Milano, Ospedale San Raffaele 27 marzo 2015

# CRITICITA' ENDOCRINO-GINECOLOGICHE NELLE DIVERSE ETA' DELLA DONNA

## Quando si parla di infertilità e quali percorsi consigliare alla paziente?

C. Cappelli

Università degli Studi di Brescia

**Per INFERTILITA' si intende l'assenza di concepimento dopo 12 mesi di rapporti mirati non protetti in donne con età ≤ 35 aa, o dopo 6 mesi in donne di età > 35 aa.**

Practice Committee of the American Society for Reproductive Medicine; Istituto Superiore di Sanità

# Ambulatorio Malattie della Tiroide

(2012-2014)

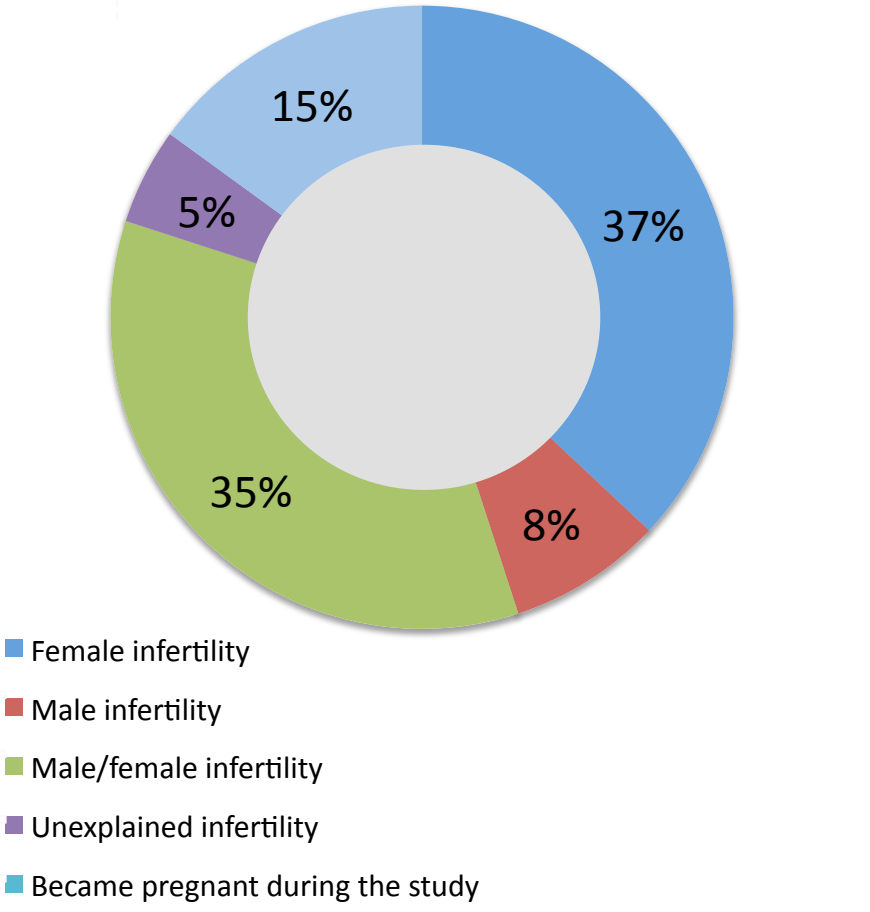
"Valutazione Endocrinologica per infertilità"

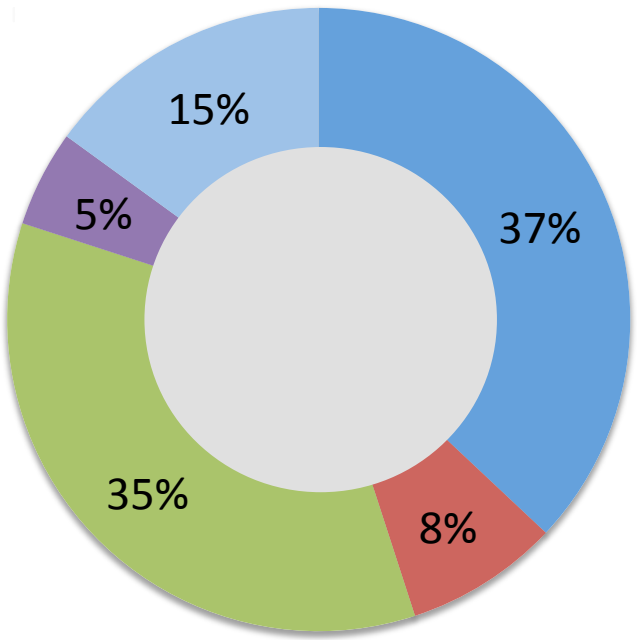
- ✓ 41 donne (24-41 aa)
  - 20 (48.8%) NON rientravano nella definizione di Infertilità
    - → 16 (≤ 35 aa) assenza concepimento dopo (7-10 mesi) rapporti mirati
    - → 4 (> 35 aa) assenza concepimento dopo (3-4 mesi) rapporti mirati

Dati personali

World Health Organization

http://http://www.who.int/reproductivehealth/topics/infertility/definitions/en/






35% Ovulatory disorders
15% Endometriosis
11% Pelvic adhesions
11% Tubal blockage
11% Other tubal abnormalities

83%

7% Hyperprolactinemia

10% Endocrine disorders

Best Pract Res Clin Endocrinol Metab. 2011 Dec;25(6):861-73.

# CAUSE DI INFERTILITA' "ENDOCRINA"

- ✓ Adenomi ipofisari secernenti
  - Prolattinoma
  - Acromegalia
  - M. di Cushing
- ✓ Patologie Surrenaliche
  - Iperplasia congenita surrenale
  - Insufficienza surrenalica
  - Sindrome di Cushing
- ✓ PCOS
- ✓ Patologie Tiroidea
  - Ipertiroidismo
  - Ipotiroidismo
  - Ipotiroidismo sub-clinico
  - Eutiroidismo con anticorpi-antitiroide positivi

# Tiroide e gravidanza: cosa sapere prima

1. Screening tiroideo in gravidanza?
2. L'importanza della iodoprofilassi;
3. Come interpretare i dosaggi ormonali  tiroidei in gravidanza;
4. L'ipotiroidismo gli anticorpi ed il trattamento
5. Procreazione assistita e tiroide

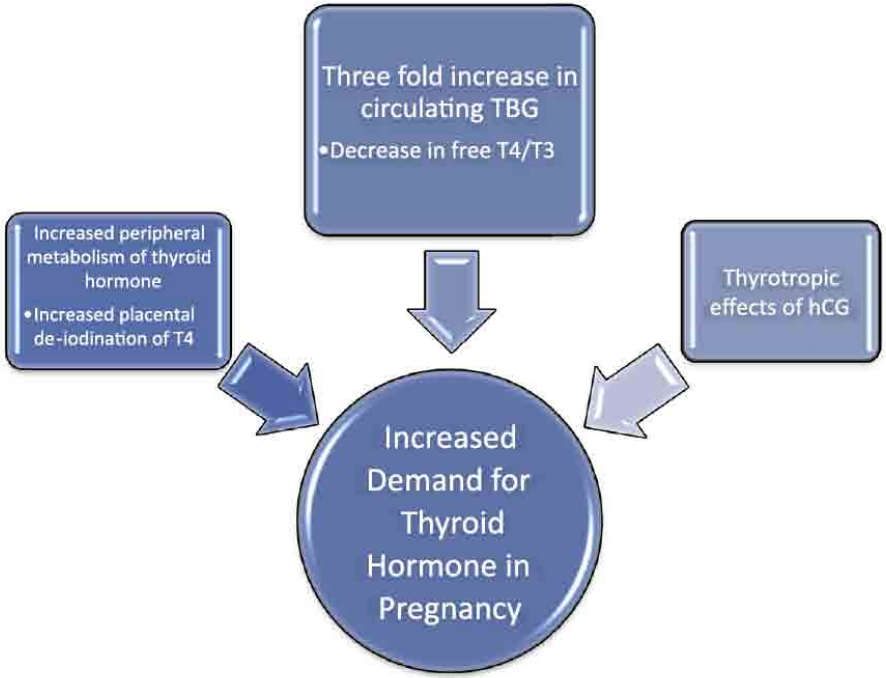
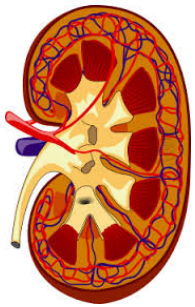



**Fig. 2.** Factors affecting demand for thyroid hormone in pregnancy.



Clearance di Iodio raddoppia

# Tiroide e gravidanza: cosa sapere prima

1.
2. L'importanza della iodoprofilassi;
3.
4.
5.

# Effetti della carenza di Iodio in gravidanza:

aborto spontaneo;

- parto pretermine;
- mortalità  perinatale;
- ipotiroidismo nella madre;
- ipotiroidismo del neonato
- gozzo nella madre;

# Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

*Sarah C Bath, Colin D Steer, Jean Golding, Pauline Emmett, Margaret P Rayman*

## Summary

**Background** As a component of thyroid hormones, iodine is essential for fetal brain development. Although the UK has long been considered iodine replete, increasing evidence suggests that it might now be mildly iodine deficient. We assessed whether mild iodine deficiency during early pregnancy was associated with an adverse effect on child cognitive development.

**Methods** We analysed mother–child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort by measuring urinary iodine concentration (and creatinine to correct for urine volume) in stored samples from 1040 first-trimester pregnant women. We selected women on the basis of a singleton pregnancy and availability of both a urine sample from the first trimester (defined as ≤13 weeks' gestation; median 10 weeks [IQR 9–12]) and a measure of intelligence quotient (IQ) in the offspring at age 8 years. Women's results for iodine-to-creatinine ratio were dichotomised to less than 150 μg/g or 150 μg/g or more on the basis of WHO criteria for iodine deficiency or sufficiency in pregnancy. We assessed the association between maternal iodine status and child IQ at age 8 years and reading ability at age 9 years. We included 21 socioeconomic, parental, and child factors as confounders.

**Findings** The group was classified as having mild-to-moderate iodine deficiency on the basis of a median urinary iodine concentration of 91·1 μg/L (IQR 53·8–143; iodine-to-creatinine ratio 110 μg/g, IQR 74–170). After adjustment for confounders, children of women with an iodine-to-creatinine ratio of less than 150 μg/g were more likely to have scores in the lowest quartile for verbal IQ (odds ratio 1·58, 95% CI 1·09–2·30; p=0·02), reading accuracy (1·69, 1·15–2·49; p=0·007), and reading comprehension (1·54, 1·06–2·23; p=0·02) than were those of mothers with ratios of 150 μg/g or more. When the less than 150 μg/g group was subdivided, scores worsened ongoing from 150 μg/g or more, to 50–150 μg/g, to less than 50 μg/g.

**Interpretation** Our results show the importance of adequate iodine status during early gestation and emphasise the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.

*Lancet* 2013; 382: 331–37

Published Online
May 22, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60436-5

See Comment page 292

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m.rayman@surrey.ac.uk

# Cosa consigliano le LG:

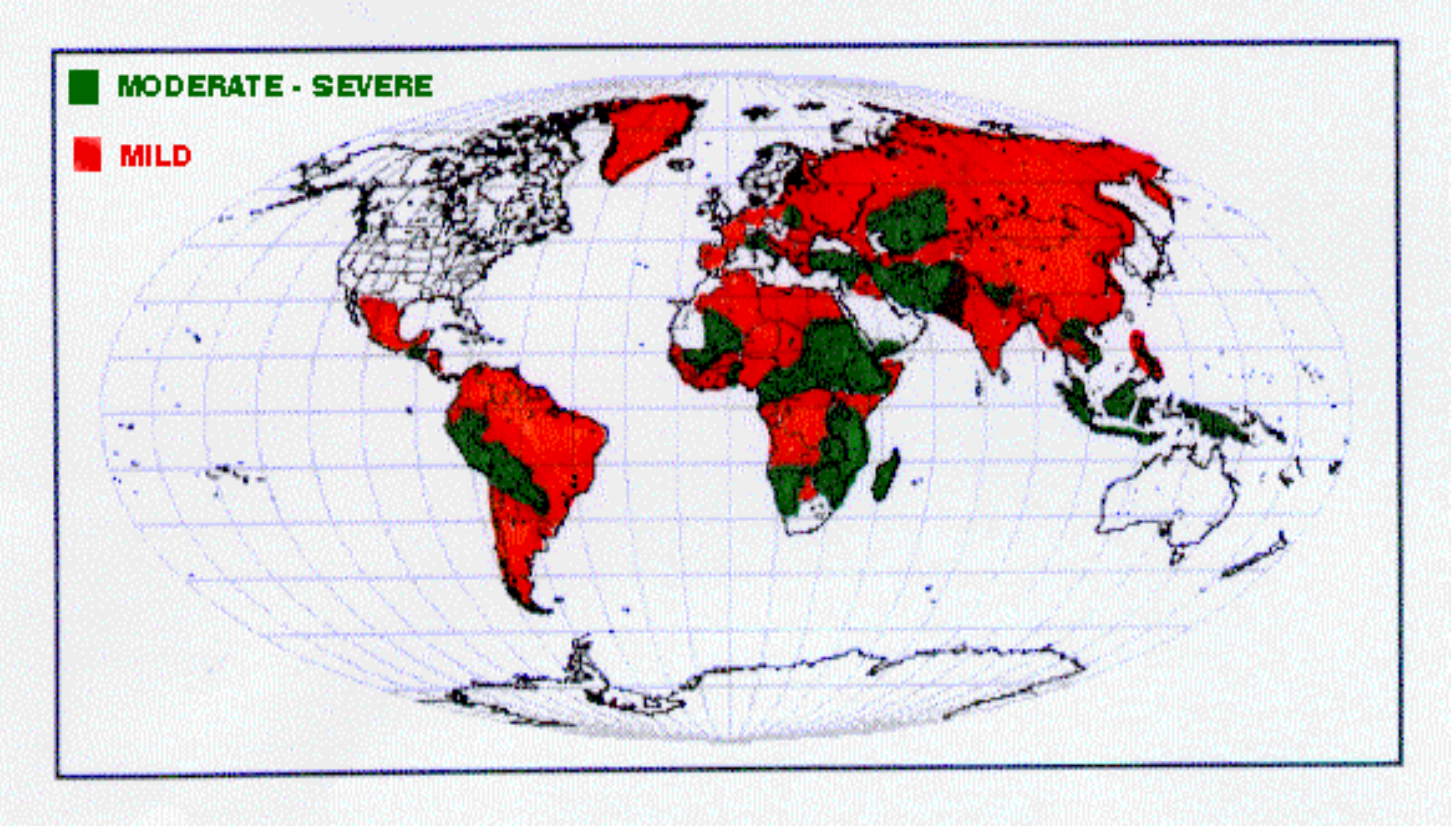
- **supplementi di iodio:**

**ATA 150 µg/die, ES 150-200 µg/die;**

- **supplementi in fase preconcezionale (ES);**
- **supplementi in l'allattamento (ATA, ES);**

# AREE A CARENZA IODICA

Purtroppo lo IODIO non è presente in tutte le aree del mondo in dosi sufficienti anzi molte nazioni presentano carenza di IODIO. L'ITALIA è una zona carente!!!

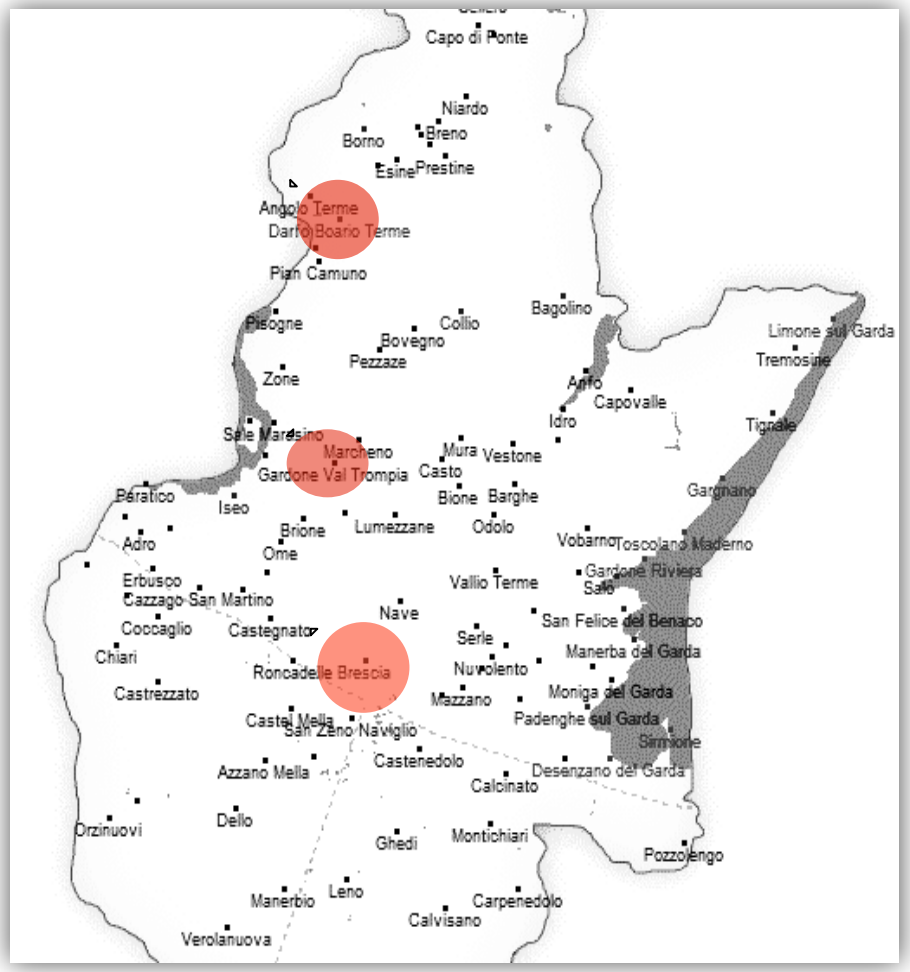


# Scuole Secondaria 1° grado: 540 studenti

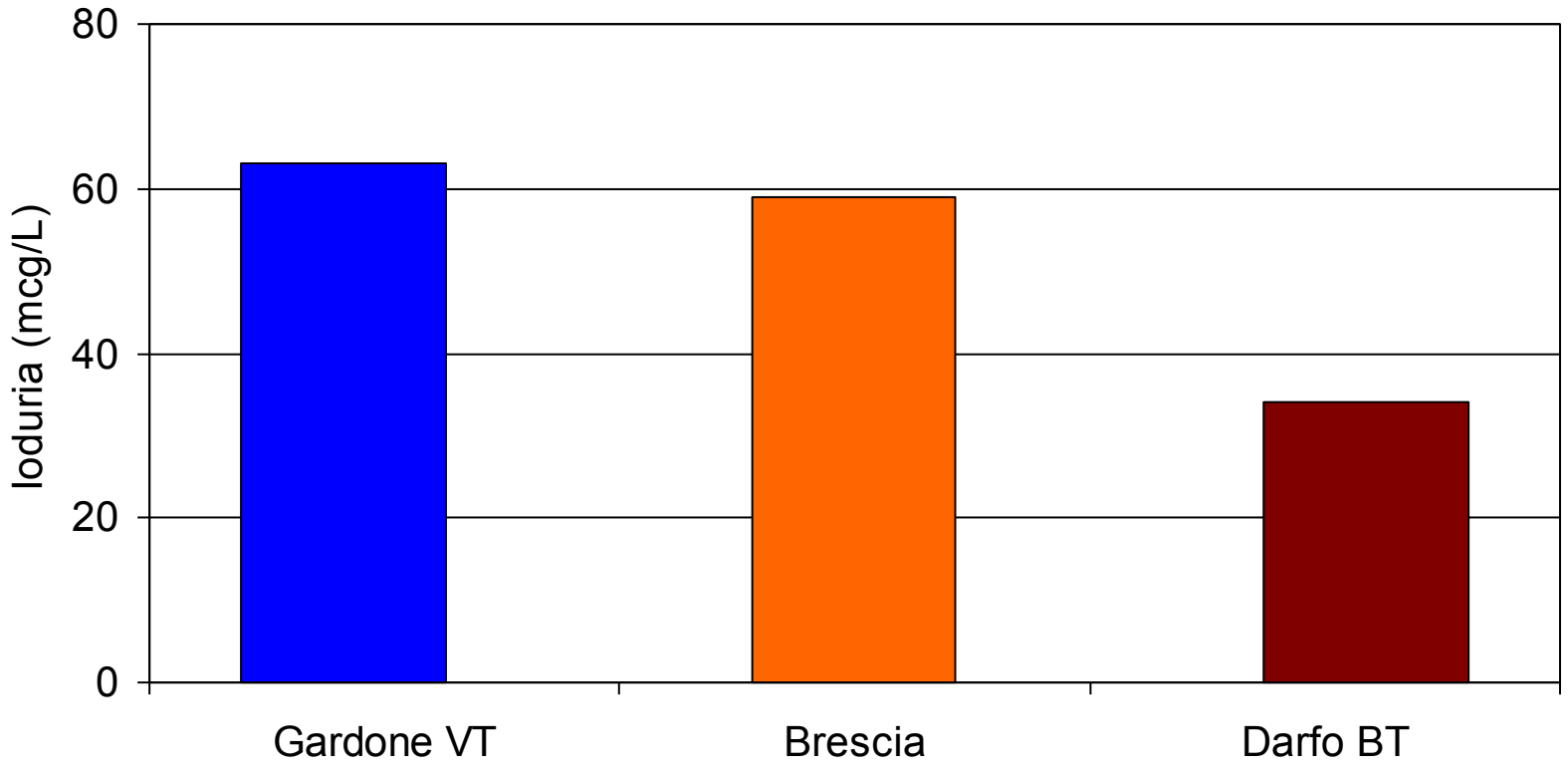
“Tovini”, Darfo Boario Terme

“Canossi”, Gardone VT

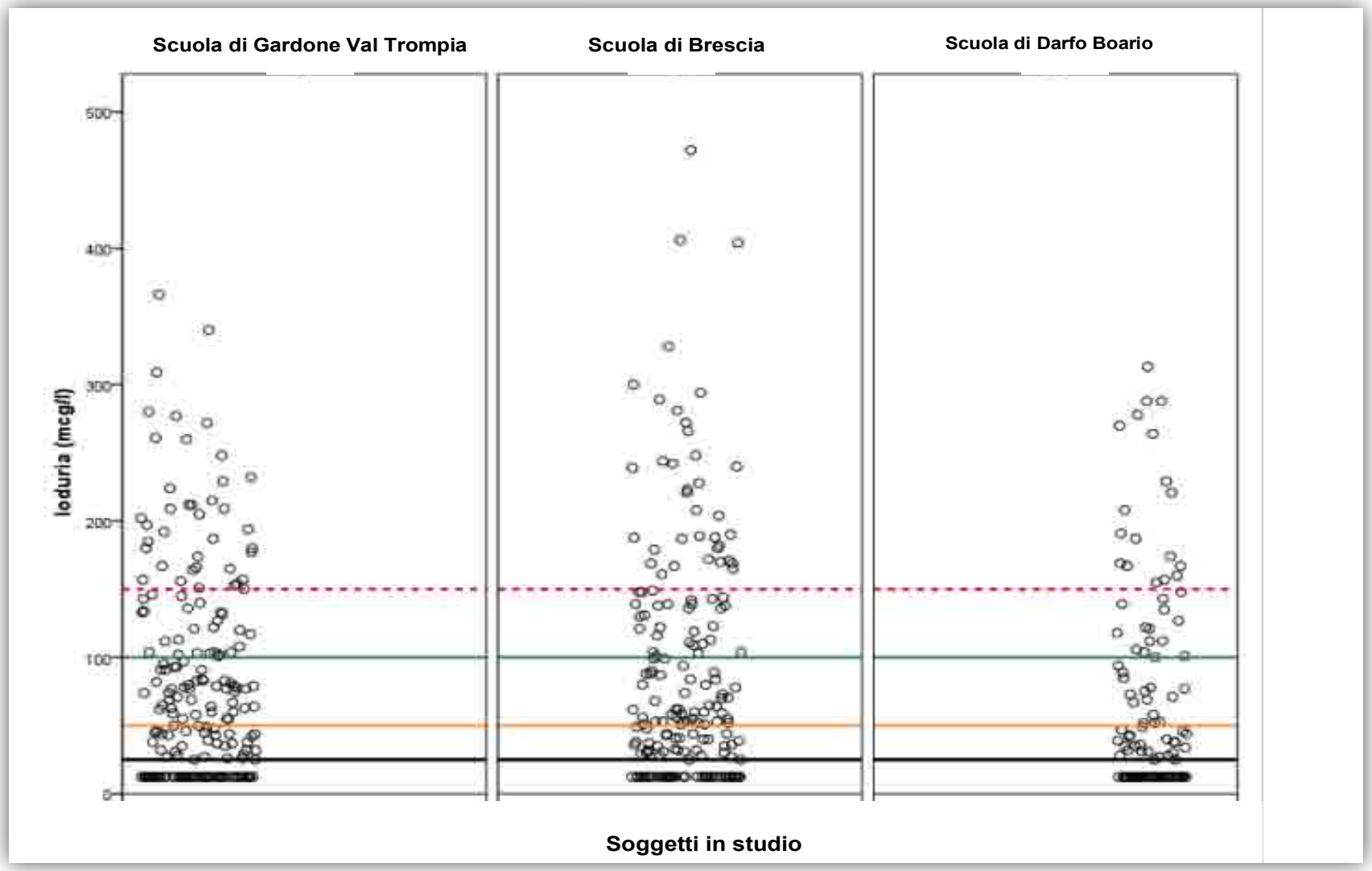
“Carducci”, Brescia



# MEDIANA IODURIA NELLE TRE SCUOLE



# Apporto iodico scuole bresciane




ISTITUTO SUPERIORE DI SANITA'

# Tiroide e gravidanza: cosa sapere prima

1.
2.
3. Come interpretare i dosaggi ormonali  tiroidei in gravidanza;
4.
5.

THYROID
Volume 21, Number 10, 2011

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]

## TSH IN GRAVIDANZA

| | |
|---|---|
| PRIMO TRIMESTRE | 0.1-2.5 mIU/L |
| SECONDO TRIMESTRE | 0.2-3.0 mIU/L |
| TERZO TRIMESTRE | 0.3-3.0 mIU/L |

# IPOTIROIDISMO IN GRAVIDANZA:

- TSH > 2.5-3.0 mIU/L ed fT4 < alla norma
- TSH > 10 mIU/L, qualunque valore di fT4

## SEMPRE DA TRATTARE


SPINACH

**Tirosint® 25** microgrammi/1 ml
**Tirosint® 50** microgrammi/1 ml
**Tirosint® 75** microgrammi/1 ml
**Tirosint® 100** microgrammi/1 ml
soluzione orale
levotiroxina sodica

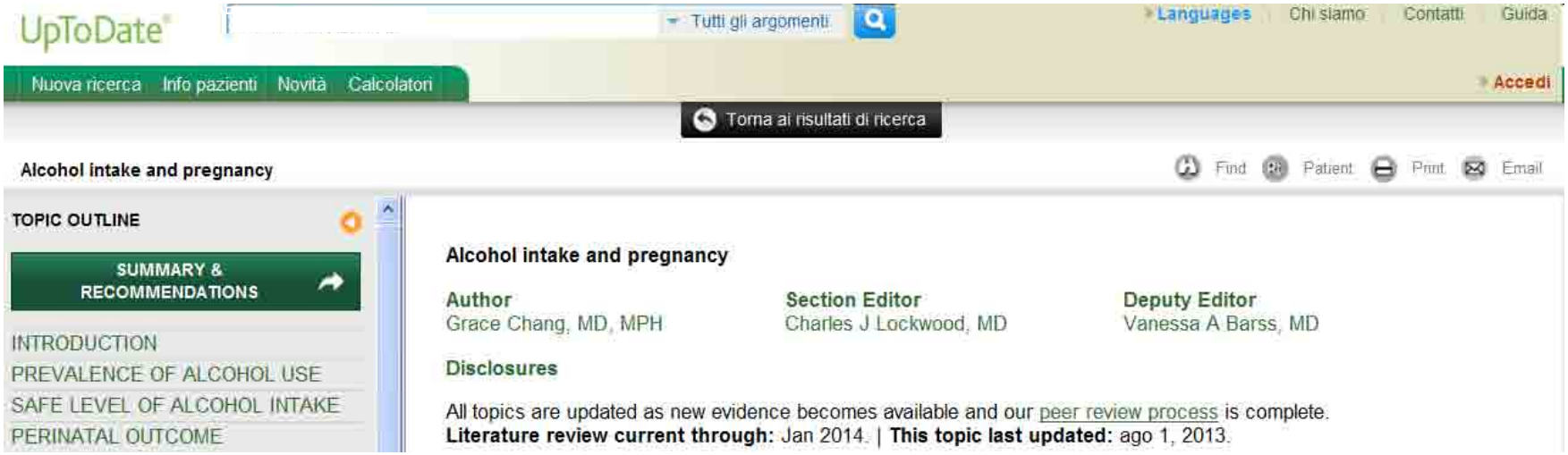
IBSA

**CATEGORIA FARMACOTERAPEUTICA**
Ormoni tiroidei.

Tirosint soluzione orale contiene 28,8 vol% di etanolo (alcol etilico). Ogni contenitore monodose contiene 243 mg di etanolo (alcol etilico). Dannoso per chi è affetto da alcolismo. Tenere in considerazione per il trattamento durante la gravidanza e l'allattamento e per il trattamento di bambini e di pazienti ad alto rischio, quali pazienti con malattie epatiche o epilettici.

***Gravidanza e allattamento***
Chiedete consiglio al medico o al farmacista prima di prendere qualsiasi medicinale.

GRAVIDANZA
Nelle donne in stato di gravidanza e durante il periodo di allattamento la somministrazione del prodotto non andrebbe interrotta, tuttavia la sua somministrazione, come per altri farmaci somministrati in gravidanza, andrebbe effettuata solo in caso di effettiva necessità e sotto il diretto controllo del medico.
I dosaggi necessari possono anche aumentare durante la gravidanza.
L'esperienza ha mostrato che non c'è evidenza di teratogenicità indotta da farmaco e/o tossicità per il feto nella specie umana ai dosaggi terapeutici raccomandati. Dosi eccessivamente alte di levotiroxina durante la gravidanza possono avere un effetto negativo sullo sviluppo fetale e postnatale.
Durante la gravidanza, la levotiroxina non deve essere somministrata in associazione con farmaci per l'ipertiroidismo (farmaci antitiroidei), poiché l'aggiunta di levotiroxina può rendere necessaria una dose più elevata di farmaco antitiroideo.




**SAFE LEVEL OF ALCOHOL INTAKE** — The Surgeon General of the United States and the Secretary of Health and Human Services recommend abstinence from alcohol for women planning pregnancy, at conception, and during pregnancy because a safe level of prenatal alcohol consumption has not been determined [7]. National guidelines in several other countries, including, but not limited to, Canada, Australia, New Zealand, France, and the United Kingdom, also recommend complete abstinence.

A systematic review did not find a significant increase in risk of low birthweight or birth of a small for gestational age infant for alcohol intake up to 10 g pure alcohol/day (about one drink per day) or an increase in preterm birth for alcohol intake up to 18 g pure alcohol/day (about 1.5 drinks per day) [10].

Endocr Pract. 2014 Sep;20(9):901-6. doi: 10.4158/EP13378.OR.

**Levothyroxine liquid solution versus tablet for replacement treatment in hypothyroid patients.**

Negro R[1], Valcavi R[2], Agrimi D[3], Toulis KA[4].

J Endocrinol Invest. 2014 Jun;37(6):583-7. doi: 10.1007/s40618-014-0082-9. Epub 2014 May 1.

**Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube.**

Pirola I[1], Daffini L, Gandossi E, Lombardi D, Formenti A, Castellano M, Cappelli C.

Horm Res Paediatr. 2014;81(1):50-4. doi: 10.1159/000356047. Epub 2013 Nov 12.

**Congenital hypothyroidism treatment in infants: a comparative study between liquid and tablet formulations of levothyroxine.**

Peroni E[1], Vigone MC, Mora S, Bassi LA, Pozzi C, Passoni A, Weber G.

Eur J Endocrinol. 2013 Nov 22;170(1):95-9. doi: 10.1530/EJE-13-0693. Print 2014 Jan.

**Oral liquid levothyroxine treatment at breakfast: a mistake?**

Cappelli C[1], Pirola I, Gandossi E, Formenti A, Castellano M.

Obes Surg. 2013 Sep;23(9):1493-6. doi: 10.1007/s11695-013-1015-y.

**Oral liquid L-thyroxine (L-t4) may be better absorbed compared to L-T4 tablets following bariatric surgery.**

Pirola I[1], Formenti AM, Gandossi E, Mittempergher F, Casella C, Agosti B, Cappelli C.


CATEGORIA FARMACOTERAPEUTICA:
Ormoni tiroidei.

PRINCIPI ATTIVI:
Ogni ml contiene 1 mg di levotiroxina sodica (come multiidrato) (equivalente a 0,97 mg di levotiroxina).

ECCIPIENTI:
Conservante antimicrobico: etanolo 15% v/v.

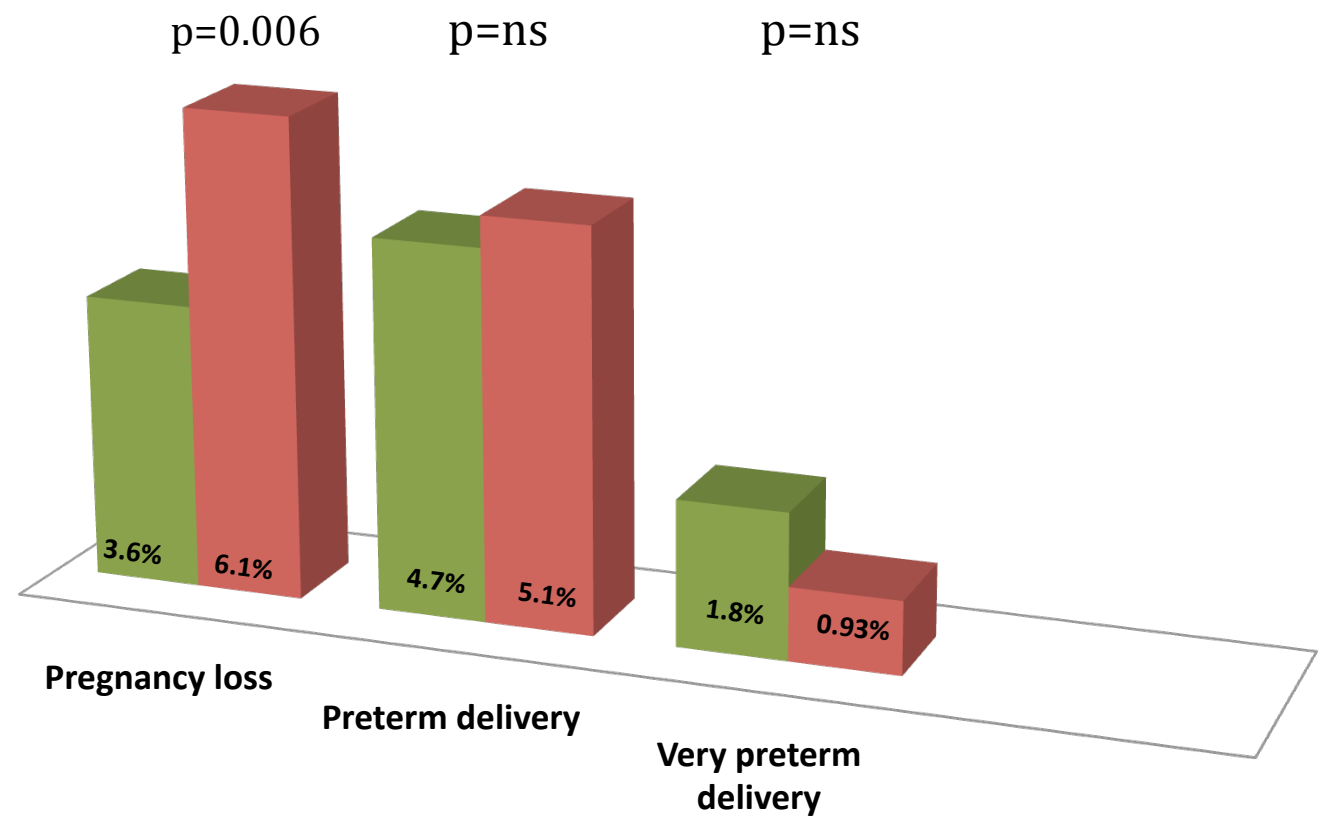
INTERAZIONI:
L'assorbimento di levotiroxina puo' essere ridotto dalla concomitante somministrazione di antiacidi, per esempio sali di alluminio o di magnesio o carbonato di calcio, sucralfato e ferro solfato. Uno studio ottenuto su 3 specie canine non ha rilevato alcuna interazione tra la contemporanea somministrazione di Leventa e Sali di ferro. La somministrazione concomitante del farmaco con i composti sopra menzionati deve essere evitata oppure, in caso di assoluta necessita', devono trascorrere almeno 2 ore.

# IPOTIROIDISMO SUBCLINICO IN GRAVIDANZA

- TSH > 2.5-3.0 mIU/L e < 10 mIU/L con fT4 normale

## DA TRATTARE ?

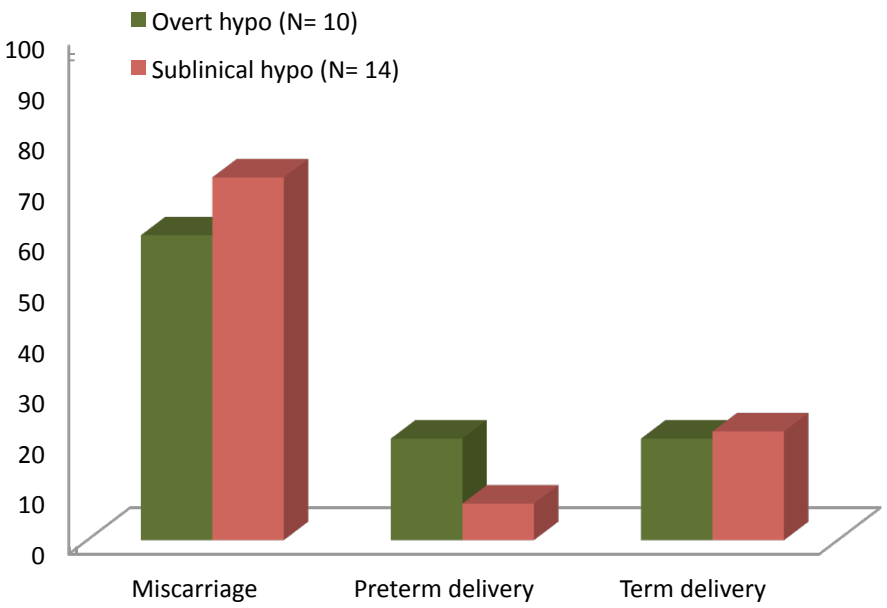
# Ipotiroidismo subclinico e Complicanze ostetriche in donne TsAb-



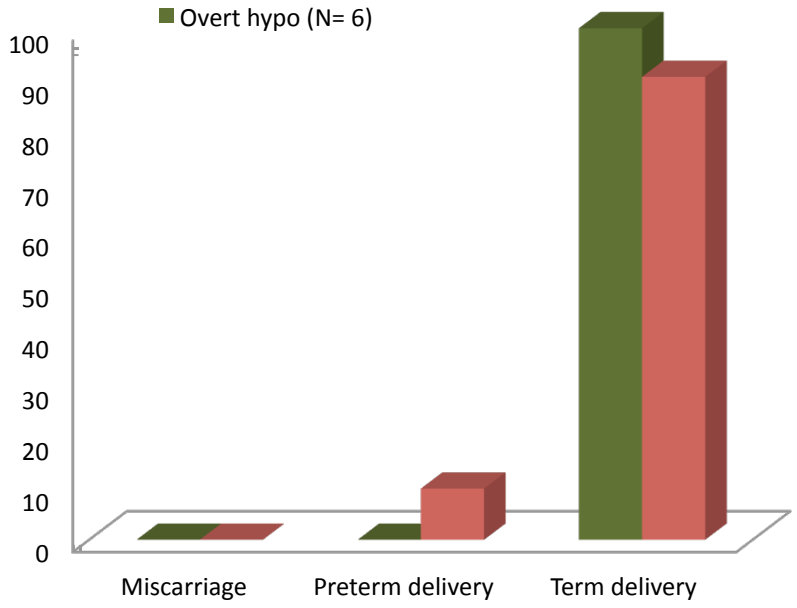

Gruppo A (3481) TSH<2.5
Gruppo B (642) 2.5≤TSH≤ 5.0

R Negro, JCEM 2010

# Ipotiroidismo subclinico e complicanze ostetriche




Inadequate treatment



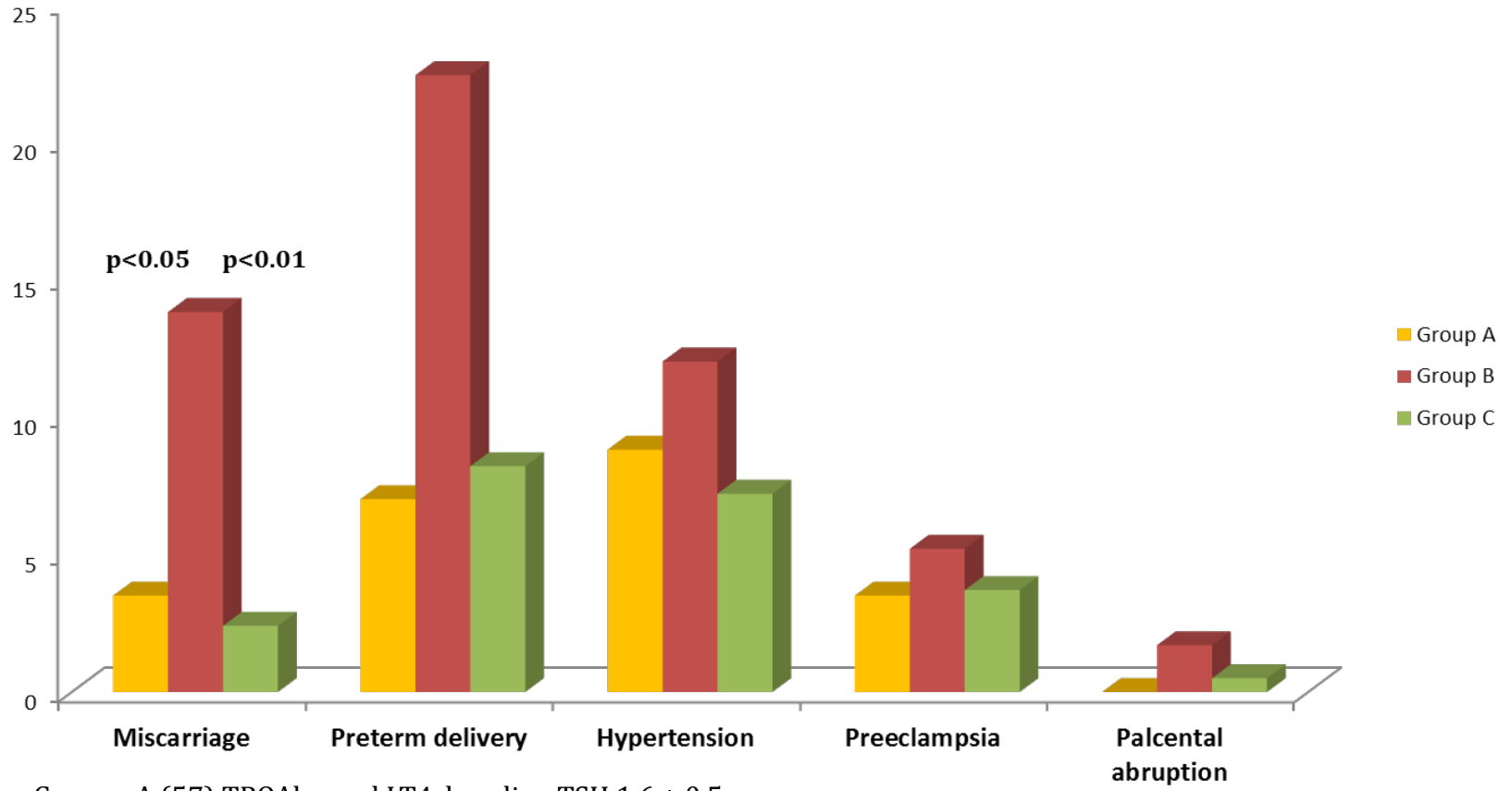

Adequate Treatment

Abalovich, Thyroid 2002

# IPOTIROIDISMO SUBCLINICO IN GRAVIDANZA

| | ATA 2011 | ATA 2012 | ES 2012 |
|---|---|---|---|
| **IPO SUBCLINICO Ab TPO +** | terapia raccomandata | terapia raccomandata | terapia raccomandata |
| **IPO SUBCLINICO Ab TPO -** | evidenze insufficienti | evidenze insufficienti | terapia raccomandata |

# Autoimmunità e Complicanze Ostetriche




Gruppo A (57) TPOAb+ and LT4, baseline TSH 1.6 ± 0.5
Gruppo B (58) TPOAb+, baseline TSH 1.7±0.4
Gruppo C (869) TPO-, TSH 1.1± 0.4

R Negro, JCEM 2006

# Tiroide e gravidanza: cosa sapere prima

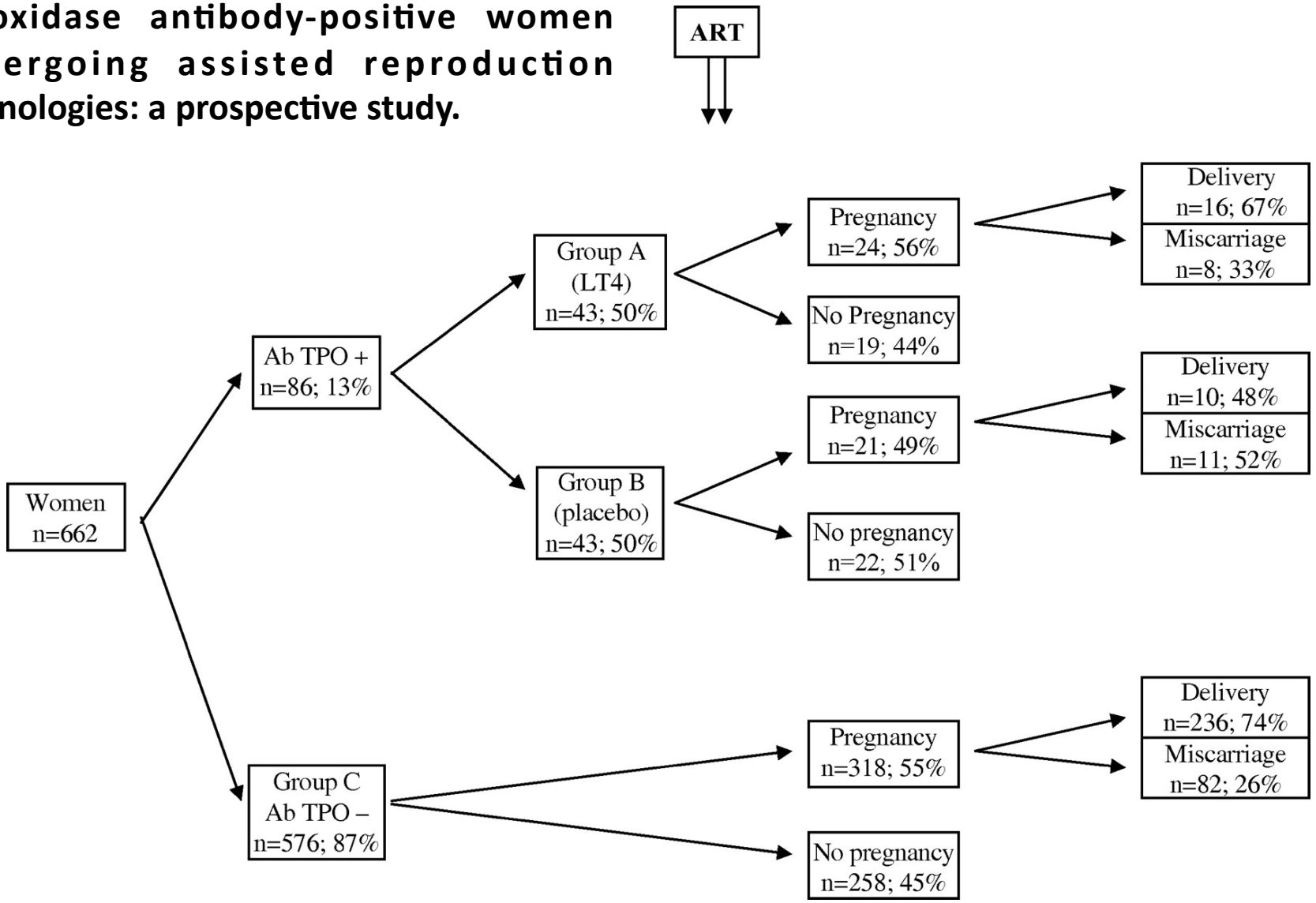
1.
2.
3.
4.
5. Procreazione assistita e tiroide

**Table 2** Comparison of COS and IVF outcome between ATA+ and ATA- group

| Variables | ATA+ Group | Control Group | P-value |
|---|---|---|---|
| Stimulation length(days) | 11.0±1.8 | 10.7±1.7 | 0.074 |
| Total Gn dose(IU) | 2302±864 | 2246±736 | 0.885 |
| E2 level on the day of HCG (pg/ml) | 2290±1101 | 2342±1173 | 0.716 |
| Number of retrieved oocytes | 10.9±6.1 | 11.8±6.9 | 0.166 |
| Fertilization Rate | 64.3%(729/1134) | 74.6%(8848/11856) | <0.001 |
| Number of available embryos | 5.3±3.9 | 6.0±4.2 | 0.01 |
| Number of embryo transferred | 2.4±0.6 | 2.3±0.6 | 0.086 |
| Pregnancy Rate | 33.3%(52/156) | 46.7%(458/981) | 0.002 |
| Implantation Rate | 17.8%(66/370) | 27.1%(611/2251) | <0.001 |
| Abortion Rate | 26.9%(14/52) | 11.8%(54/458) | 0.002 |

(Zhong, 2012)

**Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study.**




Negro R, et al. Hum Reprod. 2005 Jun;20(6):1529-33.

**Human Reproduction Update, Vol.19, No.3 pp. 251–258, 2013**
Advanced Access publication on January 17, 2013 doi:10.1093/humupd/dms052

human reproduction update

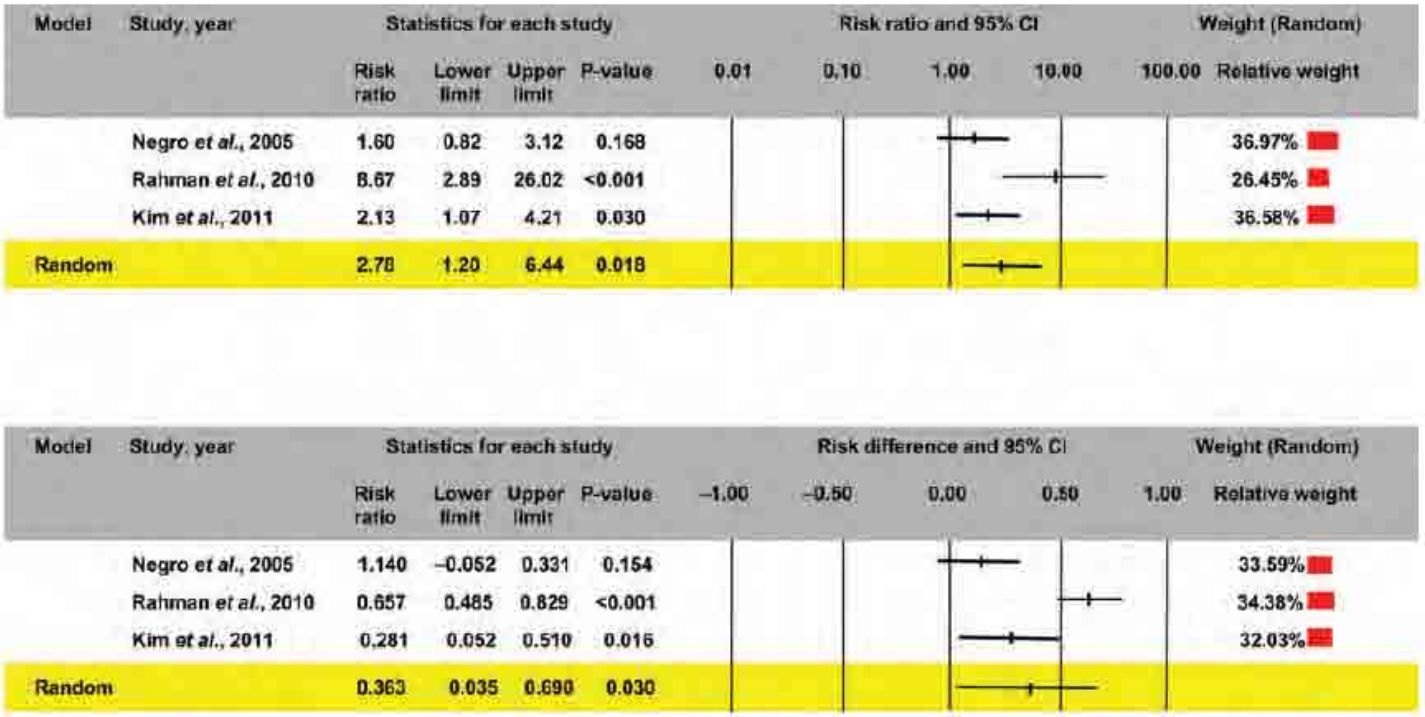
# Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs

**B. Velkeniers[1], A. Van Meerhaeghe[2], K. Poppe[1], D. Unuane[1], H. Tournaye[3], and P. Haentjens[4,5,*]**

[1]Department of Endocrinology and General Internal Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium [2]GERHPAC (Group of Applied Epistemology and Rational Clinic of the Public Hospitals from Charleroi) ISPPC - CHU-Charleroi, Charleroi, Belgium [3]Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium [4]Center for Outcomes Research and Laboratory for Experimental Surgery, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium [5]CEBAM Belgian Center for Evidence Based Medicine, Belgian Branch of the Cochrane Collaboration, Leuven, Belgium

*Correspondence address. Tel: +32-2-477-64-18; Fax: +32-2-477-64-28; E-mail: patrick.haentjens@uzbrussel.be

*Submitted on September 26, 2012; resubmitted on November 2, 2012; accepted on November 14, 2012*




**BACKGROUND:** Previous meta-analyses of observational data indicate that pregnant women with subclinical hypothyroidism have an increased risk of adverse pregnancy outcome. Potential benefits of levothyroxine (LT4) supplementation remain unclear, and no systematic review or meta-analysis of trial findings is available in a setting of assisted reproduction technologies (ART).

**METHODS:** Relevant trials published until August 2012 were identified by searching MEDLINE, EMBASE, Web of Knowledge, the Cochrane Controlled Trials Register databases and bibliographies of retrieved publications without language restrictions.

**RESULTS:** From 630 articles retrieved, we included three trials with data on 220 patients. One of these three trials stated 'live delivery' as outcome. LT4 treatment resulted in a significantly higher delivery rate, with a pooled relative risk (RR) of 2.76 (95% confidence limits 1.20–6.44; $P = 0.018$; $I^2 = 70\%$), a pooled absolute risk difference (ARD) of 36.3% (3.5–69.0%: $P = 0.030$) and a summary number needed to treat (NNT) of 3 (1–28) in favour of LT4 supplementation. LT4 treatment significantly lowered miscarriage rate with a pooled RR of 0.45 (0.24–0.82; $P = 0.010$; $I^2 = 26\%$), a pooled ARD of −31.3% (−48.2 to −14.5%: $P < 0.001$) and a summary NNT of 3 (2–7) in favour of LT4 supplementation. LT4 treatment had no effect on clinical pregnancy (RR 1.75; 0.90–3.38; $P = 0.098$; $I^2 = 82\%$). In an ART setting, no data are available on the effects of LT4 supplementation on premature delivery, arterial hypertension, placental abruption or pre-eclampsia.

# Tiroide e gravidanza: cosa sapere prima

1. Screening tiroideo in gravidanza?
2.
3.
4.
5.

The Journal of Clinical Endocrinology & Metabolism 92(8) (Supplement):S1–S47

doi: 10.1210/jc.2007-0141

**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

### *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
2. Women with a family history of thyroid disease
3. Women with a goiter
4. Women with thyroid antibodies (when known).
5. Women with symptoms or clinical signs suggestive of thyroid underfunction or overfunction, including anemia, elevated cholesterol, and hyponatremia
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

J Clin Endocrinol Metab 96: E1452–E1456, 2011)

# Thyroid Testing during Pregnancy at an Academic Boston Area Medical Center

Donny L. F. Chang, Angela M. Leung, Lewis E. Braverman, and Elizabeth N. Pearce

## Discussion

Our study of the rate of thyroid testing in pregnant women at BMC found that 80.4% of pregnant women with TSH elevation would have been missed based on current high-risk screening guidelines.

We believe these observational results support universal screening in pregnancy. However, such screening cannot be advocated in the absence of data showing that L-$T_4$ treatment improves outcomes.

The Journal of Clinical Endocrinology & Metabolism 92(8) (Supplement):S1–S47

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9. Women with prior therapeutic head or neck irradiation.
10. Women with a prior history of miscarriage or preterm delivery

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*Review Article*

# Screening for Maternal Thyroid Dysfunction in Pregnancy A Review of the Clinical Evidence and Current Guidelines

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**Targeted case finding criteria:**
(1) Age > 30 years
(2) Personal history of thyroid dysfunction
(3) Prior head or neck irradiation
(4) Prior thyroid surgery
(5) Family history
(6) Symptoms
(7) Presence of Goiter
(8) TPO Ab positivity
(9) Autoimmunity
(10) Infertility
(11) Miscarriage or preterm delivery
(12) Iodine deficient population
(13) Medications and iodinated contrast media*
(14) Morbid obesity (BMI > 40 kg/m$^2$)*

*Only for American Thyroid Association 2011 guidelines.

Box 2: Case-finding approach for high risk patients based on The Endocrine Society 2012 [11] and American Thyroid Association 2011 [12] guidelines.

**Table 2** Comparison of COS and IVF outcome between ATA+ and ATA- group

| Variables | ATA+ Group | Control Group | P-value |
|---|---|---|---|
| Stimulation length(days) | 11.0±1.8 | 10.7±1.7 | 0.074 |
| Total Gn dose(IU) | 2302±864 | 2246±736 | 0.885 |
| E2 level on the day of HCG (pg/ml) | 2290±1101 | 2342±1173 | 0.716 |
| Number of retrieved oocytes | 10.9±6.1 | 11.8±6.9 | 0.166 |
| Fertilization Rate | 64.3%(729/1134) | 74.6%(8848/11856) | <0.001 |
| Number of available embryos | 5.3±3.9 | 6.0±4.2 | 0.01 |
| Number of embryo transferred | 2.4±0.6 | 2.3±0.6 | 0.086 |
| Pregnancy Rate | 33.3%(52/156) | 46.7%(458/981) | 0.002 |
| Implantation Rate | 17.8%(66/370) | 27.1%(611/2251) | <0.001 |
| Abortion Rate | 26.9%(14/52) | 11.8%(54/458) | 0.002 |

(Zhong, 2012)