CONGRESSO NAZIONALE A.G.E.O.
Firenze, 29-30 Settembre e 1 Ottobre 2016

Gravidanza e patologia tiroidea

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Patologia autoimmune

Tiroidite cronica

Morbo di Basedow

Tiroidite silente /post partum

~10 % della popolazione

Patologia nodulare

4 % clinica

20 -30 % ecografica

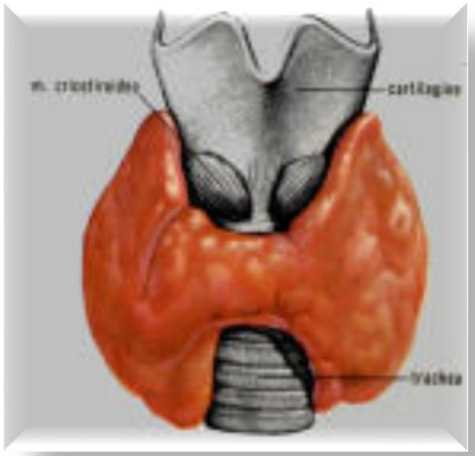
Cancro tiroideo " the fastest" cancer

da 1.5 % a 2.9 % dei cancri

IN GRAVIDANZA

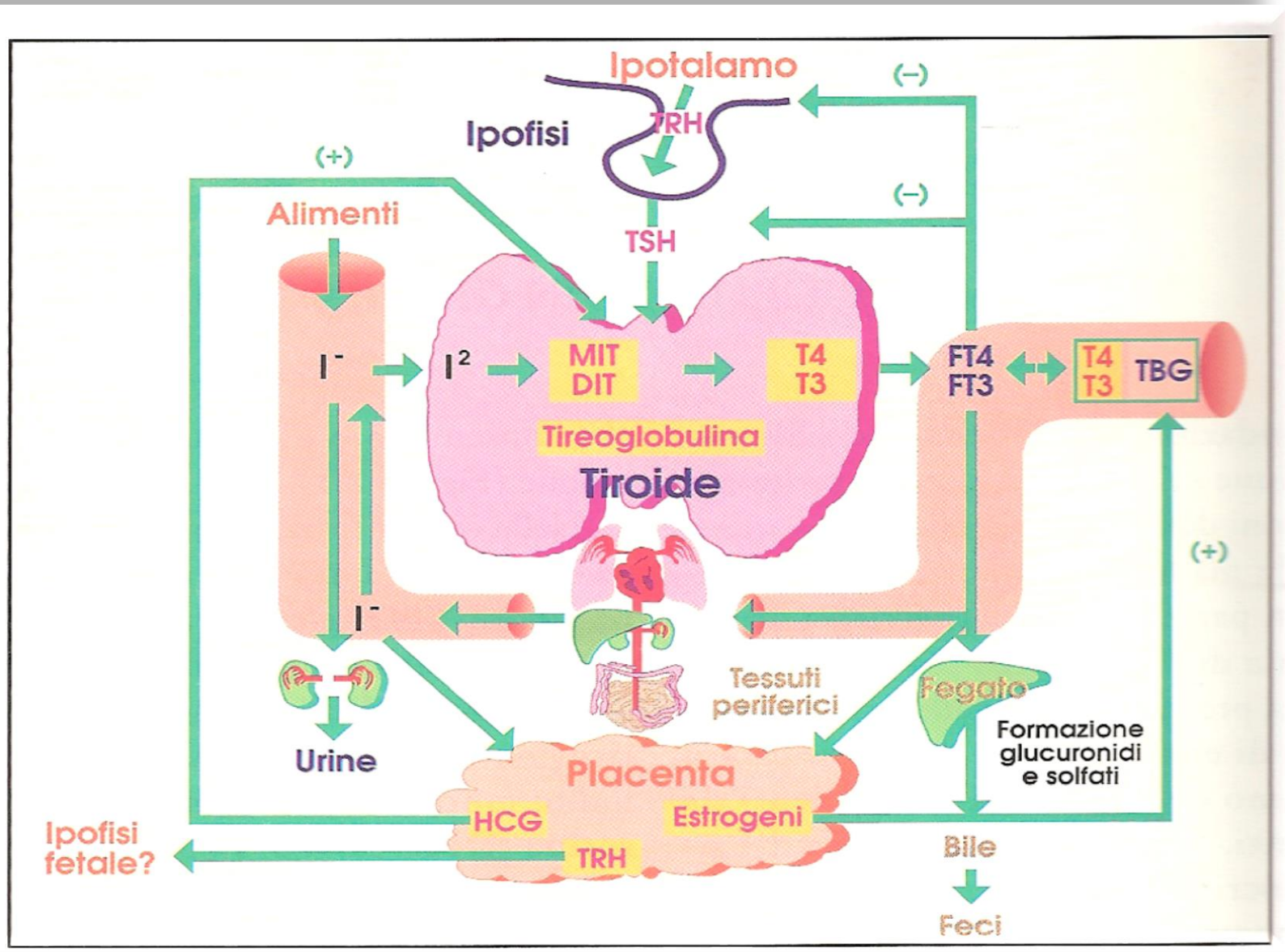
Ipotiroidismo subclinico	2.2 %
Ipotiroidismo franco	0.3 %
Ipertiroidismo	0.1 %

- IPOTIROIDISMO
- IPERTIROIDISMO
- (PATOLOGIA AUTOIMMUNE



- MODIFICA DEL FABBISOGNO IODICO
- INFLUENZA SU PATOLOGIA AUTOIMMUNE

- **Ipotiroidismo “overt”**
  FT4 basso TSH elevato (ATA, ETA AACE suggeriscono, in grav. , di considerarlo comunque per TSH > 10)
- **Ipotiroidismo subclinico**
  FT4 normale TSH modestamente elevato
  > 3.5 …? Non esiste accordo sul reale valore di cut-off
  > 2.5 1° trimestre, > 3.0 2° trimestre (ATA, ES, ETA)
- **Ipertiroidismo**
  FT4 e/o FT3 elevato e/o TSH soppresso. Attenzione in gravidanza D.D. con i valori fisiologici del 1° trimestre
- **Ipotiroxinemia materna** FT4 basso e TSH normale ??



Metabolismo dello iodio, asse ipotalamo-ipofisi-tiroide e regolazione della funzione tiroidea durante la gravidanza. I segni (+) indicano una stimolazione e i segni (-) una inibizione

Due considerazioni…

- I valori di definizione di ipo subclinico in gravidanza sembrano non essere adatti per alcune etnie es. Cinesi e Indiani
- I metodi di dosaggio del FT4 presentano limiti e ciascun laboratorio dovrebbe stabilire i propri riferimenti in condizioni di buon apporto iodico

I PUNTI CRUCIALI

- Il volume tiroideo in gravidanza aumenta del 10% in caso di buon apporto iodico
(40 % - 50 % in caso di carenza)
- **Durante i primi tre mesi l'effetto TSH simile delle BHCG determina valori di FT4 ai limiti alti e TSH più basso (V.N. Di TSH nel 1° trimestre < 2.5)**
- L'embrione dipende totalmente dagli ormoni tiroidei materni in quanto la tiroide fetale inizia a produrre ormoni nella seconda metà della gravidanza
- **Dal terzo mese in poi inizia la competizione materno fetale per lo iodio**

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

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Thyroid. 2011 October; 21(10): 1081–1125.

PMCID: PMC3472679

doi: 10.1089/thy.2011.0087

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]

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2014 European **thyroid** association **guidelines** for the management of subclinical hypothyroidism in **pregnancy** and in children.
Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. Eur **Thyroid** J. 2014 Jun;3(2):76-94. doi: 10.1159/000362597. Epub 2014 Jun 7.

Hypothyroidism in **Pregnancy**.
Lazarus J, Okosieme OE.
In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, Singer F, Vinik A, Weickert MO, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. 2015 Apr 12.

Diagnosis and management of subclinical Hypothyroidism in pregnancy.
Negro R, Stagnaro-Green A BMJ 2014

- Sia per l’ipotiroidismo che per l’ipertiroidismo bisogna considerare separatamente gli effetti sulla mamma che sul feto

1.2.1. Overt maternal hypothyroidism is known to have serious adverse effects on the fetus. Therefore, maternal hypothyroidism should be avoided. For overt hypothyroidism: USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T_4 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. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

SUBCLINICAL HYPO

- To date at leat 16 observational study between subhypo and complications of pregnancy, mostly prospective. Criticism: cut off used to define subclinical hypo and the time in gestation in which TSH was assessed
- Four main studies regarding neurological and intellectual complications. Criticism: difficult of evaluation

1.2.2. Subclinical hypothyroidism (SCH; serum TSH concentration above the upper limit of the trimester-specific reference range with a normal free T_4) may be associated with an adverse outcome for both the mother and offspring, as documented in antibody-positive women. In retrospective studies, T_4 treatment improved obstetrical outcome, but it has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T_4 replacement in women with SCH who are thyroid peroxidase antibody positive (TPO-Ab+). For obstetrical outcome: USPSTF recommendation level, B; evidence, fair (2|⊕⊕○○); for neurological outcome, USPSTF recommendation level, I; evidence, poor (2|○○○○). The panel also recommends T_4 replacement in women with SCH who are TPO-Ab negative (TPO-Ab−). For obstetrical outcome: USPSTF recommendation level, C; evidence, fair (2|⊕⊕○○); for neurological outcome: USPSTF recommendation level, I; evidence, poor (2|○○○○).

ATA e ETA in accordo

- *Plowden TC et al Sulclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss or live birth.* JCEM 2016
- Valutazione prospettica di 1228 donne con una storia di perdita di gravidanza , seguite per 6 mesi, valutazione dei parametri sopra indicati. Nessuna differenza fra TSH < o > di 2.5 e/o presenza di AbTPO

CRITICITA’

- Nessun tentativo di stratificare la differenza per diversi valori di TSH
- Pazienti che già avevano un problema (uno o più episodi di aborto)
- Follow –up circa la fertilità solo a sei mesi

Practice points (recommendations)

- Physicians must be aware that there is a potential increased risk of adverse outcome associated with SH, and at the same time that there are no substantial harmful effects due to treatment with LT4.
- Clinicians should consider the use of LT4 therapy for SH even in the absence of clear, evidence-based medicine advantages.
- As is the case for OH, the recommendation is to keep TSH levels below 2.5 mIU/L in the first trimester and below 3.0 mIU/L during the second and third trimesters.

Negro R, Mestman JH
Thyroid disease in pregnancy
Best Practice & Research Clinical Endocinology & Metabolism. 2011

1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2⊕OOO).

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|⊕⊕⊕⊕).

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|⊕⊕⊕○).

Markers predictive for development of hypothyroidism during pregnancy

TSH > 2.5

AbTPO> 1.250 U/L

2.0. Management of hyperthyroidism: maternal and fetal aspects

2.1. Management of maternal hyperthyroidism: maternal aspects

2.1.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy and gestational thyrotoxicosis because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by the presence of clinical evidence of autoimmunity, a typical goiter, and presence of TSH receptor antibodies (TRAb). TPO-Ab may be present in either case. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○).

2.1.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, antithyroid drug (ATD) therapy should be either initiated (before pregnancy if possible, and for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T_4 at or just above the upper limit of the nonpregnant reference range, USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○), or to maintain total T_4 at 1.5 times the upper limit of the normal reference range or the free T_4 index in the upper limit of the normal reference range. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

2.1.3. Propylthiouracil (PTU), if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy because of the possible association of methimazole (MMI) with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. MMI 10 mg is considered to be approximately equal to 100–150 mg of PTU. Recent analyses reported by the U.S. Food and Drug Administration (FDA) indicate that PTU may rarely be associated with severe liver toxicity. For this reason we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy, including the potential difficulties involved in switching patients from one drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1⊕⊕◯◯). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3–4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2⊕◯◯◯).

2.2. Management of maternal hyperthyroidism: fetal aspects

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 ^{131}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 (1I⊕⊕⊕○).

2.2.3. In women with TRAb or thyroid-stimulating Ig elevated at least 2- to 3-fold the normal level and in women treated with ATD, maternal free T_4 and fetal thyroid dysfunction should be screened for during the fetal anatomy ultrasound done in the 18th-22nd week and repeated every 4–6 wk or as clinically indicated. Evidence of fetal thyroid dysfunction could include thyroid enlargement, growth restriction, hydrops, presence of goiter, advanced bone age, tachycardia, or cardiac failure. If fetal hyperthyroidism is diagnosed and thought to endanger the pregnancy, treatment using MMI or PTU should be given with frequent clinical, laboratory, and ultrasound monitoring. USPSTF recommendation level: B; evidence, fair (1⊕⊕⊕○).

8.0. Screening for thyroid dysfunction during pregnancy

8.1a. Universal screening of healthy women for thyroid dysfunction *before* pregnancy is not recommended. USPSTF recommendation level: I; evidence, poor (2⊕○○○).

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8.4a the committe couldnt't reach agreement with regard to screening recommendation

- “….those who oppose universal screening cite the paucity of evidence that identification and treatment of pregnant women with SH improves maternal or neonatal outcomes…”

8.1b. However, caregivers should identity individuals at "high risk" for thyroid illness (see Table 1) on the basis of their medical history, physical exam, or prior biochemical data. When such individuals are identified, prenatal measurement of serum TSH is recommended. If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay. Although no randomized controlled trials are available to guide a response, the committee believes it is appropriate to give low-dose T_4 treatment to bring TSH below 2.5 mIU/liter. This treatment can be discontinued if the woman does not become pregnant or postpartum. USPSTF recommendation level: I; evidence, poor (2⊕○○○).

8.2a. All women considering pregnancy with known thyroid dysfunction and receiving levothyroxine should be tested for abnormal TSH concentrations *before* pregnancy. USPSTF recommendation level: B; evidence, fair (1|⊕⊕OO).

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

- Dati da studi prospettici mostrano che l'identificazione di fattori di rischio può comunque portare a mancare fra il 33 e 81% di donne con ipotiroidismo
- La ricerca dei fattori di rischio è "time consuming" e può portare a spese aggiuntive

- 2014 European **thyroid** association **guidelines** for the management of subclinical hypothyroidism in **pregnancy** and in children.
- Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B.
- Eur **Thyroid** J. 2014 Jun;3(2):76-94. doi: 10.1159/000362597. Epub 2014 Jun 7.

Favorevole allo screening universale

E LE TIROIDITI CRONICHE IN ASSENZA DI IPOTIROIDISMO?

… an association between thyroid autoimmunity, miscarriage and preterm delivery is suggested by update meta-analysis. Two explanations may be advocated for these associations: reduced functional reserve or an unfavorable autoimmune environment…

Negro R, Mestman JH
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- Antithyroid antibodies (anti TPO) are present in ovarian follicles

- Anti TPO antibodies affect post-implantation embryo development leading to fetal loss

VitaminD role….?

Practice points (recommendations)

- In euthyroid women positive for thyroid antibodies the use of IVIG is not recommended due to reasons of costs and very poor data. Treatment with LT4 seems to be more reasonable, even though not fully justifiable on the basis of evidence-based medicine.
- Given the known and definite risk for women with thyroid antibodies to develop hypothyroidism during pregnancy, it is mandatory for a woman planning a pregnancy to have TSH levels lower than 2.5 mIU/L. It is also important to check TSH and FT4 once a trimester in order to promptly correct thyroid function, when necessary.

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The condition of isolated Hypothyroxinemia in pregnancy is defined as the presence of an FT4 value below the 2.5° percentile with a TSH level within the normal range

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Practice points (recommendations)

- To date, the treatment of IH with LT4 is not recommended.
- In order to avoid the onset of even mild iodine deficiency, the use of iodized salt and/or multivitamin pills containing potassium iodine, is advised.

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L’importanza dello iodio

- Lo iodio di per sé influenza lo sviluppo del sistema nervoso centrale mielinizzazione, differenziazione neuronale e sinaptogenesi

- Lieve deficit iodico è ritenuto causa di ipotiroidismo materno e determina incremento di volume della tiroide materna

- Lieve deficit iodico può dunque peggiorare un gozzo nodulare

6.0. Iodine nutrition during pregnancy

6.1. Women in the childbearing age should have an average iodine intake of 150 μg/d. As long as possible before pregnancy and during pregnancy and breastfeeding, women should increase their daily iodine intake to 250 μg on average. USPSTF recommendation level: A; evidence, good (1⊕⊕⊕O).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily recommended nutrient intake (RNI) for iodine, *i.e.* 500 μg iodine per day. USPSTF recommendation level: I; evidence, poor (2I⊕○○○).

6.5. We recommend that once-daily prenatal vitamins contain 150–200 μg iodine and that this be in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception. Preparations containing iron supplements should be separated from thyroid hormone administration by at least 4 h. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

CONCLUSIONI

- Screening universale nelle donne pre gravidanza e al momento del test positivo.
  Accettabili anche esami nei 6 mesi precedenti
- **Necessità di interpretare i test ad "hoc"**
- Trattare sempre e prontamente i disturbi di funzione tiroidea con particolare riferimento però ad evitare l'overtreatment nell'ipertiroidismo
- **Indispensabile la collaborazione tra endocrinologo e ginecologo**