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Per la qualità clinica in Endocrinologia



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Screening tiroideo pre-gravidico: tutte o nessuna

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**Esiste una correlazione tra ormone tiroideo,
autoimmunità tiroidea e riproduzione?**



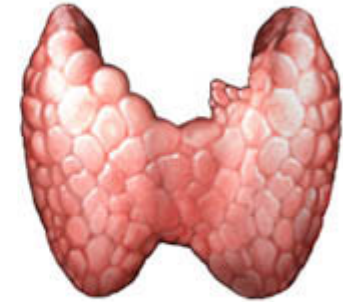
**La valutazione della funzione tiroidea nelle donne
con desiderio di maternità ha qualche
valore aggiunto?**

TABLE 1. Synopsis of hormonal changes in male and female thyrotoxicosis and hypothyroidism

	Thyrotoxicosis		Hypothyroidism	
	Males	Females	Males	Females
SHBG	↑	↑	↓ or N	↓
E ₂	N or ↑	↑	N	↓
Estrone	-	↑	-	↓
Production rate of estrogens	-	→	-	→ or ↓
Metabolic clearance rate of estrogens or androgens	↓	↓	↓	↓
Free E ₂	↑	→	-	N
Testosterone	↑	↑	↓	↓
Δ4- Androstendione	-	↑	↓	↓
DHEA	↑	↑	↓	-
Free testosterone	→	-	↓	N
Bioavailable testosterone	↑	-	-	-
conversion of testosterone to Δ4- Androstendione	↑	→ or ↑	↓	↑
Androgen conversion to Estrone	↑	↑	-	-
Progesterone	↑	↓ or →	-	↓ or →
LH	↑ or →	↑ or →	N	N
FSH	↑ or →	↑ or →	N	N
After GnRH				
LH	↑	↑	↓	↓
FSH	↑	↑	↓	↓

SHBG, sex hormone binding globulin; E₂, estradiol, T, testosterone; DHEA, dehydroepiandrosterone, ↑, increase; ↓, decrease, →, no change, N, normal; -, not available

Una alterata funzione tiroidea porta ad effetti negativi nella madre e nel feto



Ipotiroidismo:

- **conclamato** in 0.5% delle donne in gravidanza
- **subclinico** in 0.25-2.5% delle donne in gravidanza negli USA con picchi fino al 10%
aborto, parto pretermine, eclampsia, pre-eclampsia, distacco di placenta

Iperitiroidismo:

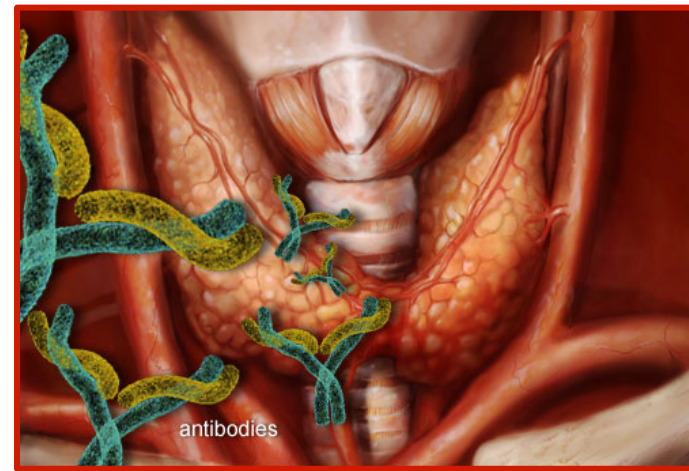
- **conclamato** in 0.1-0.4% delle gravidanze (causa più frequente morbo di Graves)
aborto, insufficienza cardiaca congestizia, crisi tireotossica, parto pretermine, Pre-eclampsia, aumentata morbidity e mortalità prenatale
- **subclinico** non è stato associato ad outcomes negativi a livello materno e/o fetale
Si raccomanda solo follow-up, non terapia



Una ridotta disponibilità di ormoni materni può incidere negativamente sullo sviluppo neurologico del feto e molti studi hanno riportato un ridotto QI in bambini nati da madri con ipotiroidismo conclamato (Haddow et al., 1999), ipotiroxinemia (Pop et al., 1999) o positività autoanticorpale (Pop et al., 1995)

Autoimmunità tiroidea

Anticorpi anti-TPO e anti-Tg si repertano nel 10-20% delle donne in età fertile (Thangaratinam et al. 2011), la maggior parte delle quali sono eutiroidee



La presenza di Ab-TPO in donne eutiroidee può associarsi ad aborto nel primo trimestre e a parto pretermine

La presenza di Ab-TPO aumenta il rischio di sviluppare ipotiroidismo lieve durante o, in caso di stimolazione ovarica , già prima della gravidanza

Poppe K et al, 2008

Nel 16% dei casi: TSH > 4 mU/l durante il primo trimestre di gravidanza (Glinoeer et al. 1994)

Nel 33%-50% dei casi: tiroidite post-partum (Lazarus, 1998)

Screening ?

Guidelines !



American College of Obstetrics and Gynecology (2007)

Without evidence that identification and treatment of pregnant women with subclinical hypothyroidism improves maternal or infant outcomes, routine screening for subclinical hypothyroidism currently is not recommended

thyroid testing in pregnancy should be performed on symptomatic women and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease (e.g., diabetes mellitus)

The Cochrane Collaboration (2010)

At present, universal screening would not be based on firm evidence

Until convincing data from randomised-controlled trials become available, targeted thyroid function testing in pregnancy should be implemented in **women at risk for thyroid disease** (e.g., pregestational diabetics), those with a **family history of thyroid disease** and **symptomatic** women.

Consideration could be given to screening women with a personal history of **preterm birth or recurrent miscarriage**.

Society of Maternal-Fetal Medicine (2012)

thyroid testing for pregnant women “at risk,”
such as those with known thyroid disease,
symptoms of overt thyroid disease, suspected
goiter, and autoimmune medical disorders such as
Type 1 diabetes mellitus.

The Endocrine Society (2012)

The committee could not reach agreement with regard to testing recommendations for all newly pregnant women, therefore 2 versions were presented.

TSH screening of **all** pregnant women
by the ninth week
or at the time of their first visit

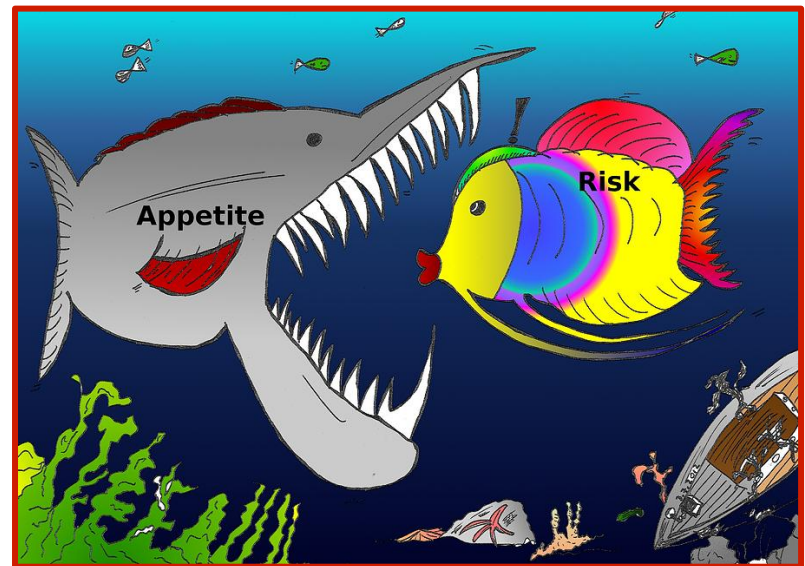


aggressive case finding to identify and test high-risk women for elevated TSH by the ninth week or at the time of their first visit
Where the local practice environment is appropriate, testing of **all** women by week 9 of pregnancy or at the first prenatal visit is reasonable.



Ma quali sono le pazienti a rischio?

- Age > 30 years
- Personal history of thyroid dysfunction
- Prior head or neck irradiation
- Prior thyroid surgery
- Family history
- Symptoms
- Presence of goiter
- TPO Ab positivity
- Autoimmunity
- Infertility
- Miscarriage or preterm delivery
- Iodine deficient population
- Medications and iodinated contrast media*
- Morbid obesity (BMI > 40 kg/m²)*



The Endocrine Society 2012 and American Thyroid Association 2011 guidelines

*Only for American Thyroid Association 2011 guidelines

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

TABLE 2. Screening thyroid function in early pregnancy^a

	Normal TSH ^a				Raised TSH ^a		
	Normal FT4	High FT4	Low FT4	Total	Normal FT4	Low FT4	Total
All women (n = 1560)	1274 (81.7)	3 (0.2)	122 (7.8)	1399 (89.7)	24 (1.5)	16 (1)	40 (2.6)
Low-risk women (n = 1147) ^b	959 (83.6)	3 (0.3)	89 (7.8)	1051 (91.6)	8 (0.7)	4 (0.3)	12 (1.0)
High-risk women (n = 413) ^c	315 (76.3)	0	33 (8.0)	348 (84.3)	16 (3.9)	12 (2.9)	28 (6.8)
Women with known thyroid disorder (n = 89)	56 (62.9)	0	3 (3.4)	59 (66.3)	11 (12.4)	6 (6.7)	17 (19.1)
Women with autoimmune disorders (n = 17)	13 (76.5)	0	1 (5.9)	14 (82.4)	2 (11.8)	0	2 (11.8)
Women with thyroid disorder in family (n = 356)	274 (77)	0	31 (8.7)	305 (85.7)	10 (2.8)	10 (2.8)	20 (5.6)
Women on T ₄ (n = 35)	18 (51.4)	0	1 (2.9)	19 (54.3)	6 (17.1)	2 (5.7)	8 (22.9)
Women with TPOAbs (n = 126)	92 (73)	0	8 (6.3)	100 (79.4)	9 (7.1)	8 (6.3)	17 (13.5)

Targeted thyroid function testing of only the high-risk group would miss about one third of pregnant women with overt/subclinical hypothyroidism

Hyperthyroidism and pregnancy. An Italian Thyroid Association (AIT) and Italian Association of Clinical Endocrinologists (AME) joint statement for clinical practice

(2011)

R. Negro¹, P. Beck-Peccoz², L. Chiovato³, P. Garofalo⁴, R. Guglielmi⁵, E. Papini⁵, M. Tonacchera⁶, F. Vermiglio⁷, P. Vitti⁶, M. Zini⁸, and A. Pinchera⁶

IS A TSH DETERMINATION ADVISABLE AS A SCREENING TEST IN ALL PREGNANT WOMEN?

The answer is definitely **yes**, even though not only TSH but also free T4 (FT4) should be measured in all pregnant women (**universal screening**). Indeed, this panel would guarantee the timely diagnosis of both thyroid hypo- and hyperfunction and would also permit to detect border-line functional thyroid disorders such as subclinical hypo/hyperthyroidism or isolated hypothyroxinemia (normal TSH with FT4 levels below the trimester-specific reference for gestational age).

...and before pregnancy?



Screening or non screening?

Chang DL et al. *Screening for maternal thyroid dysfunction in pregnancy: a review of the clinical evidence and current guidelines.* J Thyroid Res. 2013



American Thyroid Association (2011)

Universal screening of healthy women for thyroid dysfunction before pregnancy **is not recommended.** However, caregivers should identify individuals at high risk for thyroid illness on the basis of their medical history, physical exam, or prior biochemical data.

Joint Guidelines from the American Association of Clinical Endocrinologists and the American Thyroid Association (2012)

Universal screening is **not recommended** for patients who are pregnant or are planning pregnancy, including assisted reproduction. **Aggressive case finding, rather than universal screening, should be considered for patients who are planning pregnancy**

COST-EFFECTIVENESS



OBSTETRICS

The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism

2009

Stephen F. Thung, MD; Edmund F. Funai, MD; William A. Grobman, MD, MBA

2 screening strategies during pregnancy for subclinical hypothyroidism (SH):

- no routine screening of serum TSH
- routine screening of TSH levels. Women with subclinical hypothyroidism received thyroid hormone replacement

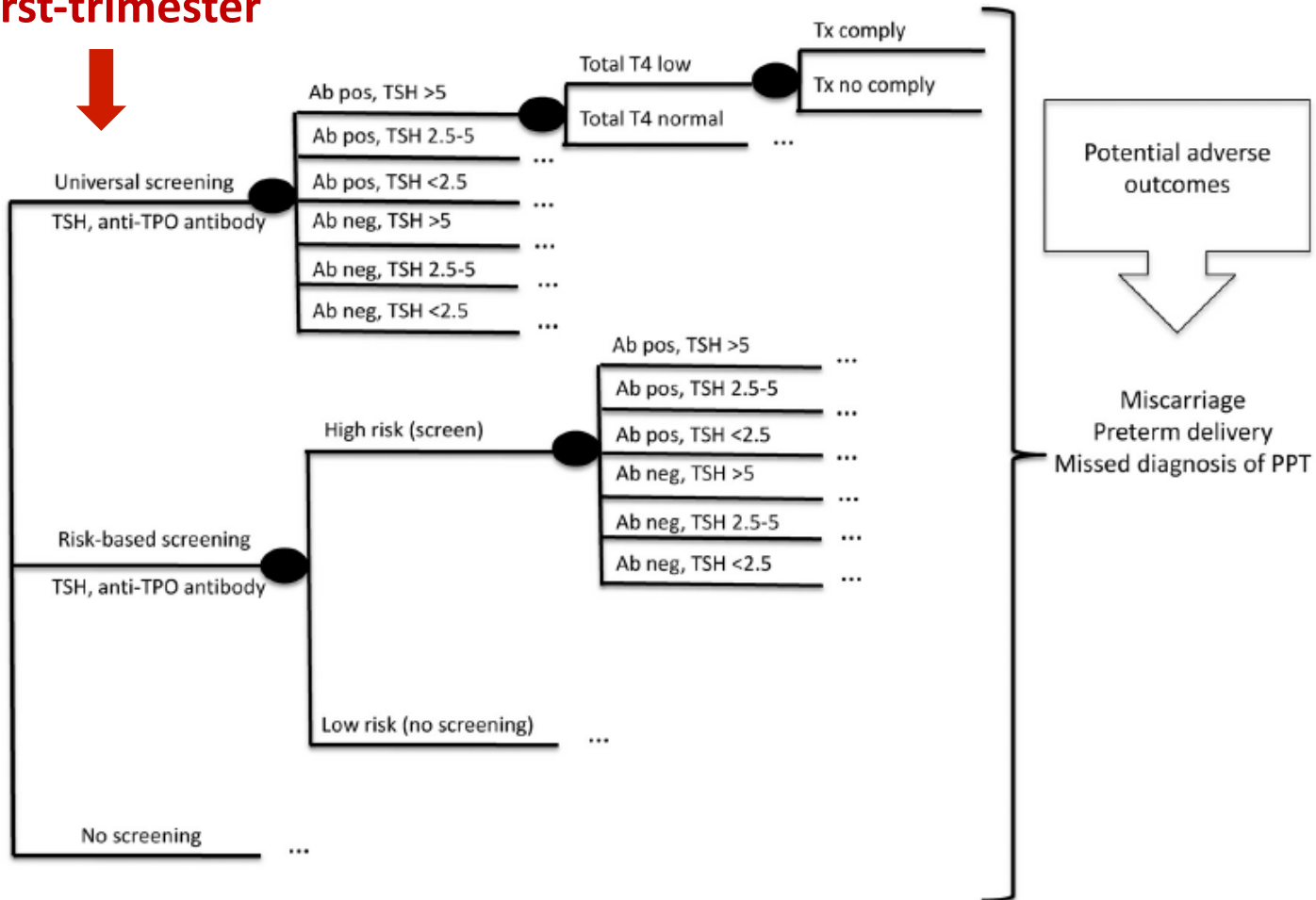
Our model predicts that universal screening is the dominant strategy (with SH prevalence of **2.5%**). For every 100,000 pregnant women who were screened, \$8,356,383 are saved, and 589.3 QALYs are gained

When SH prevalence is reduced to **0.25%**, screening remains cost-effective at \$21,664/QALY gained

Screening for subclinical hypothyroidism in pregnancy will be a cost-effective strategy under a wide range of circumstances

A decision-analytic model compared the incremental cost per quality-adjusted life-year (QALY) gained among the following:
1) universal screening, 2) high-risk screening, and 3) no screening.

first-trimester



Both universal screening and risk-based screening of pregnant women in the first trimester for AITD are highly cost-effective strategies compared with no screening (incremental cost-effectiveness ratios of \$7,138/QALY and \$6,753/QALY)

Universal screening is also highly cost-effective compared with screening of only high-risk women

Screening remained cost-effective in various clinical scenarios, including when only overt hypothyroidism was assumed to have adverse obstetrical outcomes.

Universal screening was cost-saving in the scenario of untreated maternal hypothyroidism resulting in decreased child intelligence, with levothyroxine therapy being preventive

The medical community should seriously consider screening all pregnant women for AITD

Thyroid Function during Pregnancy: Who and How Should We Screen?

Moderator: Ann M. Gronowski^{1*}

Experts: James Haddow,² Sarah Kilpatrick,³ John H. Lazarus,⁴ and Roberto Negro⁵

- **Do you feel that women should have thyroid function testing performed during pregnancy? If so, who should be tested, and what should be measured (i.e., TSH, TPO, iodine) and what cutoffs do you recommend?**
- Lazarus (UK): screening universale I trimestre
 - TSH >2.5 mUI/l dosare fT4
 - TSH >5 mUI/l dosare Ab-anti TPO
- Killpatrick (USA): screening solo su fattori di rischio, trattare ipotiroidismo subclinico solo se TPOAb +
- Negro (Italia): screening universale
- Haddow (USA): screening universale (vantaggi a lungo termine materni)

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What is your opinion about treating pregnant women with subclinical hypothyroidism before or during pregnancy?

- Lazarus (UK): trattare prima del concepimento e durante la gravidanza
- Negro (Italia): trattare prima del concepimento e durante la gravidanza
- Haddow (USA): iniziare terapia con T4 e provare a sospendere dopo il parto

Attitudes of ATA Survey Respondents Toward Screening and Treatment of Hypothyroidism in Pregnancy

Pavani Srimatkandada,¹ Alex Stagnaro-Green,² and Elizabeth N. Pearce¹

ATA meeting 2012

561 partecipanti

risposte al questionario '*screening or not*' : 24%

pro: 64%

contro:18%

ACOG 2009

500 membri

pro screening universale: 36%

screening solo se fattori di rischio: 11.5%

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

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

TSH should be measured at the beginning of pregnancy if screening is performed. If TSH is elevated, FT₄ and TPOAb should be determined. This will enable SCH or overt hypothyroidism to be diagnosed,

In the case of elevated TSH and negative TPOAb, TgAb should be measured. Thyroid ultrasound may be performed to evaluate hypo-echogenicity or an inhomogeneous echo pattern. (2S)

POTENZIALI RISCHI DELLO SCREENING UNIVERSALE



Costi del trattamento e del follow up

Possibile errata interpretazione dei valori di funzionalità tiroidea e trattamento inappropriato

Inappropriato dosaggio della T4 nelle donne con ipotiroidismo lieve con conseguente insufficiente o eccessivo dosaggio (**necessità di specialisti!**)

Necessità di stretto monitoraggio nelle pazienti che hanno iniziato T4
(circa il 40% dei pazienti in T4 non hanno TSH a target)



Fondazione Ca' Granda Policlinico



TSH (e Ab-TPO) nello screening pre concezionale

**TSH (e Ab-TPO) nel I trimestre se non eseguito in fase
pre concezionale**

Grazie per l'attenzione!
laura.fugazzola@unimi.it

