

V Corso AGGIORNAMENTO AME IN ENDOCRINOLOGIA CLINICA



**20/22
MARZO
2014**

AGRIGENTO



L'IPERTIROIDISMO SUBCLINICO **Difesa: perché, chi e quando non trattare**

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Accettare o non accettare l'incarico?

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism...

The relationship between FT4 and TSH (when the pituitary-thyroid axis is intact) is an inverse log-linear relationship; therefore, small changes in FT4 result in large changes in serum TSH concentrations. Serum TSH levels are considerably more sensitive than direct thyroid hormone measurements for assessing thyroid hormone excess.

Subclinical hyperthyroidism is defined as a normal serum FT4 estimate and normal total T3 or FT3 estimate, with subnormal serum TSH concentration.

Tireotossicosi subclinica iatrogena
Tireotossicosi subclinica endogena
Bernadette Biondi



L'ipertiroidismo subclinico (IperSub) è caratterizzato da normali valori degli ormoni tiroidei in presenza di bassi valori di TSH. Una valutazione del TSH con metodica ultrasensibile consente di distinguere una forma di lieve di IperSub, in cui il TSH è basso ma ancora dosabile (0.1-0.4 mIU/L), da una forma più severa di IperSub, in cui il TSH è indosabile e completamente soppresso.

Management of Subclinical Hyperthyroidism

[Silvia Santos Palacios](#),¹ [Eider Pascual-Corrales](#),¹ and [Juan Carlos Galofre](#)^{1,*}

Need for Treatment

In endocrinology, the necessity of treatment for patients with subclinical hyperthyroidism is an open question. The criteria for treatment of this disorder are controversial, and individualized judgment is mandatory in order to evaluate the grade and clinical consequences of the disorder in a given patient. Since prospective studies show that isolated low serum TSH levels spontaneously return to normal in nearly 50% of patients, caution and regular monitoring are the recommended initial approaches. Additionally, only 5% of individuals with subclinical disease develop overt dysfunction yearly.

THYROID
Volume 21, Number 6, 2011
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DOI: 10.1089/thy.2010.0417

**ORIGINAL STUDIES, REVIEWS,
AND SCHOLARLY DIALOG**

HYPERTHYROIDISM, OTHER CAUSES OF THYROTOXICOSIS,
AND THYROID HORMONE ACTION

Hyperthyroidism and “Other Causes of Thyrotoxicosis”: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists

The American Thyroid Association and American Association of Clinical Endocrinologists
Taskforce on Hyperthyroidism and Other Causes of Thyrotoxicosis

[R] How should SH be managed?

[R1] Frequency and causes of SH

SH has a prevalence of about 1% in the general population (245). In older persons, TMNG is probably the most common cause of SH, with other etiologies of endogenous SH, including GD, solitary autonomously functioning nodules, and various forms of thyroiditis (246,247), the latter of which would be more strictly termed “subclinical thyrotoxicosis.”

[R] How should SH be managed?

[R1] Frequency and causes of SH

Some otherwise healthy older persons may have low serum TSH levels, low normal serum levels of free T₄ estimates and T₃, and no evidence of thyroid or pituitary disease, suggesting an altered set point of the pituitary-thyroid axis (248,249). This situation can mimic SH biochemically, and it may be difficult to rule out clinically, although scintigraphic studies suggesting autonomous thyroid function would favor SH. Other causes of a suppressed TSH but normal estimated free T₄ and T₃ include corticosteroid therapy, central hypothyroidism, and non-thyroidal illness.

[R] How should SH be managed?

[R1] Frequency and causes of SH

Once SH has been detected, it is important to document that it is a persistent problem by repeating the serum TSH at 3 or 6 months. Some reports suggest that a subnormal serum TSH may spontaneously resolve, especially if the levels are >0.05 mU/L (250–252). Patients with GD rather than a TMNG as the cause of SH may be more likely to spontaneously remit (253).

■ RECOMMENDATION 65

Technical remarks: A TSH level of <0.1 mU/L on repeated measurement over a 3–6-month period is considered to be persistent, effectively ruling out transient thyroiditis as a cause.

■ RECOMMENDATION 66

Technical remarks: A TSH level between 0.1 and 0.5 mU/L on repeated measurement over a 3–6-month period is considered persistent, effectively ruling out transient thyroiditis as a cause.

[R2] Clinical significance of SH

Since SH is a mild form of hyperthyroidism, deleterious effects on the cardiovascular system and the skeleton might be expected in some patients,

Postmenopausal women with SH may have increased fracture rates even with only mildly suppressed serum TSH levels (259)

There are also preliminary data suggesting an increase in bone turnover (262) and lower bone density in premenopausal women with SH (263).

One cross-sectional (266) and one longitudinal (267) study of older individuals showed no changes in cognitive function, whereas two others suggested an association between SH and dementia in older persons (268,269). Finally, there is the potential risk of progression to overt hyperthyroidism if SH is left untreated. This risk is probably somewhere between 0.5% and 1% per year (270,271).

Data on the effects of SH on mortality are conflicting.

[R3] When to treat SH

■ RECOMMENDATION 65

When TSH is persistently <0.1 mU/L, treatment of SH should be strongly considered in all individuals ≥ 65 years of age, and in postmenopausal women who are not on estrogens or bisphosphonates; patients with cardiac risk factors, heart disease or osteoporosis; and individuals with hyperthyroid symptoms. 2/++0

■ **RECOMMENDATION 66**

When TSH is persistently below the lower limit of normal but ≥ 0.1 mU/L, treatment of SH should be considered in individuals ≥ 65 years of age and in patients with cardiac disease or symptoms of hyperthyroidism. 2/+00

Treatment of SH is controversial, since no controlled intervention studies to show benefit have been performed. However, a panel of experts determined that the evidence for benefit was sufficient to warrant therapy of SH in older individuals whose serum TSH level was <0.1 mU/L (276). This was based primarily on the studies showing an increased rate of atrial fibrillation and altered skeletal health with a suppressed level of TSH described above.

There are insufficient data for or against treatment of SH in younger persons or premenopausal women with SH and serum TSH <0.1 mU/L. One uncontrolled study of middle-aged patients showed an improvement in hyperthyroid symptoms with therapy (256). Although this study did not include younger individuals, the task force elected to recommend treatment of all SH patients younger than 65 years of age with persistent TSH <0.1 mU/L and hyperthyroid symptoms.

■ RECOMMENDATION 67

If SH is to be treated, the treatment should be based on the etiology of the thyroid dysfunction and follow the same principles as outlined for the treatment of overt hyperthyroidism. 1/+00

Some patients with SH due to GD may remit spontaneously without therapy, so that continued observation without therapy is reasonable for younger patients with SH due to GD. A small subset of elderly patients with persistently low TSH and no evidence of true thyroid dysfunction can be followed without intervention, especially when the serum FT₄ estimate and T₃ levels are in the lower half of the normal range. Treatment with beta-adrenergic blockade may be sufficient to control the cardiovascular-related morbidity from SH, especially that of atrial fibrillation (258).

TABLE 8. SUBCLINICAL HYPERTHYROIDISM: WHEN TO TREAT

Factor		TSH (<0.1 mU/L)		TSH (0.1–0.5 mU/L) ^a
Age > 65	→	Yes		Consider treating
Age < 65 with comorbidities				
Heart disease	→	Yes		Consider treating
Osteoporosis	→	Yes	→	No
Menopausal		Consider treating		Consider treating
Hyperthyroid symptoms	→	Yes		Consider treating
Age < 65, asymptomatic		Consider treating	→	No

^aWhere 0.5 mU/L is the lower limit of the normal range.

■ RECOMMENDATION 69

Transient hCG-mediated thyrotropin suppression in early pregnancy should not be treated with antithyroid drug therapy. 1/+00

Once the diagnosis of hyperthyroidism is made in a pregnant woman, attention should be focused on determining the etiology of the disorder and whether it warrants treatment. Clinical features that may indicate the presence of significant hyperthyroidism include failure to gain weight, heat intolerance, excessive sweating, and tachycardia, beyond that normally associated with pregnancy.

The two most common types of biochemical hyperthyroidism that occur during pregnancy are gestational hyperthyroidism (e.g., hCG-mediated transient TSH suppression) and GD. Gestational hyperthyroidism is a generally asymptomatic, mild biochemical hyperthyroidism that may be observed in the first trimester of normal pregnancy. It is presumably caused by the high serum hCG of early pregnancy (281) and is not associated with adverse pregnancy outcomes (289). Pregnant women having gestational hyperthyroidism with emesis, and particularly hyperemesis, may develop more profound abnormalities in thyroid function, with biochemically overt hyperthyroidism and clinical symptoms and signs of hyperthyroidism.

THYROID
Volume 21, Number 6, 2011
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DOI: 10.1089/thy.2010.0417



■ RECOMMENDATION 70

Antithyroid drug therapy should be used for hyperthyroidism due to GD that requires treatment during pregnancy. Propylthiouracil should be used when antithyroid drug therapy is started during the first trimester. Methimazole should be used when antithyroid drug therapy is started after the first trimester. 1/+00

■ RECOMMENDATION 72

GD during pregnancy should be treated with the lowest possible dose of antithyroid drugs needed to keep the mother's thyroid hormone levels slightly above the normal range for total T_4 and T_3 values in pregnancy and the TSH suppressed. Free T_4 estimates should be kept at or slightly above the upper limit of the nonpregnant reference range. Thyroid function should be assessed monthly, and the antithyroid drug dose adjusted as required. 1/+00

■ **RECOMMENDATION 74**

TRAb levels should be measured when the etiology of hyperthyroidism in pregnancy is uncertain. **1/+00**



Review Article

Management of Hyperthyroidism in Pregnancy: Comparison of Recommendations of American Thyroid Association and Endocrine Society

Shahram Alamdari, Fereidoun Azizi, Hossein Delshad, Farzaneh Sarvghadi,
Atieh Amouzegar, and Ladan Mehran

TABLE 4: Comparison of recommendations of American Thyroid Association and Endocrine Society on other aspects of hyperthyroidism in pregnancy.

Topic	Recommendations	
	American Thyroid Association (2011)	Endocrine Society (2012)
Management of gestational hyperthyroidism	<p>The appropriate management of women with gestational hyperthyroidism and hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed.</p> <p>ATDs are not recommended for the management of gestational hyperthyroidism.</p> <p>Same (T)</p>	<p>Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free T4 do not require ATD treatment. Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total T3 values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement.</p> <p>Women with hyperemesis gravidarum and diagnosed to have Graves' hyperthyroidism (free T4 above the reference range or total T4 > 150% of top normal pregnancy value, TSH < 0.01 mIU/liter, and presence of TRAb) will require ATD treatment, as clinically necessary.</p>

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

The management of women with gestational hyperthyroidism depends on the severity of symptoms. Antithyroid drugs are not indicated, since the serum T4 returns to normal by 14-18 weeks gestation

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

R 25

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

R26

ATDs are not recommended for management of gestational hyperthyroidism. Level D - USPSTF.

Hashimoto's thyroiditis in childhood: presentation modes and evolution over time

Filippo De Luca, Simona Santucci, Domenico Corica, Elda Pitrolo, Marika Romeo and Tommaso Aversa

The transient hyperthyroid phase of HT is known as hashitoxicosis (Htx), and is believed to result from unregulated release of stored thyroid hormones during inflammatory-mediated destruction of the thyroid gland. Htx has been reported as the second commonest cause of thyrotoxicosis in childhood, after GD. Therefore, differential diagnosis of Htx from GD can be particularly challenging when the diagnosis is only based on clinical and biochemical features.

According to a very recent prospective study aiming to investigate long-term outcome of HT in the children presenting with overt hyperthyroidism, a definitive resolution of hyperthyroidism is generally observed on average eight months after Htx diagnosis, even though there is a wide variability between subjects. **According to that report, management of children with Htx may require a prolonged clinical and biochemical follow-up, but pharmacological treatment is only required in selected cases** and non-pharmacological therapies are never needed. Hyperthyroid phase in children with Htx is always followed by definitive resolution, with no relapses and persistent and euthyroidism or hypothyroidism.

Subclinical hyperthyroidism when presenting as initial manifestation of juvenile Hashimoto's thyroiditis: first report on its natural history

T. Aversa · M. Valenzise · A. Corrias ·
M. Salerno · A. Mussa · D. Capalbo ·
G. Salzano · F. De Luca · M. Wasniewska



a) HT should be included among the causes of endogenous SH in pediatric age; (b) in children with HT-related SH, spontaneous normalization of TSH levels occurs within the first 24 months after diagnosis, as well as in age-matched patients with Htx; (c) in both these conditions, a further deterioration of thyroid function might re-present in some patients during follow-up; (d) Ht-related SH and Htx might be possibly seen as different biochemical stages along the same continuum.

CONCLUSIONI

Prima di trattare una tireotossicosi subclinica vanno escluse cause transitorie di soppressione del TSH:

- tiroiditi (subacuta, silente e post-partum)
- malattie psichiatriche
- malattie croniche debilitanti non tiroidee
- farmaci (ormoni tiroidei, alte dosi di steroidi, dopamina, dobutamina, amiodarone)
- "disfunzione" ipofisaria.

CONCLUSIONI

Il trattamento della tireotossicosi subclinica non deve essere effettuato nelle seguenti condizioni:

- TSH transitoriamente basso-indosabile
- TSH basso ma dosabile in pazienti giovani completamente asintomatici e in assenza di malattie cardiovascolari
- TSH basso o indosabile in donne in gravidanza con ormoni tiroidei nella norma
- TSH basso o indosabile durante terapia con farmaci che interferiscono con la funzione tiroidea
- quando è voluto (terapia soppressiva con L-T4)

ATTENZIONE SELETTIVA

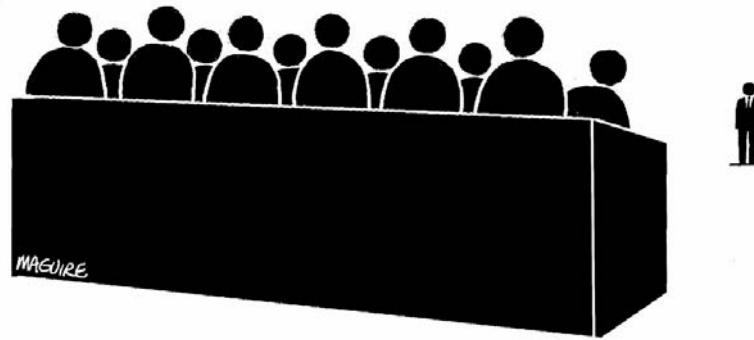




NEI CASI MENZIONATI LA DIFESA CHIEDE L'ASSOLUZIONE



- ✓ per non doversi procedere (art 529 C.P.P.)
- ✓ perché il fatto non sussiste (art 530 C.P.P.)
- ✓ perché il fatto non è previsto dalla Legge come reato (art 530 C.P.P.)



- **non doversi procedere** (errore di laboratorio)
- **il fatto non sussiste** (i risultati sono corretti ma non sono espressione di tireotossicosi...: farmaci, comorbilità)
- **il fatto non è previsto dalla Legge come reato** (c'è realmente una tireotossicosi subclinica ma non è "dannosa", è transitoria, non merita una cura)

**In attesa
della
sentenza
Vi ringrazio
per
l'attenzione**

.....

