



Roma, 9-12 novembre 2017



ITALIAN CHAPTER



# Simposio

**GESTIONE INTEGRATA DELLE TIREOPATIE IN GRAVIDANZA**

**Test di laboratorio: vecchi e nuovi cut-off**

*Adele Latina*



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# Conflitti di interesse



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Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

nessuno



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# Indice



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- Modificazioni fisiologiche degli ormoni tiroidei in gravidanza
- TSH basso vs ipertiroidismo
- Concetto di ‘valori normali’
- Ipotiroidismo “overt” e subclinico: vecchi e nuovi cut-off



# Modifiche fisiologiche OT in gravidanza

- Effetti stimolatori hCG → aumentata produzione T4
- Aumento TBG e riduzione albumina
- Aumentata escrezione urinaria iodio
- Passaggio trans-placentare di iodio e T4





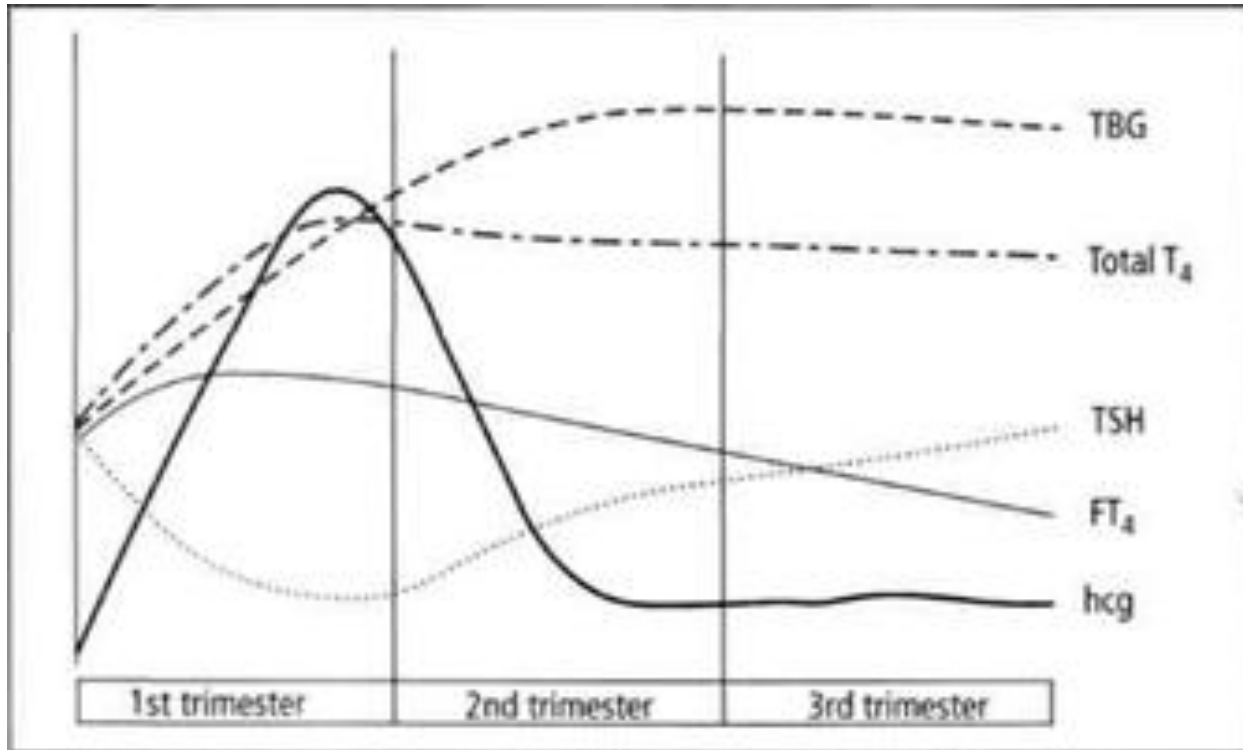
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# Modifiche fisiologiche OT in gravidanza





# La gravidanza normale: TSH

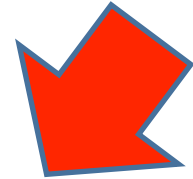


Non gravida

0.4 mU/L

4.0 mU/L

Gravida



Riduzione di 0.1-0.2 mU/L

Riduzione di 0.5-1.0 mU/L

Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. *Thyroid* 2004.

Negro R Significance and management of low TSH in pregnancy. In: Lazarus J, Pirags V, Butz S (eds) *The Thyroid and Reproduction* 2009.



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# TSH basso ed effetto hCG



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- TSH < 0.1 mU/L in ~ 5% delle gravide a partire dalla 11<sup>a</sup> s.g.
- TSH < 0.2 nel 67% se hCG > 200,000 IU/L e nel 100% se > 400,000 IU/L
- Diagnosi di ipertiroidismo (< 0.5%): TSH soppresso e OT superiori alla norma, TRAb +
- D.D. con tireotossicosi gravidica (no storia di tireopatia, gozzo, OTC; mild; emesi)

Lambert-Messerlian G, et al. FaSTER Research Consortium 2008 First- and second trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. Am J Obstet Gynecol.

Lockwood CM, Grenache DG, Gronowski AM 2009 Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 19:863–868.



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# Intervalli di riferimento



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Basati su 2.5- 97.5°percentile  
di una corrispondente popolazione  
con ottimale apporto iodico,  
senza tireopatia nota e con AbTPO negativi

✓ di donne gravide



De Groot L, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012.

Stagnaro-Green A, et al. ATA Guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011.

Lazarus J, et al. 2014 ETA guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014.





# La gravidanza normale



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TABLE 4. REFERENCE RANGES FOR THYROTROPIN AND FREE THYROXINE DURING EARLY PREGNANCY WORLDWIDE

Author, country (reference) (analyzing method)	N	Gestation (week)	TSH, mIU/L		FT4, pmol/L (ng/dL)		Iodine intake/adequacy	Mean BMI	Ethnicities
			Median	2.5th- 97.5th	Median	2.5th- 97.5th (Median, 2.5th-97.5th)			
Bestwick et al., Italy (24) (AutoDELPIA)	5505	<16	1.07	0.04-3.19	9.3	7.4-12.2 (0.73, 0.58-0.95)	Moderate-mild <sup>a</sup>	NR	
Bestwick et al., UK (24) (Advia Centaur)	16,334	<16	1.11	0.06-3.50	9.9	10.9-17.9 (1.08, 0.85-1.40)	Moderate-mild <sup>a</sup>	NR	
Boccos-Terraz et al., Spain (264) (Architect)	481	<14	0.94	0.41-2.63	9.9	10.8-17.8 (1.08, 0.84-1.38)	Mild	NR	Caucasian (93%)
Gilbert et al., Australia (271) <sup>a</sup> (Architect)	1817	9-15	0.74	0.02-2.15	13.5	10.4-17.8 (1.05, 0.81-1.39)	Borderline	NR	Australian
Lambert-Messerlian et al., USA (270) <sup>a</sup> (Immulin 2000)	8351	T1	1.00	0.12-3.37	14.2	10.4-17.8 (1.0, 0.81-1.38)	Mild	NR	Caucasian (67%) and Hispanic (23%) <sup>b</sup>
La'ulu et al., USA (139,265) <sup>a</sup>	2172	10-13	0.94	0.02-2.69	14.7	11.4-18.6 (1.15, 0.89-1.45)	Mild	NR	Hispanic (37%), Caucasian (29%), African American (27%), Asian (8%)
	2683	14-20	1.14	0.15-3.11	12.0	9.3-15.2 (0.94, 0.73-1.19)			
Li et al., China (17) (Cobas Eleasy 601)	640	7-12	1.67	0.10-4.34	15.8	12.3-20.9 (1.13, 0.86-1.63)	Borderline	NR	Chinese (presumed)
Mäkitie et al., Finland (266) (Architect i2000)	1111	7-12	1.11	0.08-3.54	15.3	11.7-22.8 (1.07, 0.81-1.38)	Sufficient <sup>c</sup>	22.4	Finnish (presumed)
Medini et al., the Netherlands (267) (Vitros ECI)	1111	7-12	1.11	0.11-4.24	14.6	11.3-23.4 (1.03, 0.81-1.38)	Sufficient <sup>c</sup>	24.5	Dutch (52%), Surinamese/Antillean (12%), Turkish (8%), Moroccan (6%)
Pease et al., USA (142) (Advia Centaur)	1111	7-12	1.11	0.03-4.04	14.7	10.4-22.0 (1.03, 0.81-1.38)	Sufficient <sup>c</sup>	NR	White (77%) and African American (10%)
Quinn et al., Russia (272) (Abbott AxSYM)	349	12	2.00	0.04-3.60	21.2 <sup>b</sup>	1.5-2.9 <sup>d</sup>	—	NR	Russian (presumed)
Springer et al., Czech Republic (268) <sup>a</sup> (ADVIA Centaur)	4337	9-11	1.21	0.09-4.67	—	—	—	NR	Caucasian (99%)
Stoicker et al., Switzerland (262) (Architect i2000SR)	575	6-12	0.95	0.06-3.67	19.9	10.5-18.5 (1.08, 0.82-1.44)	Sufficient	NR	Swiss (presumed)
	528	T2	1.02	0.20-4.68	12.2	9.5-15.7 (0.85, 0.74-1.22)			
Vaidya et al., UK (Modular E 170) (274)	1089	<12	1.08	0.07-2.82	14.6	10.7-19.4 (1.12, 0.83-1.39)	Mild-moderate	NR	Caucasian (91) and South Asian (4)

0.02 – 0.35

2.15 – 4.68

7.4 – 12.9

12.2 – 23.4

320



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# Dosaggio della FT<sub>4</sub>



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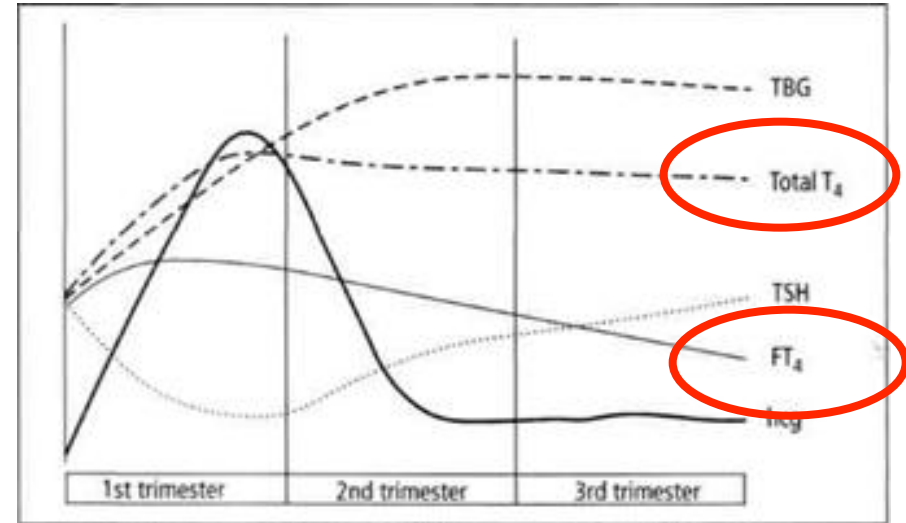


Dialisi all'equilibrio: gold standard

Ultrafiltrazione + cromatografia liquida/  
spettrometria tandem mass:  
laboriosi, costosi, non disponibili  
ovunque

Metodi immunometrici automatici:

- aumento TBG / diminuzione albumina
- anticorpi eterofili



Range di normalità di FT<sub>4</sub>: trimestre-, popolazione- e metodo-specifico



# TSH normale



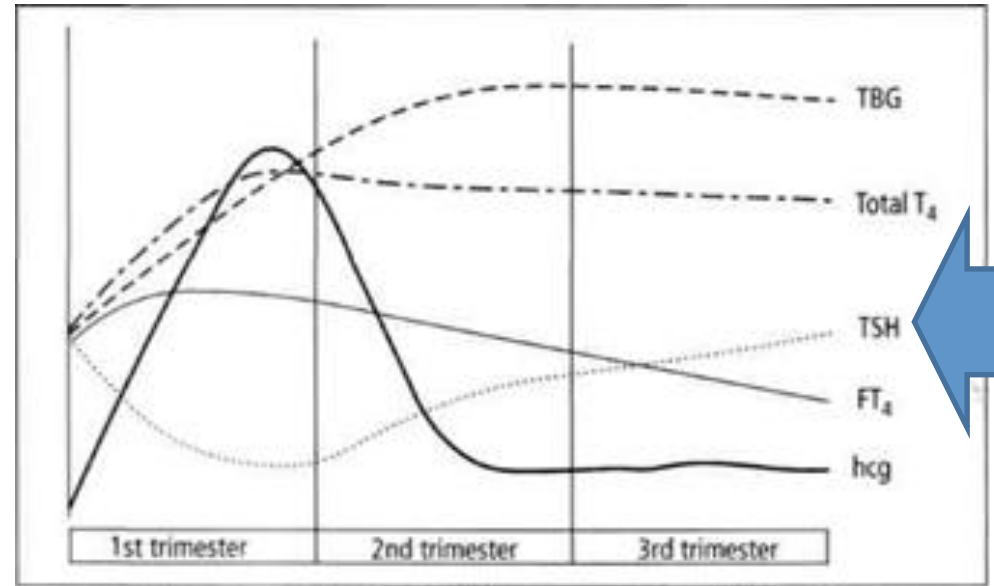
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Metodo di dosaggio (III generazione: sensibilità funzionale 0.01 mU/L)

Variabilità intra-individuale

Influenza di: etnia, apporto iodico, stato anticorpale, età, n. gravidanze, BMI, fumo



Range di normalità di TSH: trimestre-, popolazione- e metodo-specifico

Spencer CA. Assay of Thyroid Hormones and Related Substances. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.

Pop VJ, et al. Maternal thyroid parameters, body mass index and subsequent weight gain during pregnancy in healthy euthyroid women. Clin Endocrinol (Oxf) 2013.



# Ipotiroidismo



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3% delle gravidanze (comprese forme subcliniche)

‘Overt’:

- TSH oltre il limite superiore del range di riferimento con FT4 ridotta (80% AbTPO +)
- TSH > 10 mU/L



# Ipotiroidismo subclinico: 'vecchi' cut-off



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THYROID  
Volume 21, Number 10, 2011  
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DOI: 10.1089/thy.2011.0087

PREGNANCY AND FETAL DEVELOPMENT

## 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),<sup>1</sup> Marcos Abalovich,<sup>2</sup> Erik Alexander,<sup>3</sup> Fereidoun Azizi,<sup>4</sup> Jorge Mestman,<sup>5</sup>  
Roberto Negro,<sup>6</sup> Angelita Nixon,<sup>7</sup> Elizabeth N. Pearce,<sup>8</sup> Offie P. Soldin,<sup>9</sup>  
Scott Sullivan,<sup>10</sup> and Wilmar Wiersinga<sup>11</sup>

SPECIAL FEATURE

Clinical Practice Guideline

### 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

### Guidelines

European  
Thyroid Journal

Eur Thyroid J 2014;3:76-94  
DOI: 10.1159/000362597

Received: February 13, 2014  
Accepted after revision: April 1, 2014  
Published online: June 7, 2014

### 2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children

John Lazarus<sup>a</sup> Rosalind S. Brown<sup>c</sup> Chantal Daumerie<sup>d</sup>  
Alicja Hubalewska-Dydejczyk<sup>e</sup> Roberto Negro<sup>f</sup> Bijay Vaidya<sup>b</sup>



# Ipotiroidismo subclinico: 'vecchi' cut-off



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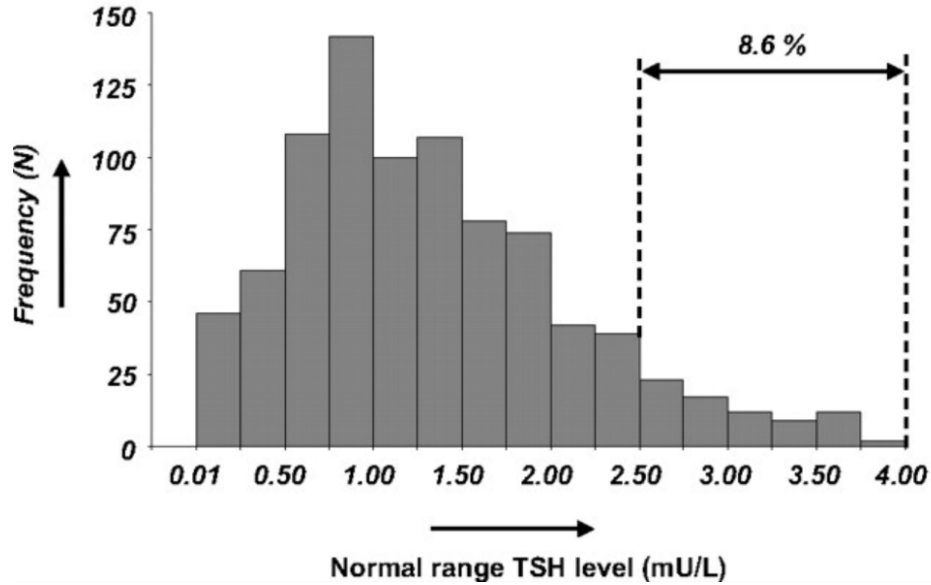
TSH	Primo trimestre	Secondo trimestre	Terzo trimestre
Haddow	0.08-2.73	0.39-2.70	
Stricker	0.09-2.83	0.20-2.79	0.31-2.90
Panesar	0.30-2.30	0.03-3.10	0.13-3.50
Soldin	0.24-2.99	0.46-2.95	0.43-2.78
Vermiglio	0.03-2.30	0.29-2.80	0.34-3.00

Primo trimestre	Secondo trimestre	Terzo trimestre
0.1-2.5	0.2-3.0	0.3-3.5

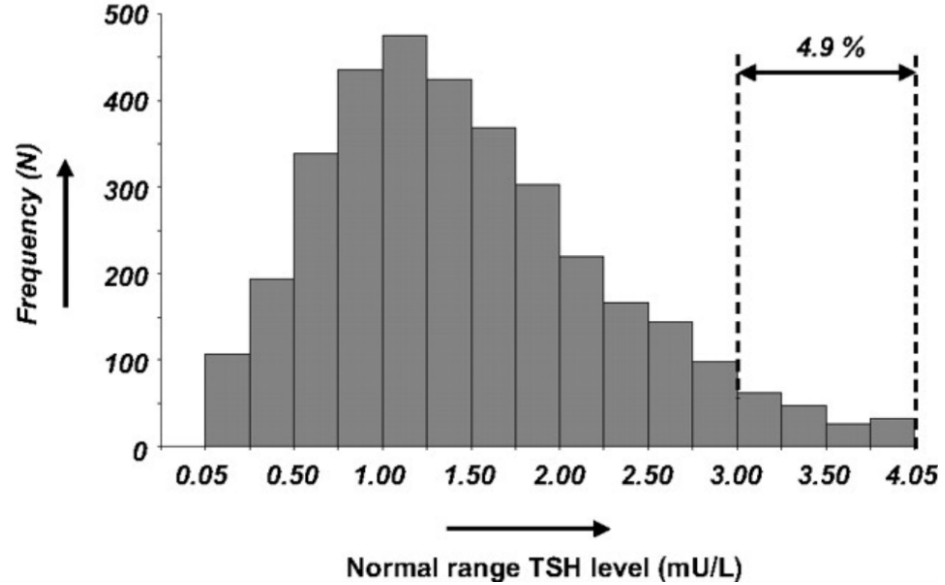
Stagnaro-Green et al. ATA Guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011.  
 Lazarus J et al. 2014 ETA guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014.



First trimester



Second trimester





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TSH	Primo trimestre	Secondo trimestre	Terzo trimestre
Marwaha RK (India) 2008	0.60-5.00	0.44-5.78	0.74-5.70
Yan YQ (China) 2011	0.03-4.51	0.05-4.50	0.47-4.54
Li C (China) 2014	0.12-5.08		

Clinical Chemistry 61:5  
704-713 (2015)

## Mini-Review

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# Thyroid Function in Pregnancy: What Is Normal?

Marco Medici,<sup>1,2†</sup> Tim LM. Korevaar,<sup>1,2†</sup> W. Edward Visser,<sup>1,2</sup> Theo J. Visser,<sup>1,2</sup> and Robin P. Peeters<sup>1,2</sup>

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# Ipotiroidismo subclinico: nuovi cut-off



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THYROID

Volume 27, Number 3, 2017

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DOI: 10.1089/thy.2016.0457

**SPECIAL ARTICLE**

## 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,<sup>1,\*</sup> Elizabeth N. Pearce,<sup>2,\*</sup> Gregory A. Brent,<sup>3</sup> Rosalind S. Brown,<sup>4</sup> Herbert Chen,<sup>5</sup>  
Chrysoula Dosiou,<sup>6</sup> William A. Grobman,<sup>7</sup> Peter Laurberg,<sup>8,†</sup> John H. Lazarus,<sup>9</sup> Susan J. Mandel,<sup>10</sup>  
Robin P. Peeters,<sup>11</sup> and Scott Sullivan<sup>12</sup>



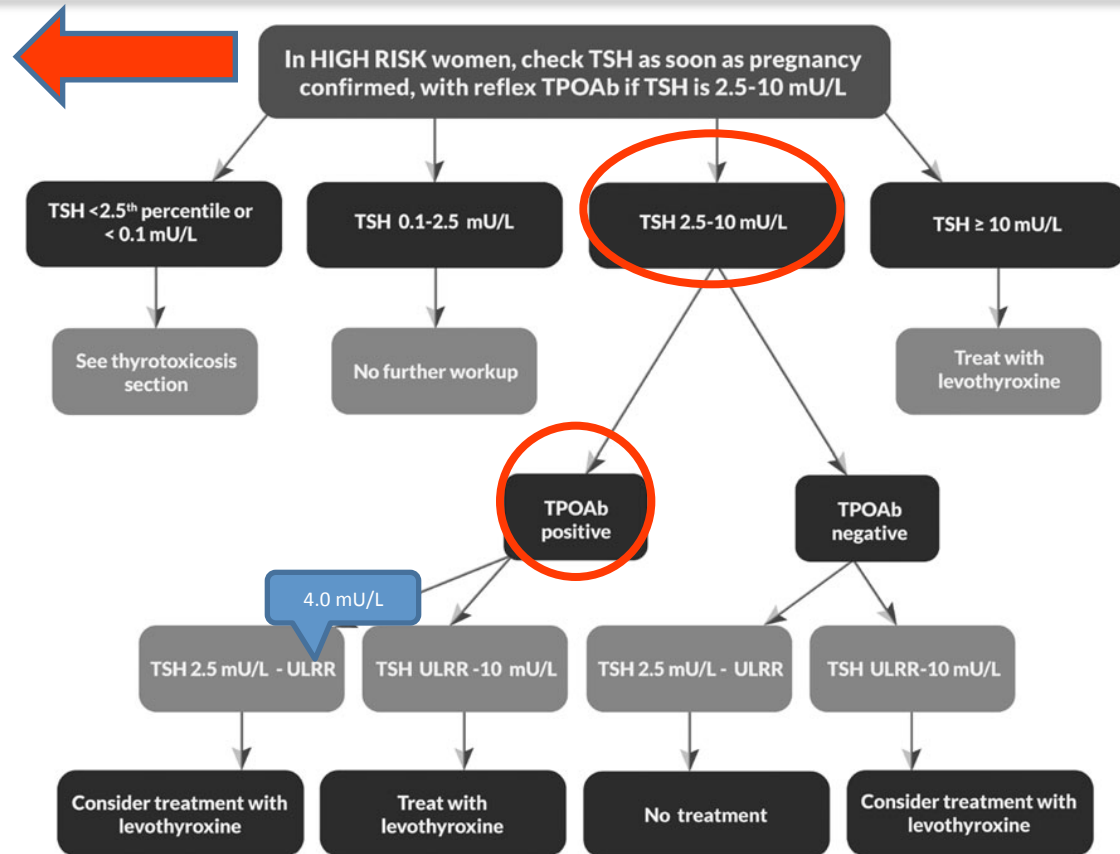
# Ipotiroidismo subclinico: nuovi cut-off



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- Storia di tireopatia
- Segni/sintomi di disfunzione tiroidea
- Gozzo
- Nota positività AbTPO
- Età > 30 anni
- Diabete tipo 1 o altre patologie autoimmuni
- Storia di poli-abortività o parto pretermine o infertilità
- Pregressa irradiazione del capo o del collo o precedente chirurgia tiroidea
- Familiarità per tireopatia autoimmune o disfunzioni tiroidee
- Grave obesità
- Terapia con amiodarone/litio o recente esposizione a mdc iodato
- Due o più precedenti gravidanze
- Residenza in area iodo-carente





# Alterata correlazione hCG/FT4/TSH in AbTPO+



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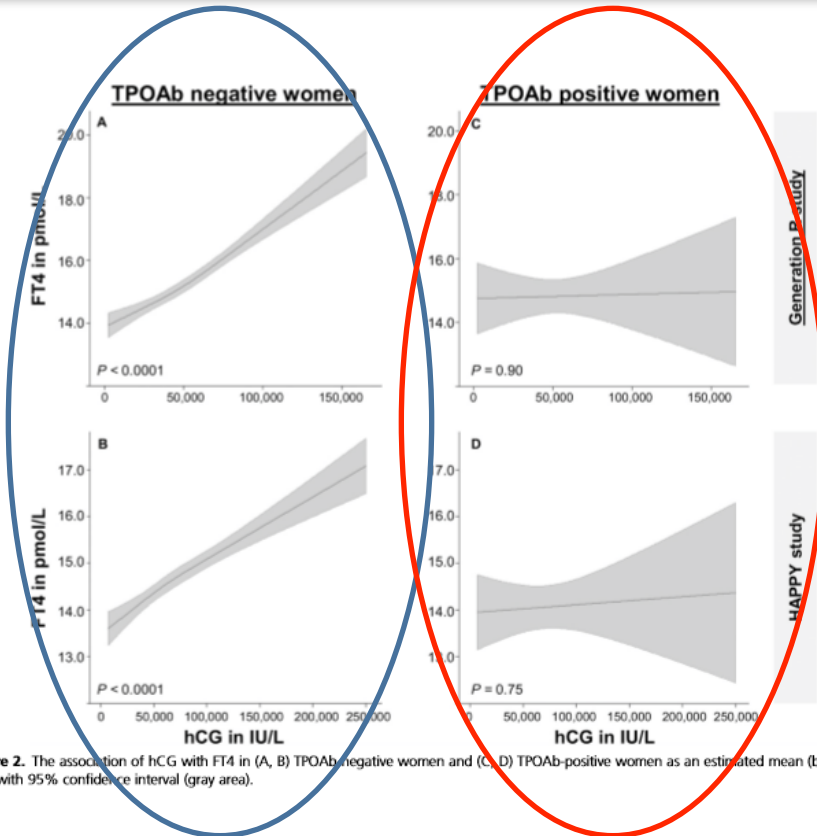


Figure 2. The association of hCG with FT4 in (A, B) TPOAb-negative women and (C, D) TPOAb-positive women as an estimated mean (black line) with 95% confidence interval (gray area).

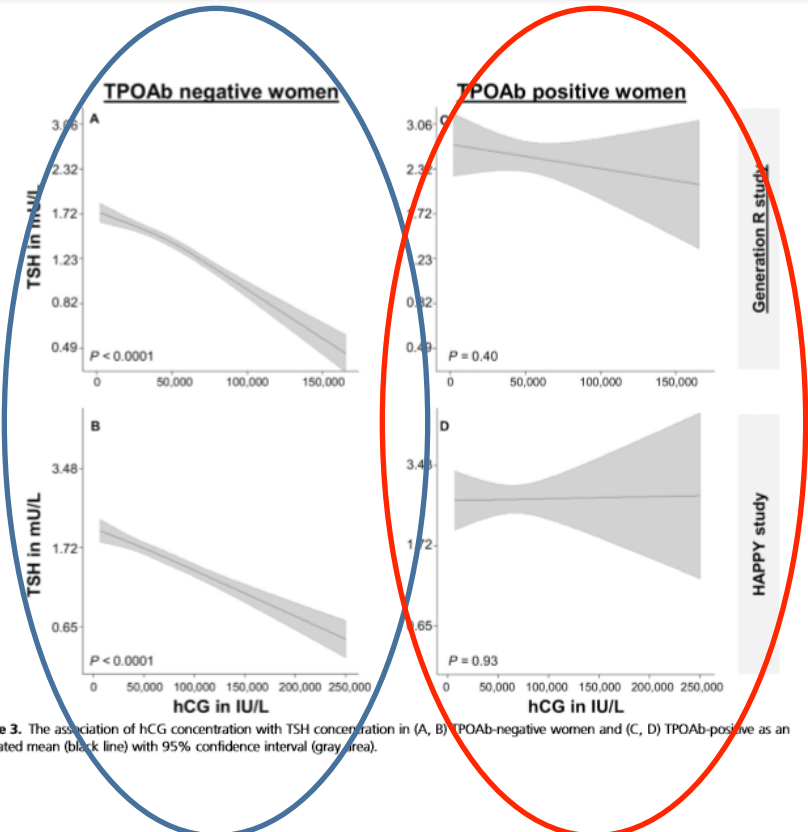


Figure 3. The association of hCG concentration with TSH concentration in (A, B) TPOAb-negative women and (C, D) TPOAb-positive as an estimated mean (black line) with 95% confidence interval (gray area).



# Conclusioni



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Individuare range di normalità di TSH e FT4 popolazione-specifici e trimestre-specifici

Donne ad alto rischio: appena possibile dosaggio TSH

Cut-off 2.5 mU/L se AbTPO+, 4.0 mU/L se AbTPO-



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*Grazie per l'attenzione*