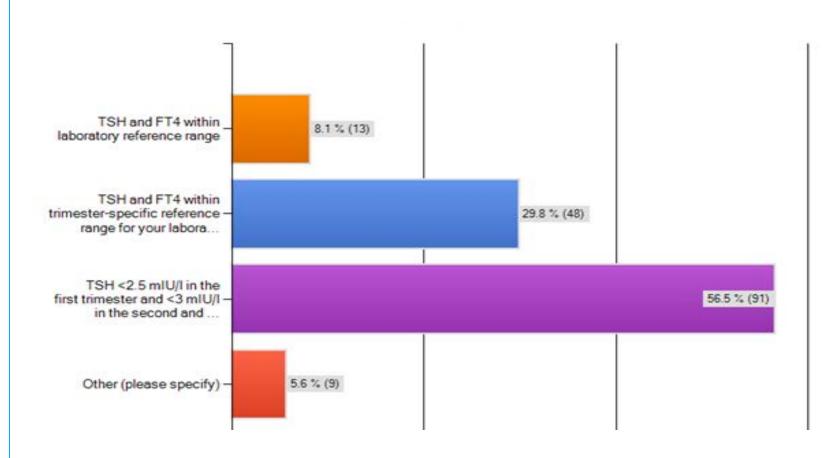


## What do you perceive as the risk(s) from overt hypothyroidism in the above patient who was diagnosed and treated adequately in the late first trimester?



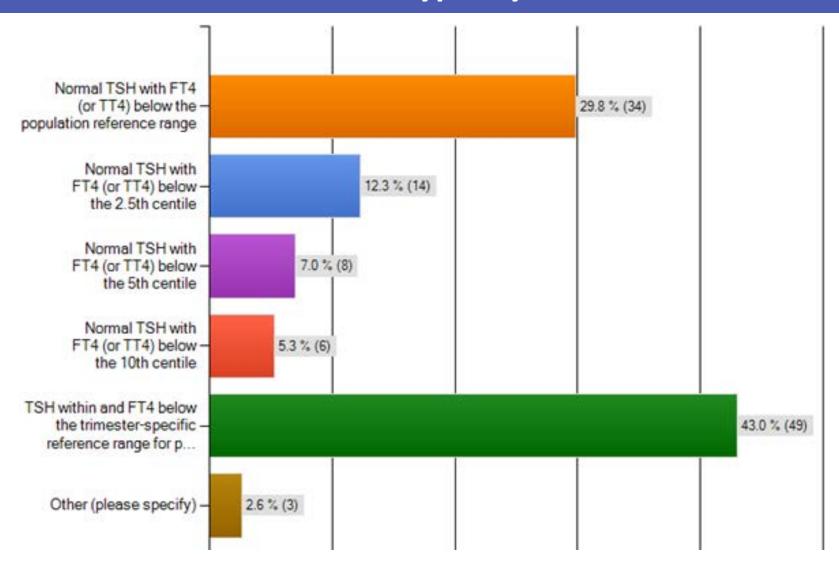
Outcome depends upon T4 level: 2

## What are the target thyroid test results you aim to achieve with L-thyroxine replacement in pregnancy?



Various target TSH levels +/- FT4 or FT3 targets: 9

## If you treat isolated hypothyroxinemia, how do you define isolated hypothyroxinemia?



### PARTICULAR CONDITIONS

	Treat	Follow up	Don't treat or Follow up
Isolated Hypothyroxinemia (TSH<2.5 mIU/l and low FT4)	38.5%	48.0%	13.5%
Isolated thyroid Ab+ (TSH<2.5 mIU/l)	9.6%	74.0%	16.4%

Most studies have shown an association between maternal hypothyroxinaemia and impaired neuropsychological development of offspring

A large interventional study failed to show any benefit from treating IH

Both ATA and Endocrine Society guidelines recommend against the treatment of maternal hypothyroxinaemia in pregnancy

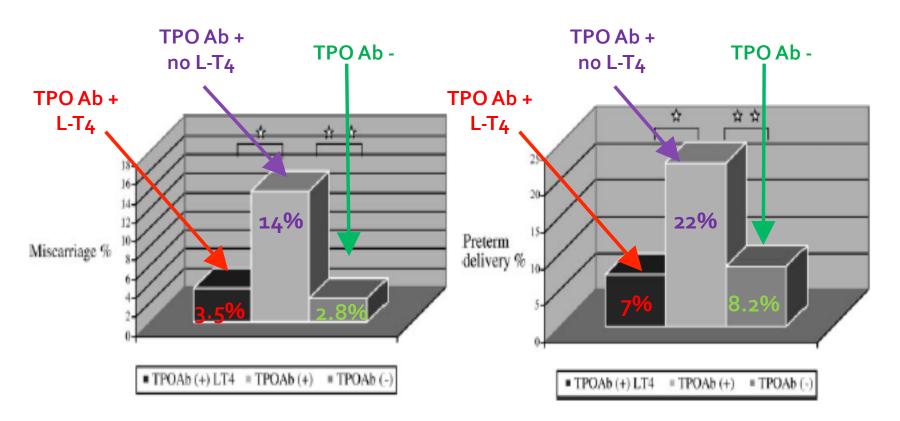
## In the survey nearly 40% of the responders would treat IH

Pop VJ et al. Clin Endocrinol (Oxf) 1999 Henrichs J et al. JCEM 2010 Moleti M et al. J Thyroid Res 2011 Oken E et al. JCEM 2009 Casey BM et al. Obstet Gynecol 2007 Lazarus J et al, N Engl J Med 2012

## Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications

Roberto Negro, Gianni Formoso, Tiziana Mangieri, Antonio Pezzarossa, Davide Dazzi, and Haslinda Hassan

Department of Endocrinology (R.N., G.F.), Azienda Ospedaliera L.E./1, 73100 Lecce, Italy; Department of Obstetrics and Gynecology (T.M.), Casa di Cura "Salus", 72100 Brindisi, Italy; Department of Internal Medicine (A.P., D.D.), Azienda Ospedaliera PR, "Di Vaio" Hospital, 43036 Fidenza, Italy; and Endocrine Unit (H.H.), Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam BA 1000



# HOW SHOULD TAb+ EUTHYROID WOMEN BE MONITORED AND TREATED DURING PREGNANCY?

#### ■ RECOMMENDATION 20

Euthyroid women (not receiving LT<sub>4</sub>) who are TAb+ require monitoring for hypothyroidism during pregnancy. Serum TSH should be evaluated every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation. **Level B-USPSTF** 

Stagnaro-Green et al. Thyroid 2011

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 ⊕⊕⊕○).

### Acknowledgements

Mariacarla Moleti Beatrice Di Bella Silvia Presti Giacomo Sturniolo

**Kriss Poppe** 

All respondents for completing the questionnaire

The executive committee of the ETA for giving us a permission to carry out the survey