Associazione Medici Endocrinologi
Per la qualità clinica in Endocrinologia

TIROIDE, DALLA GESTAZIONE ALLA TERZA ETÀ

Evento accreditato ECM

BRESCIA, 18 APRILE 2015

Ormoni tiroidei e spermatogenesi

A. Delbarba, MD

A.O. Spedali Civili di Brescia

Elementi di anatomia testicolare

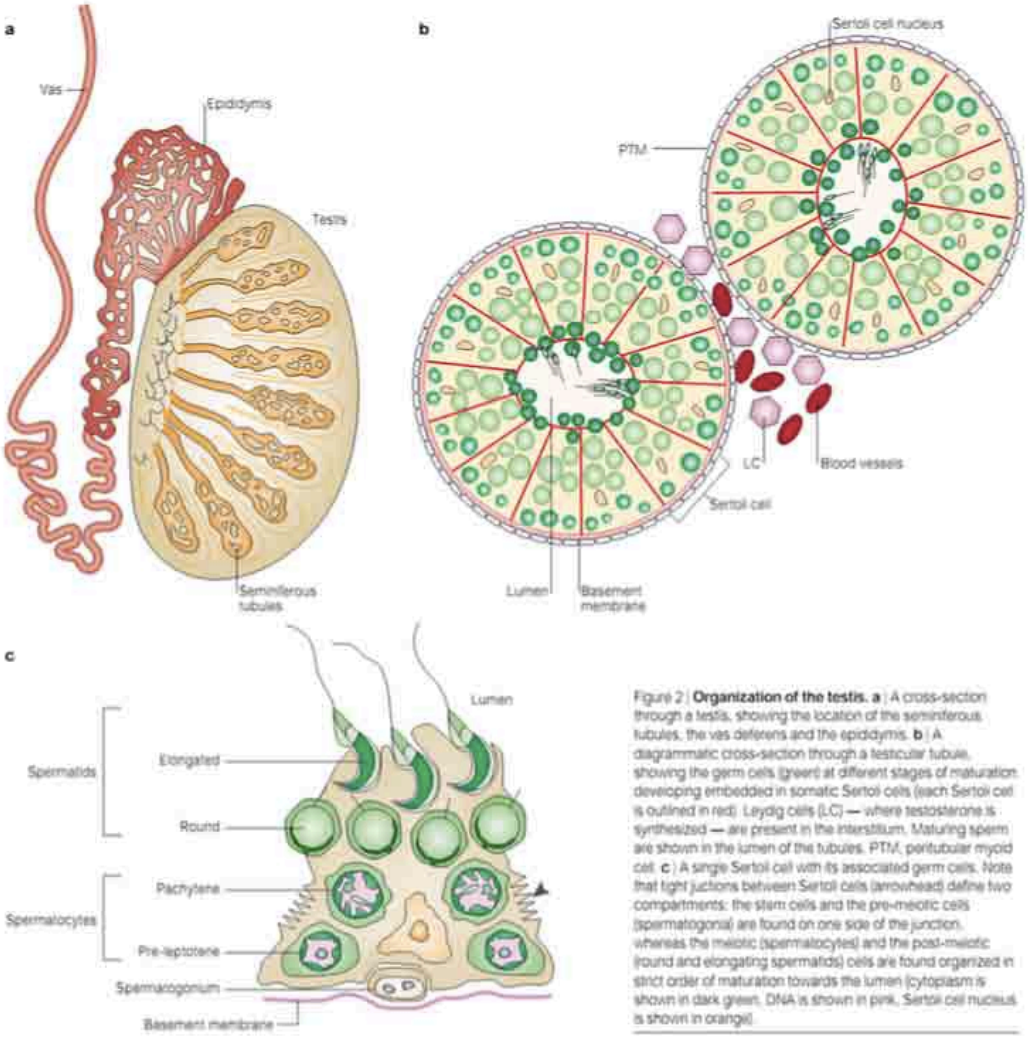
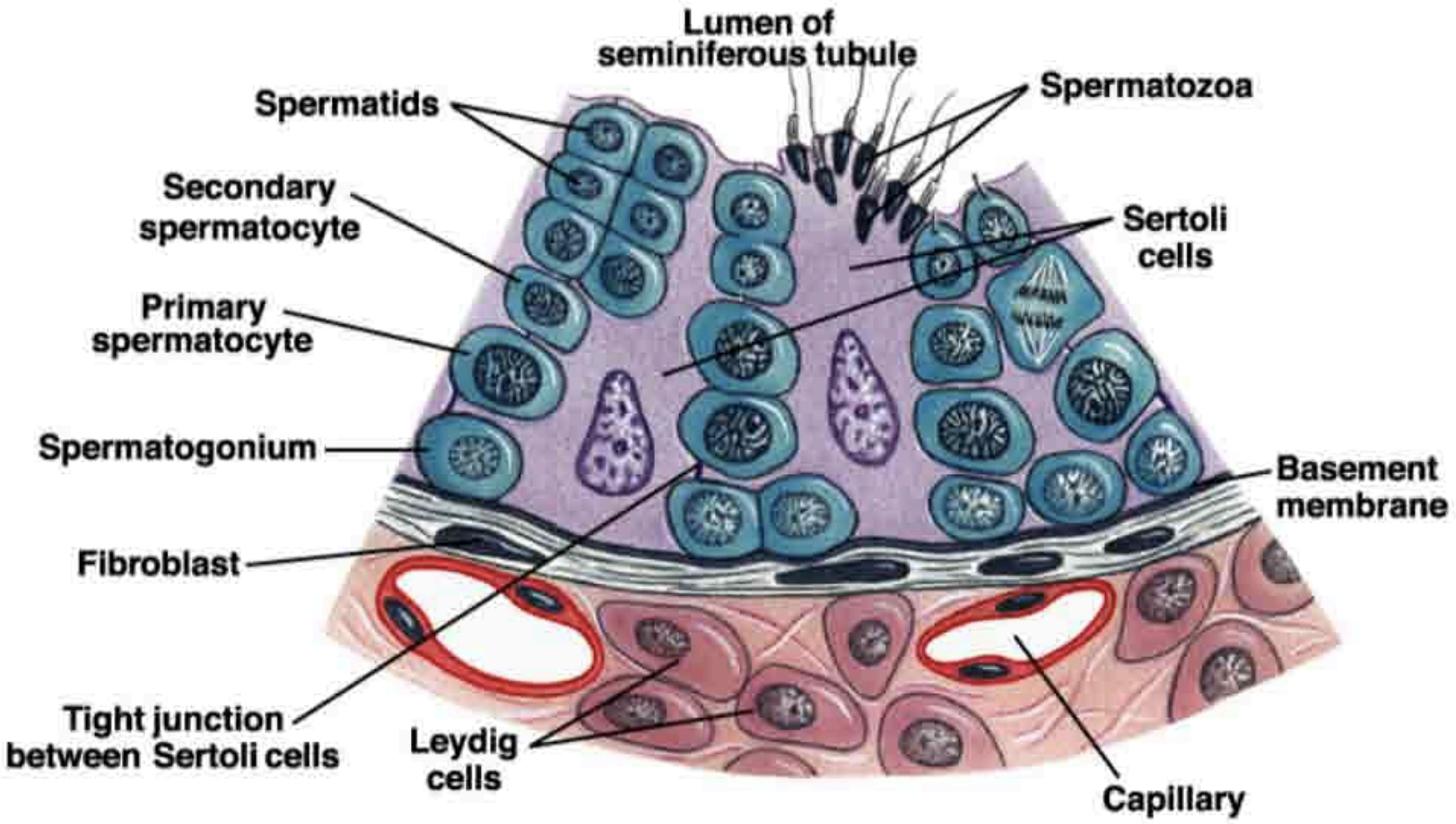
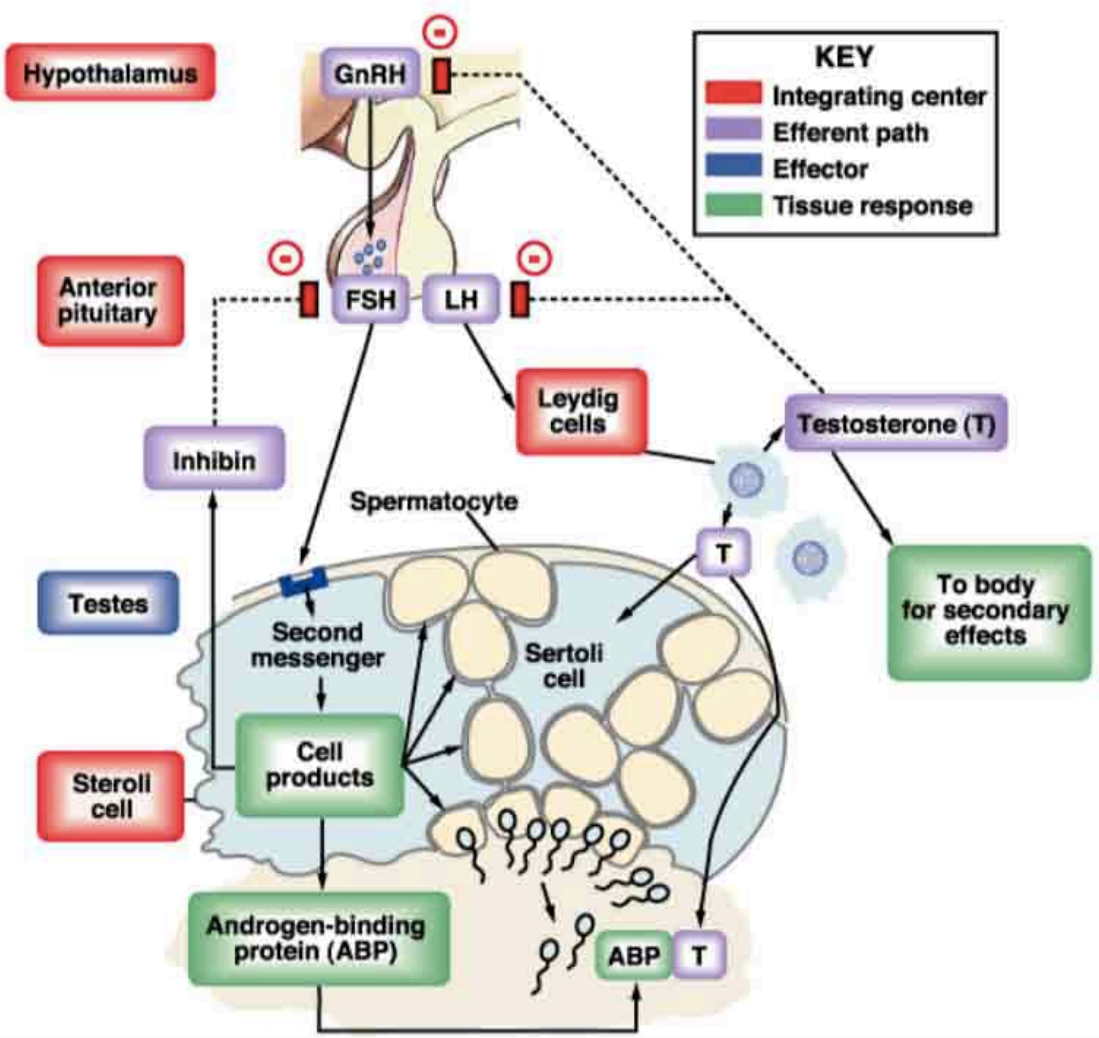


Figure 2 | **Organization of the testis. a** | A cross-section through a testis, showing the location of the seminiferous tubules, the vas deferens and the epididymis. **b** | A diagrammatic cross-section through a testicular tubule, showing the germ cells (green) at different stages of maturation developing embedded in somatic Sertoli cells (each Sertoli cell is outlined in red). Leydig cells (LC) — where testosterone is synthesized — are present in the interstitium. Maturing sperm are shown in the lumen of the tubules. PTM, peritubular myoid cell. **c** | A single Sertoli cell with its associated germ cells. Note that tight junctions between Sertoli cells (arrowhead) define two compartments: the stem cells and the pre-meiotic cells (spermatogonia) are found on one side of the junction, whereas the meiotic (spermatocytes) and the post-meiotic (round and elongating spermatids) cells are found organized in strict order of maturation towards the lumen (cytoplasm is shown in dark green, DNA is shown in pink, Sertoli cell nucleus is shown in orange).

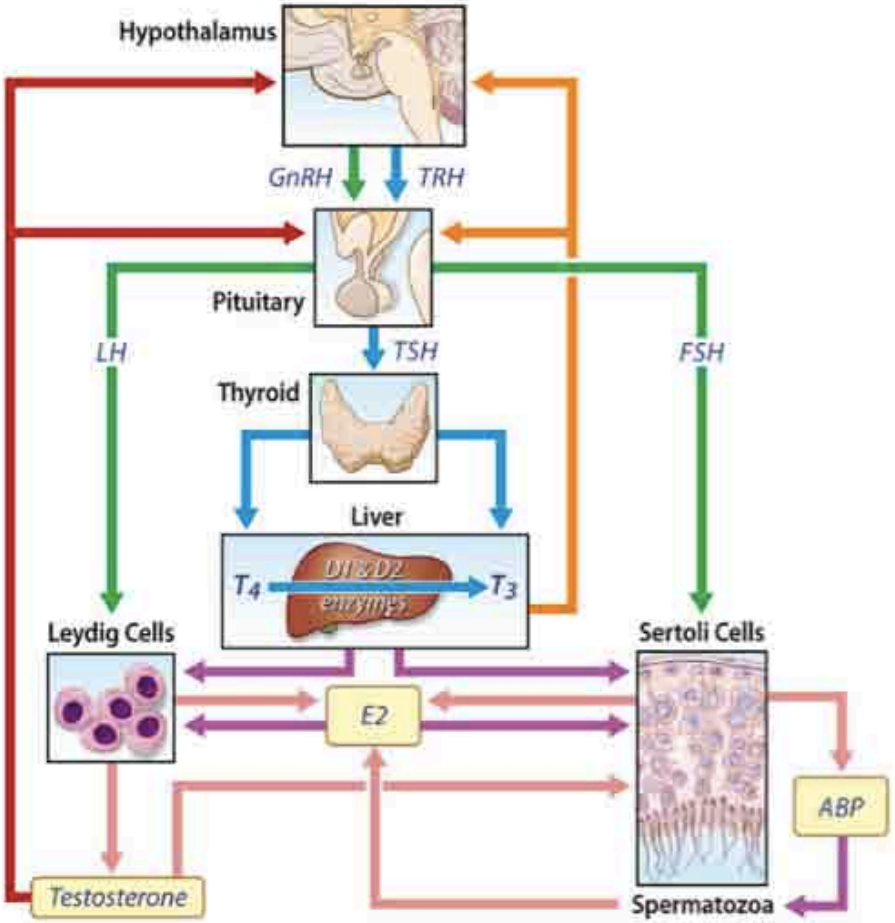
Spaccato istologico tessuto testicolare



Asse Ipotalamo - ipofisi - gonadi

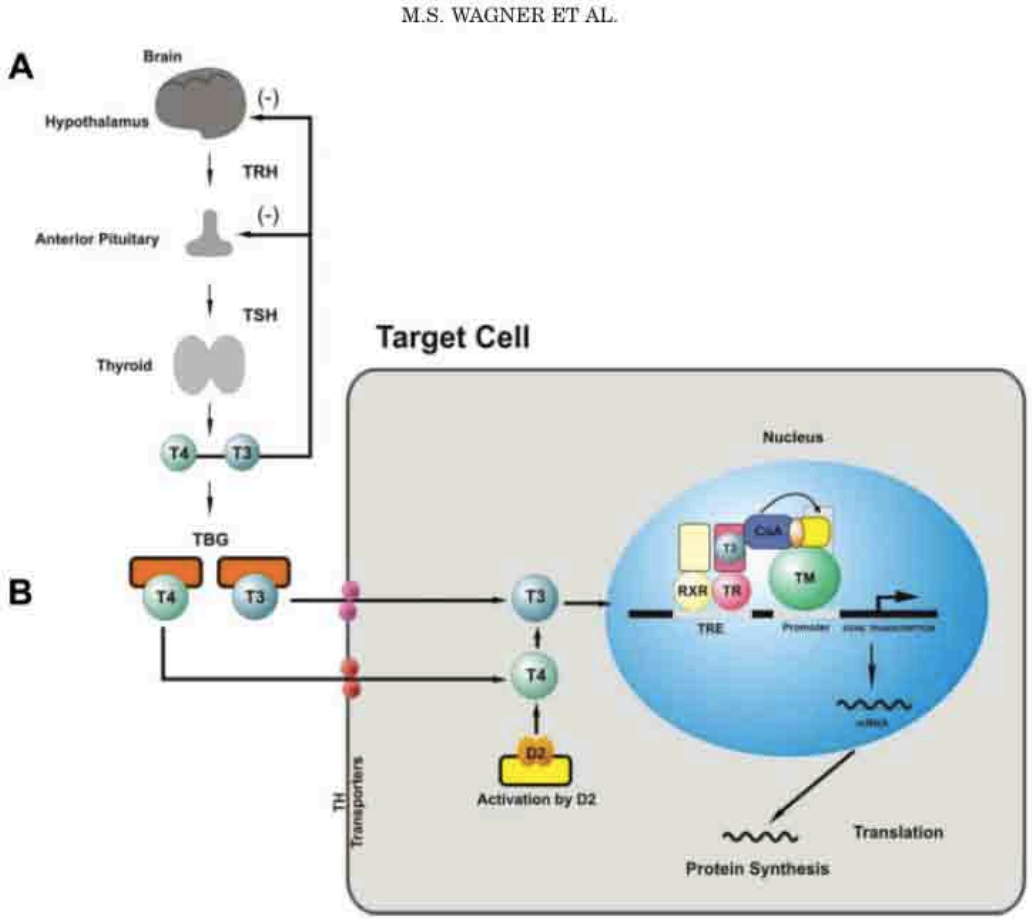


Intreccio asse tiroideo e gonadico



[Frontiers in Bioscience E3, 843-855, June 1, 2011]

Via transcrizionale genomica



MICROSCOPY RESEARCH AND TECHNIQUE 72:796–808 (2009)

Via transcrizionale non genomica

- Modulazione dei potenziali di membrana che coinvolgono i canali del potassio (Sertoli).
- Fosforilazione della Vimentina, componente proteica del citoscheletro (Sertoli).
- Aumento livelli GLUT1 mRNA agendo sulla stabilità biologica della struttura proteica.
- Modulazione delle Gap Junction tramite azione sul citoscheletro (Citocalasina D).

J Endocrinol. 2008 December ; 199(3): 351–365.

Lo stato dell'arte in letteratura

Endocr Rev. 1995 Aug;16(4):443-59.

Thyroid hormone and male gonadal function.

Jannini EA[1], Ulisse S, D'Armiento M.

Author information

Endocr Rev. 2010 Oct;31(5):702-55. doi: 10.1210/er.2009-0041. Epub 2010 Jun 23.

Thyroid function and human reproductive health.

Krassas GE[1], Poppe K, Glinoer D.

Author information

La fine del dogma

Thyroid Function and Human Reproductive Health

G. E. Krassas, K. Poppe, and D. Glinoer Endocrine Reviews, October 2010, 31(5):0000–0000

I. Introduction

Two comprehensive review articles on thyroid function and reproductive health were published in *Endocrine Reviews* more than a decade ago (1, 2). In the first article, entitled "Thyroid Hormone and Male Gonadal Function," Jannini *et al.* (1) concluded that "the classic assumption that adult male gonad is unresponsive to thyroid

Abbreviations: AITD, Autoimmune thyroid diseases; ART, assisted reproduction tech-

"the classic assumption that adult male gonad is unresponsive to thyroid hormone is no longer tenable; the seminiferous epithelium of prepubertal testis can now be considered a thyroid hormone-responsive tissue"

Dal 1995 …

- Controversy exists regarding the impact of thyroid diseases on male reproduction. This is due to various reasons:

1. the apparent clinical irrelevance of signs and symptoms related to male gonadal function, compared with the systemic effects of hyper- and hypothyroidism;
2. the paucity of well controlled clinical studies, due to the fact that thyroid diseases are more common in females than in males;
3. the demonstration in the 1950s that the adult male gonad of experimental animals is metabolically unresponsive to thyroid hormone.

Jannini et al., Endocr Rev 1995

Dal 1995 …

- Since then, the concept that the testis is unaffected by iodothyronines became widely accepted.
- Indeed, in experimental studies on the effect of thyroid hormone in various tissues, the testis has been used as a negative control.

Jannini et al., Endocr Rev 1995

AI 2010 …

- Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction.
- Male reproduction is adversely affected by both thyrotoxicosis and hypothyroidism.

Krassas et al., Endocr Rev 2010

Che cosa è cambiato?

- Nel testicolo sono presenti:
  - Recettori per gli ormoni tiroidei (TR alfa1 e TR alfa2)
  - Deiodinasi (prevalentemente D2)
- Ormoni tiroidei regolano proliferazione e differenziazione cellule di Sertoli e BTB (blood-testis-barrier).
- Ormoni tiroidei regolano differenziazione cellule di Leydig (e steroidogenesi?).

Tuttavia…

- Ruolo degli ormoni tiroidei durante lo sviluppo del testicolo ben noto.

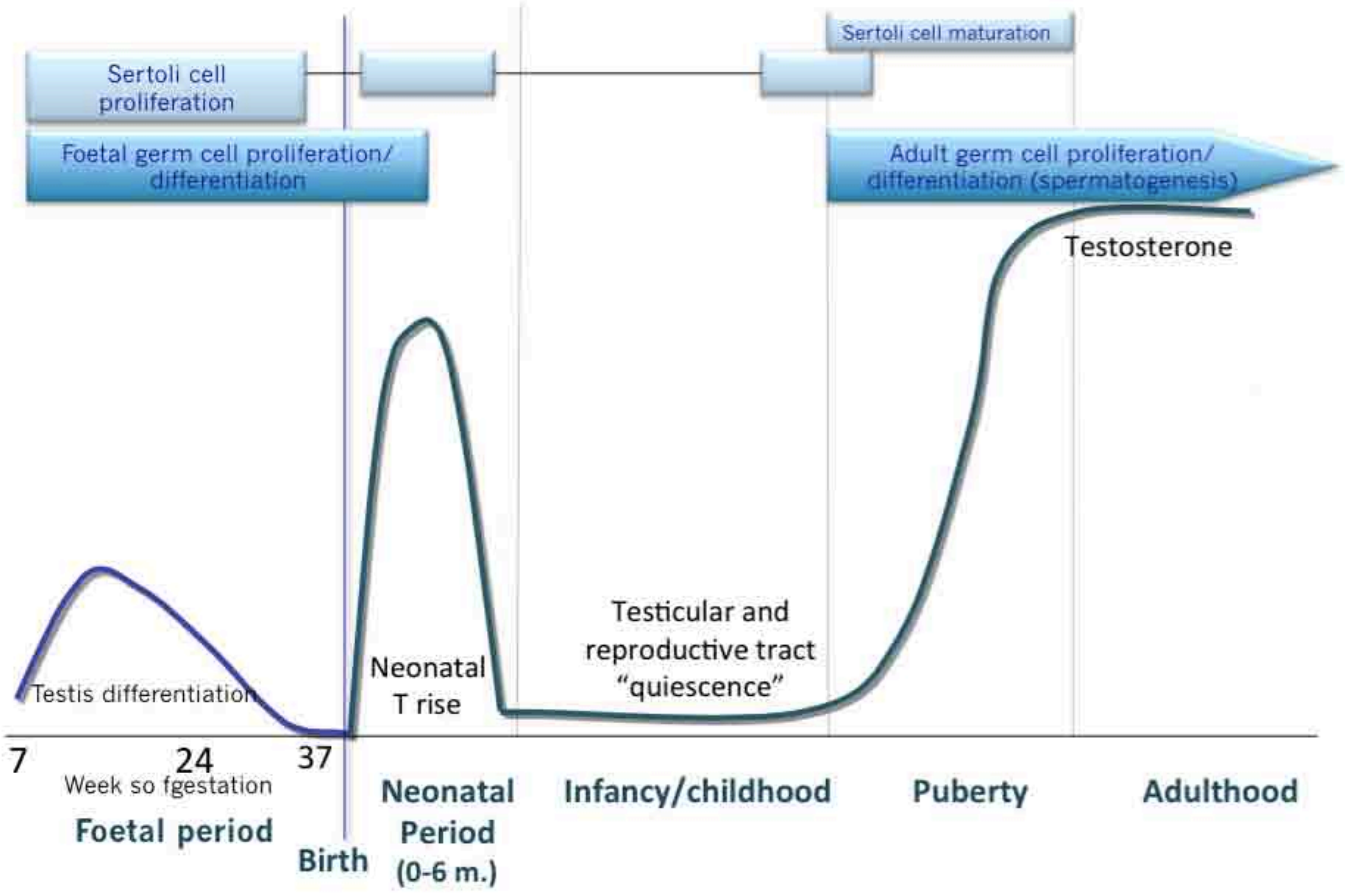
- Ruolo nel testicolo adulto e nella spermatogenesi?

Tiroide e testicolo

Parameter	Effects	References
Sertoli cell		
Proliferation	↓	Cooke et al., 1994 van Haaster et al., 1993 Joyce et al., 1993
$p27^{Kip1}$ expression	↑	Buzzard et al., 2003 Holsberger et al., 2003
Connexin43 expression	↑	Gilleron et al., 2006
ABP production	↓	Fugassa et al., 1987 Palmero et al., 1989
Androgen receptor	↑	Arambepola et al., 1998
Aromatase	↓	Andò et al., 2001 Catalano et al., 2003
GLUT1	↑	Ulisse et al., 1992
NCAM	↓	Laslett et al., 2000
IGF-1	↑	Palmero et al., 1990
Lactate	↑	Palmero et al., 1995
Inhibin	↑	van Haaster et al., 1992
Laminin	↑	Ulisse et al., 1998
Leydig cell		
Differentiation	↑	Teerds et al., 1998 Ariyaratne et al., 2000a
Steroidogenesis	↑	Manna et al., 1999
StAR protein	↑	Manna et al., 2001b Manna et al., 2001a
Adult testicular morphology	Maintain normal	Sakai et al., 2004 Oncu et al., 2004 Maran and Aruldhas, 2002

MICROSCOPY RESEARCH AND TECHNIQUE 72:796–808 (2009)

Fisiologia della maturazione testicolare



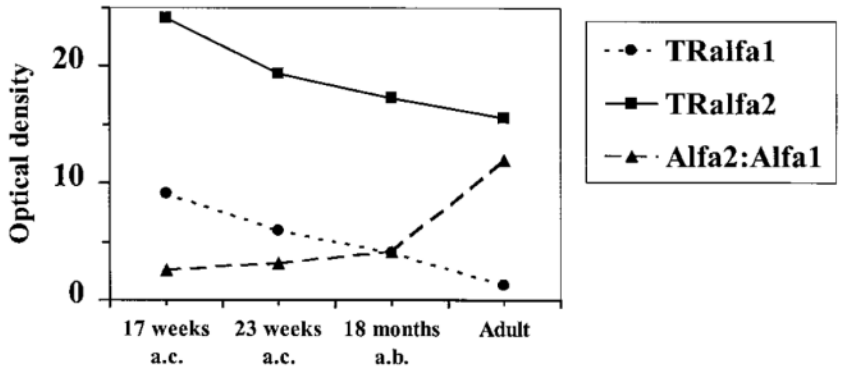
Modified from Sharpe RM, 2010

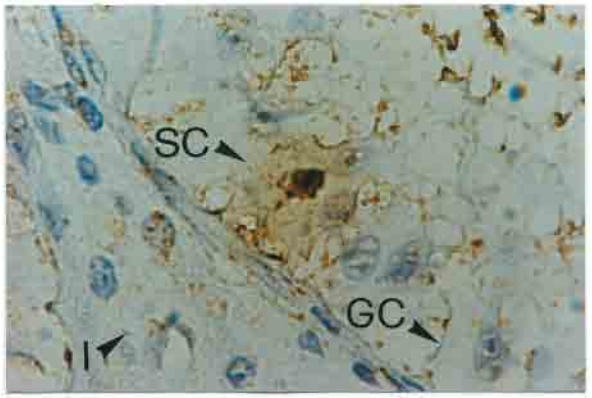
Recettore tiroideo e testicolo

0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism
Vol. 85, No. 9
Printed in U.S.A.

Ontogenetic Pattern of Thyroid Hormone Receptor Expression in the Human Testis

EMMANUELE A. JANNINI, ANNA CRESCENZI, NADIA RUCCI, EMILIANO SCREPONI, ELEONORA CAROSA, ANNA DE MATTEIS, ENRICO MACCHIA, GIULIA D'AMATI, AND MASSIMINO D'ARMIENTO





Studi preclinici – Rats – Sertoli cells

- Hypothyroidism induced in neonatal rats → impaired testicular devolopment, including testicular growth, germ cell maturation and seminiferous tubule formation *(Francavilla et al., 1991; Palmero et al., 1989)*. [estension of the proliferative period of Sertoli cells and delay in their maturation]

- Transient juvenile hyperthyroidism → opposite effects, resulting in 50% decrease in testis size and reduction in sperm production *(van Haaster et al., 1993)*. [premature cessation of Sertoli proliferation, with a concomitant of their maturation].

Studi preclinici - Rats - Leydig cells

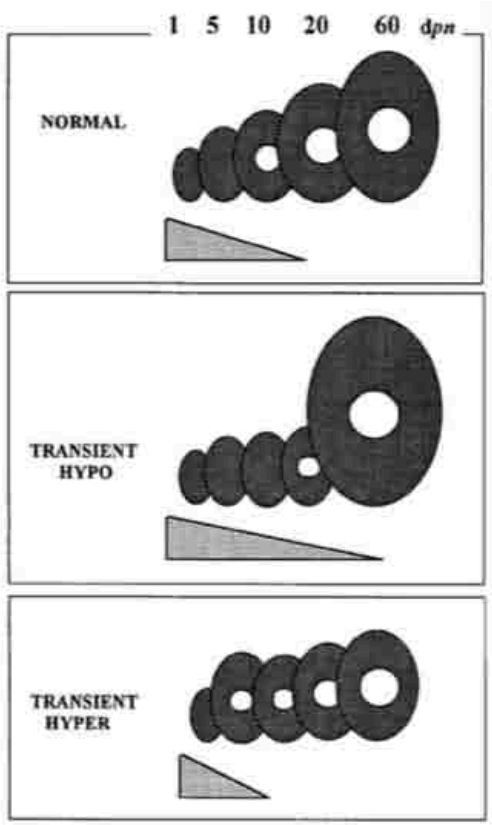
- Transient neonatal hypothyroidism → arrest in Leydig cell differentiation with increase in the size of the adult Leydig cell population (Maran et al., 2000; Mendis-Handagama and Ariyaratne, 2004).

- Neonatal-prepuberal hyperthyroidism → stimulation of Leydig cell differentiation (and steroidogenesis) (Ariyaratne et al., 2000; Mendis-Handagama and Ariyaratne, 2001; Teerds et al., 1998).

Riassumendo …

Physiological/elevated (hyperthyroidism) T3 level:
Inhibits SC proliferation
Promotes SC differentiation

Reduced (hypothyroidism) T3 level:
Promotes SC proliferation
Delays SC differentiation
Delays BTB assembly



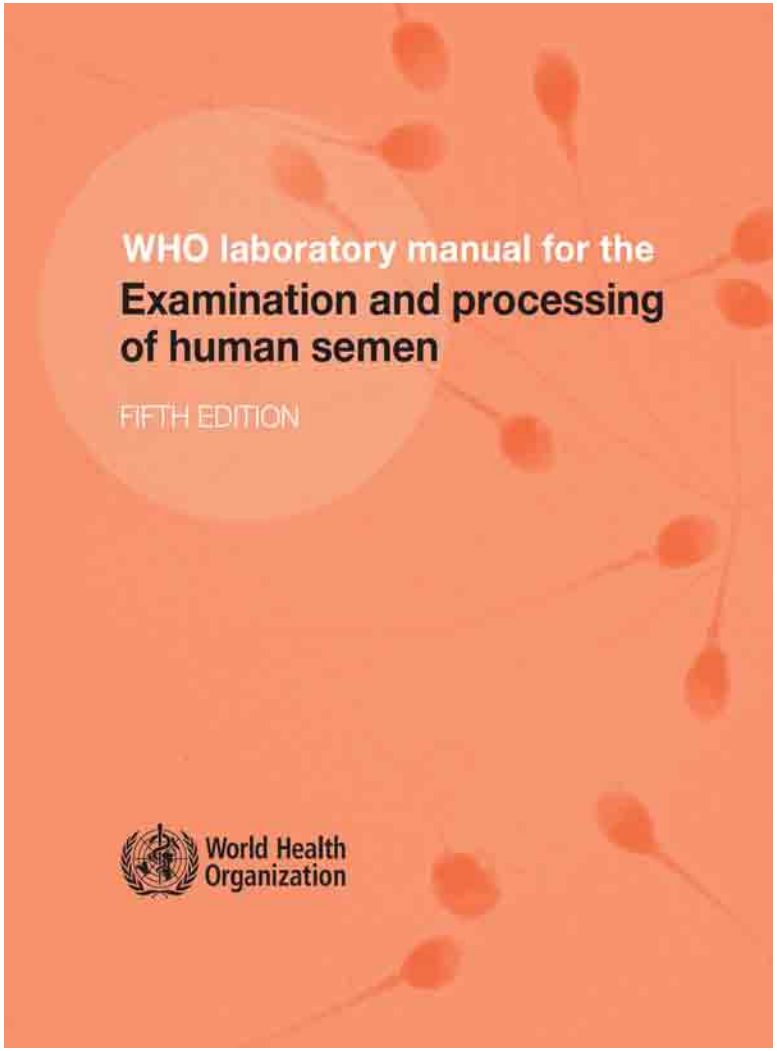
Jannini et al., 1995

- Promotes LC differentiation
  Promotes steroidogenesis
- Delays LC differentiation

Animals *vs* humans

- The major role of thyroid hormones on testis function is during development.
- Induction of hypothyroidism in mature male rat has little effect on histopathology of the testes, spermatogenesis or serum testosterone concentrations.
- Although, there is still controversy regarding the impact of thyroid diseases on human spermatogenesis and fertility; hormonal changes and modifications in sperm quality are more frequent in men with thyrotoxicosis and hypothiroidism.

Parametri liquido seminale

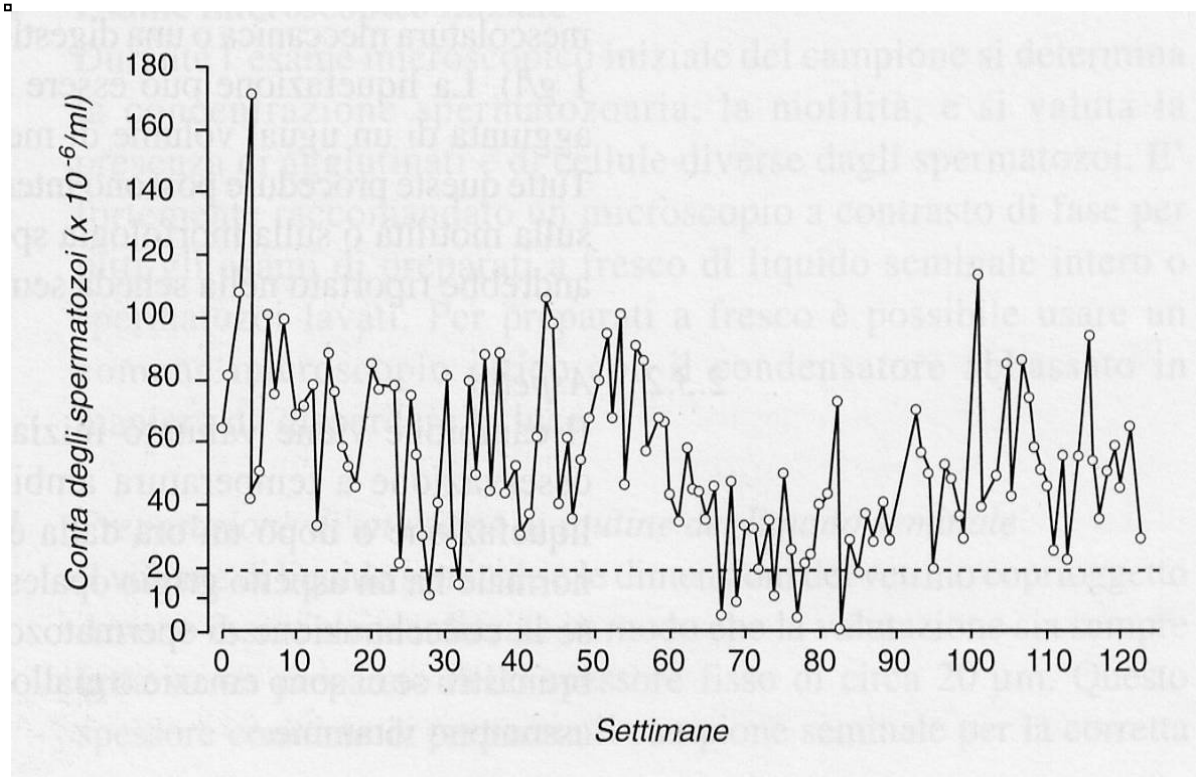


Limite minimo di riferimento WHO 2010

Volume	1.5 (1.4-1.7) mL
Concentrazione	15 (12-16) x 10^6/mL
Numero totale di spermatozoi	39 (33-46) x 10^6/ eiac
Motilità progressiva	32 (31-34) %
Morfologia (forme normali)	4 (3.0-4.0) %
Vitalità	58 (55-63) %

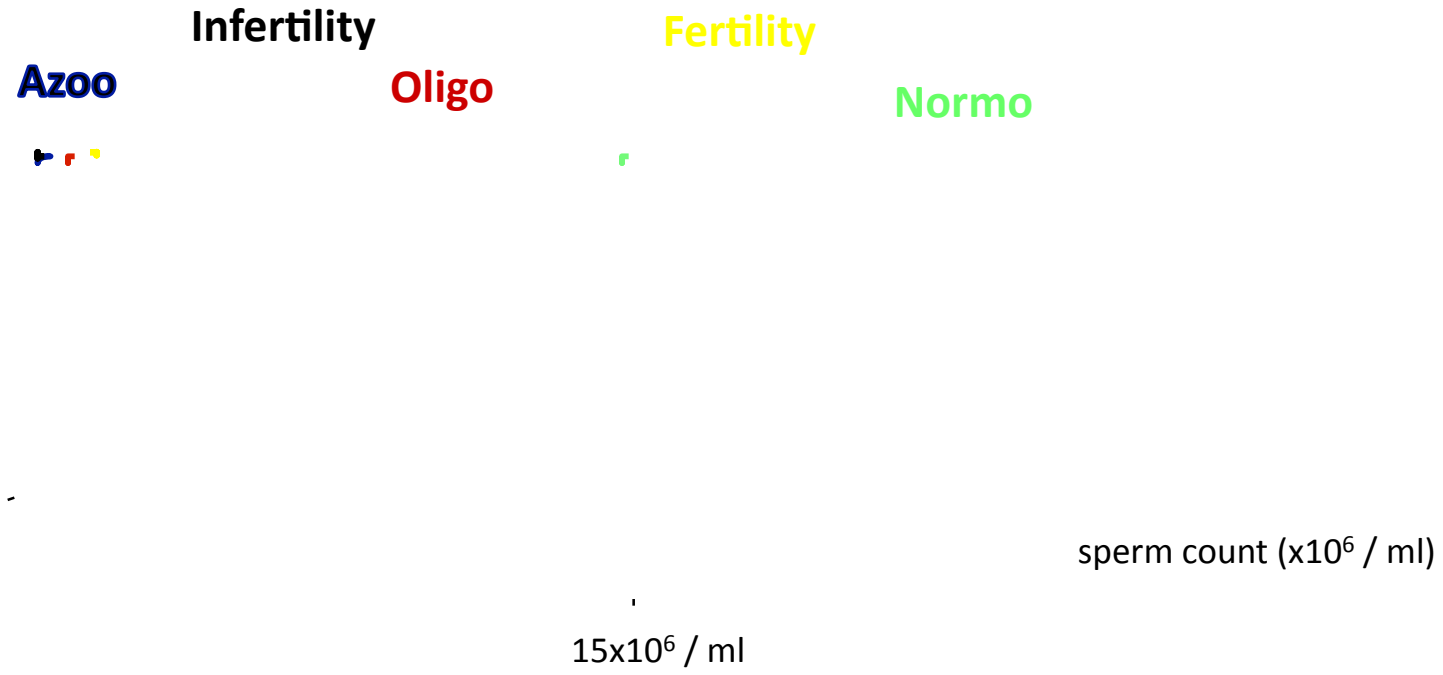
Variazioni fisiologiche seminali

Concentrazioni in un soggetto sano nell'arco di 120 settimane



Normo

Fertility vs Infertility

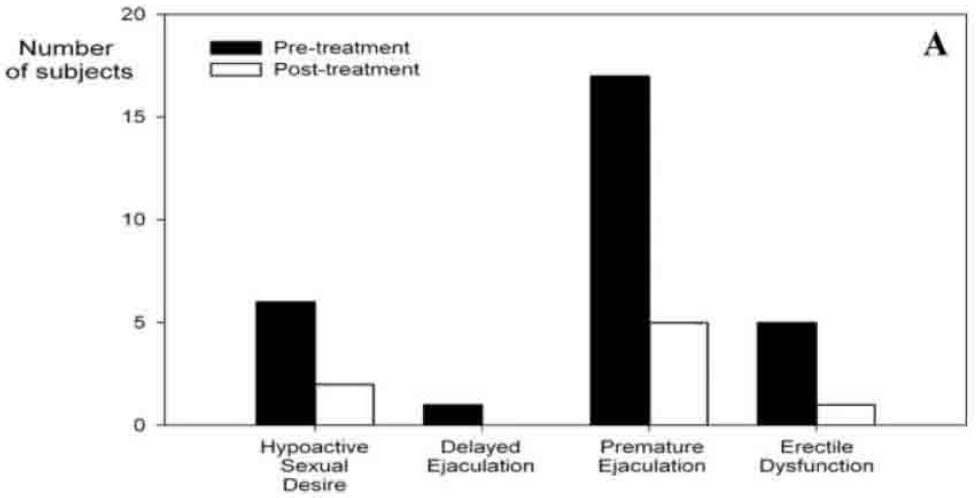


Ipertiroidismo e ormoni

	Thyrotoxicosis	
	Males	Females
SHBG	↑	↑
E_2	N or ↑	↑
Estrone		↑
Production rate of estrogens		→
Metabolic clearance rate of estrogens or androgens	↓	↓
Free E_2	↑	→
Testosterone	↑	↑
Δ4-Androstenedione		↑
DHEA	↑	↑
Free testosterone	→	
Bioavailable testosterone	↑	
Conversion of testosterone to Δ4-androstenedione	↑	→ or ↑
Androgen conversion to estrone	↑	↑
Progesterone	↑	↓ or →
LH	↑ or →	↑ or →
FSH	↑ or →	↑ or →
After GnRH		
LH	↑	↑
FSH	↑	↑

↑, increase; ↓, decrease; →, no change; N, normal; –, not

Multiple abnormalities of the hypothalamic-pituitary-gonadal axis, reversible with restoration of a euthyroid status.



Endocrine Reviews, October 2010, 31(5):702–755

Ipertiroidismo e testicolo

First author (Ref.)	No. of patients investigated	Results
In thyrotoxic men		
Clyde (45)	3	Two had severe and one had borderline oligospermia; all had decreased sperm motility.
Kidd (46)	5	All had sperm counts less than 40×10^6 per ml.
Hudson (47)	16	Sperm densities were low, but not different from controls. Motility was significantly lower in hyperthyroid patients.
Abalovich (6)	21	Nine patients had decreased sperm counts; 18 patients had decreased sperm motility.
Krassas (43)	23	Mean sperm densities were low but did not differ from controls. Sperm motility was significantly lower in hyperthyroid patients.

Endocrine Reviews, October 2010, 31(5):702–755

Ipertiroidismo - conclusioni

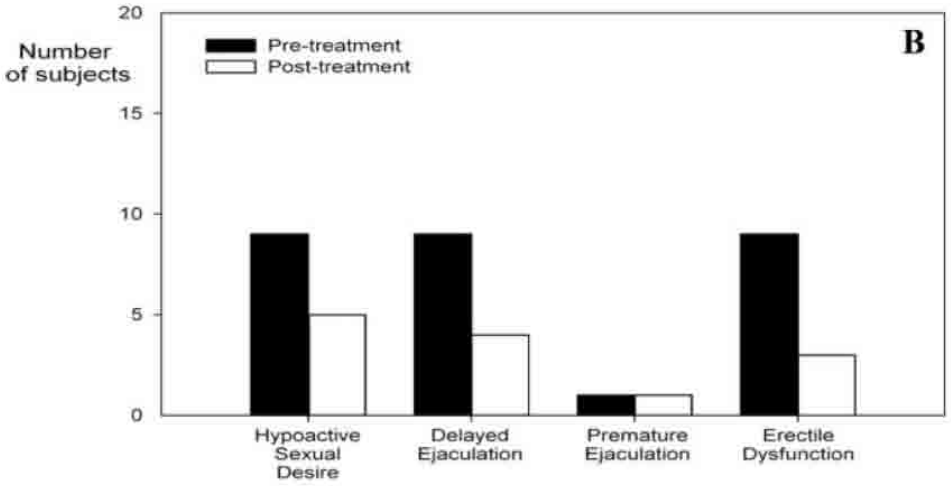
- Gli ipertiroidei presentano alterazioni dei parametri seminali, specie a livello della motilità.
- I parametri seminali migliorano quando si raggiunge l'eutiroidismo biochimico.
- La ripresa della spermatogenesi è indipendente dal tipo di trattamento (farmacologico o radiometabolico).
- Necessità di ampliare la casistica (e studi RCT).

Ipotiroidismo e ormoni

	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-Androstenedione		↑	↓	↓
DHEA	↑	↑	↓	
Free testosterone	→		↓	N
Bioavailable testosterone	↑			
Conversion of testosterone to Δ4-androstenedione	↑	→ or ↑	↓	↑
Androgen conversion to estrone	↑	↑		
Progesterone	↑	↓ or →		↓ or →
LH	↑ or →	↑ or →	N	N
FSH	↑ or →	↑ or →	N	N
After GnRH				
LH	↑	↑	↓	↓
FSH	↑	↑	↓	↓

↑, Increase; ↓, decrease; →, no change; N, normal; –, not available.

Main defect at the hypothalamus and/or pituitary level, reversible with restoration of a euthyroid status.



Endocrine Reviews, October 2010, 31(5):702–755

Ipotiroidismo e testicolo

First author (Ref.)	No. of patients investigated	Results
In hypothyroid men		
Griboff (92)	5	Normal sperm count. Semen exposure to room air produced loss of sperm motility in two patients.
De la Balze (93)	6	Histological abnormalities found in all in testicular biopsies.
Wortsman (94)	8	Seven of eight patients showed varying degrees of testicular atrophy.
Corrales Hernandez (95)	10	No abnormalities found.
Jaya Kumar (96)	8	Five of eight patients had sperm analysis done. No original data.
Krassas (97)	25	Morphology was the only sperm parameter significantly affected. Motility was also affected, but differences were not statistically significant.

Endocrine Reviews, October 2010, 31(5):702–755

Ipotiroidismo - conclusioni

- Gli ipotiroidei presentano alterazioni dei parametri seminali, specie a livello della morfologia.
- I parametri seminali migliorano quando si raggiunge l'eutiroidismo biochimico.
- Necessità di ampliare la casistica (e studi RCT).

AI 2014 …

Review Article

Thyroid and male reproduction

Anand Kumar, Skand Shekhar[1], Bodhana Dhole

Department of Reproductive Biology, All India Institute of Medical Sciences, New Delhi, Intern, [1]University College of Medical Sciences, Delhi, India

In PTU induced hypothyroid rats there was a significant fall in their seminal vesicle and prostate gland weight.

In hypothyroidism resulted in a decrease in fucose, sialic acid and fructose levels irrespective of the duration of hypothyroidism (prostate gland).

Hypothyroid men showed a decreased risk of prostate cancer when compared to euthyroid men, although no associations between hyperthyroidism and risk of prostate cancer could be established.

Indian Journal of Endocrinology and Metabolism / Jan-Feb 2014 / Vol 18 | Issue 1

Tiroide e stress ossidativo

Altered thyroid status influences oxidative stress and enzymatic antioxidant defense in rat testis

- **Hyperthyroidism** in the rat testis was associated with increased lipid peroxidation and increased activity of antioxidant defense enzymes such as glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), and catalase (CAT).

- **Hypothyroidism** (congenital and transient) induced oxidative stress by reducing the levels of testicular enzymatic and non-enzymatic defenses as superoxide dismutase (SOD), GR, GPx, and CATas well as GSH.

Tiroide anticorpi e infertilità

FERTILITY AND STERILITY®
VOL. 76, NO. 2, AUGUST 2001

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Thyroid hormones and thyroid antibodies in infertile males

Harald Trummer, M.D.,[a] Sigrid Ramschak-Schwarzer, M.D.,[b] Josef Haas, Ph.D.,[c] Helga Habermann, M.D.,[a] Karl Pummer, M.D.,[a] and Georg Leb, M.D.[b]

In 35 (11.5%) men, a thyroid dysfunction was diagnosed. The distribution of thyroid dysfunction was equal between normozoospermic (11.1%) and pathozoospermic (11.8%) men.

There was no correlation between elevated or decreased bTSH, fT4, and fT3 values with the results of semen analysis. No patient suffered from a manifest thyroid dysfunction. All kinds of thyroid dysfunction were clinically insignificant and were classified as latent thyroid dysfunction.

Thyroid antibodies were elevated in 23 patients (7.5%). TGA were elevated in 8, TPO-Ab in 10, both TGA and TPO-Ab in 2, and TRAK in 3 patients, respectively. When correlated with the results of semen analysis, TPO antibodies were significantly elevated in pathozoospermia (6.7% vs. 1.6%, $P=.036$) and asthenozoospermia (7.2% vs. 1.6%, $P=.049$), as compared with normozoospermia. TGA and TRAK did not at all correlate with the results of semen analysis.

Radioiodioterapia e testicolo

Clinical Endocrinology (2014)

doi: 10.1111/cen.12514

ORIGINAL ARTICLE

Effects of radioiodine treatment for differentiated thyroid cancer on testis function

Domenico Canale, Claudia Ceccarelli, Carolina Caglieresi, Agnese Moscatelli, Silvia Gavioli, Pierina Santini, Rossella Elisei and Paolo Vitti

- Despite fertility of male patients with thyroid cancer is an important issue, a recent systematic review on the gonadal effects of therapeutic radioactive iodine included only seven papers. (Sawka A.M., Clinical Endocrinology 2008).
- This is amazing, considering that most patients with Differentiated Thyroid Cancer are diagnosed in their reproductive years.
- As the majority of patients are diagnosed and treated at an early stage, their expected disease-related survival is excellent, therefore the fertility potential should be a concern in these patients.

Radioiodioterapia e testicolo

Clinical Endocrinology (2014)

doi: 10.1111/cen.12514

ORIGINAL ARTICLE

Effects of radioiodine treatment for differentiated thyroid cancer on testis function

Domenico Canale, Claudia Ceccarelli, Carolina Caglieresi, Agnese Moscatelli, Silvia Gavioli, Pierina Santini, Rossella Elisei and Paolo Vitti

- The single ablative RAI (1100 MBq – 30 mCi) treatment in cancer patients is better tolerated respect multiple RAI (mean 12790 MBq – 350 mCi) treatments regard testis function.
- Multiple treatments for recurrent or metastatic desease may cause a permanent impairment of one or more parameters related to the reproduction potential of male patients (FSH, conta nemaspermica, volume testicolare).
- Young cancer patients, particurarly those with node o lung metastasis, who will probably undergo repeated treatments should be aware of the potential risk to their fertility. An evaluation of testicular function is thus advisable. When an impairment of fertility is already present, the option of freezing semen should be considered.

Take home messages

- Gli ormoni tiroidei svolgono un ruolo centrale nello sviluppo e nella maturazione testicolare.
- Le patologie tiroidee sono in grado, nell'uomo adulto, di alterare le normali funzioni testicolari, la spermatogenesi, l'asse endocrino gonadico e di indurre disfunzioni sessuali.
- Il ripristino della condizione di eutiroidismo è in grado di per se di ristabilire la normali funzioni testicolari.
- I pazienti che si sottopongono a radioiodioterapia per neoplasie ben differenziate della tiroide dovrebbe sottoporsi ad una valutazione andrologica preliminare, in particolare se si prospetta l'indicazione a dosi elevate di radiazioni ionizzanti.