



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



Tiroidite autoimmune e fecondazione assistita

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Disclosure statement



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**Nessun conflitto di
interessi**



Infertilità



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Colpisce il 15% di coppie in età riproduttiva (circa 6 milioni di coppie)



0,8-4,1% dei bambini nati in Europa sono nati da procedure di PMA



De Mouzon, 2010 Registro Europeo

Numero totale di **74.292** coppie trattate

95.110 cicli di trattamento nel 2015, **12.836** nati vivi (2.6% del totale dei bimbi nati nel 2015)



Registro nazionale Procreazione medicalmente assistita (Pma) dell' Istituto superiore di sanità



Infertilità: soluzioni terapeutiche



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PMA

Insieme di tutti quei trattamenti per la fertilità nei quali i gameti, sia femminili (ovociti) che maschili (spermatozoi), vengono trattati al fine di determinare il processo riproduttivo.

Tecniche di primo livello

Inseminazione Intrauterina semplice (HIUI homologous intra uterine insemination) con seme del partner.

Tecniche di secondo e terzo livello

FIVET (fecondazione in vitro embryo transfer)

ICSI (iniezione intracitoplasmatica di un singolo spermatozoo).



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Inseminazione intrauterina: IUI



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Blanda stimolazione ovarica mediante somministrazione di clomifene citrato (os) ed hCG (i.m.)

0.2-0.5 ml sospensione di sperma processato introdotto nella cavità uterina



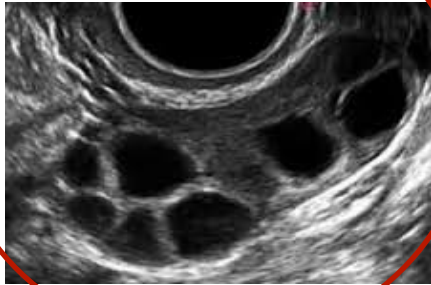
INSEMINAZIONE IN VITRO: FIVET-ICSI



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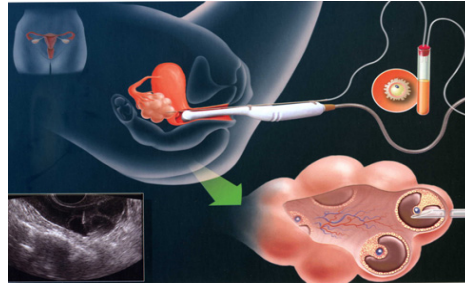
Stimolazione



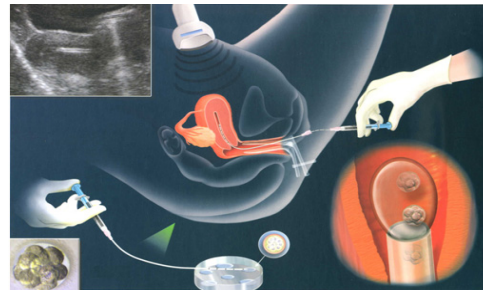
Biopsia dell'embrione



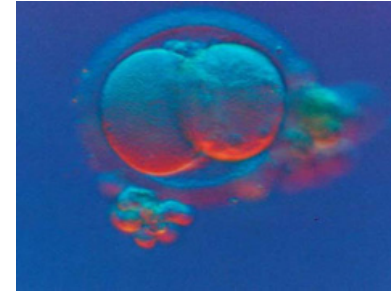
Pick-up oociti



Transfer dell'embrione



Coltura in vitro degli embrioni



Verifica dello stato di gravidanza



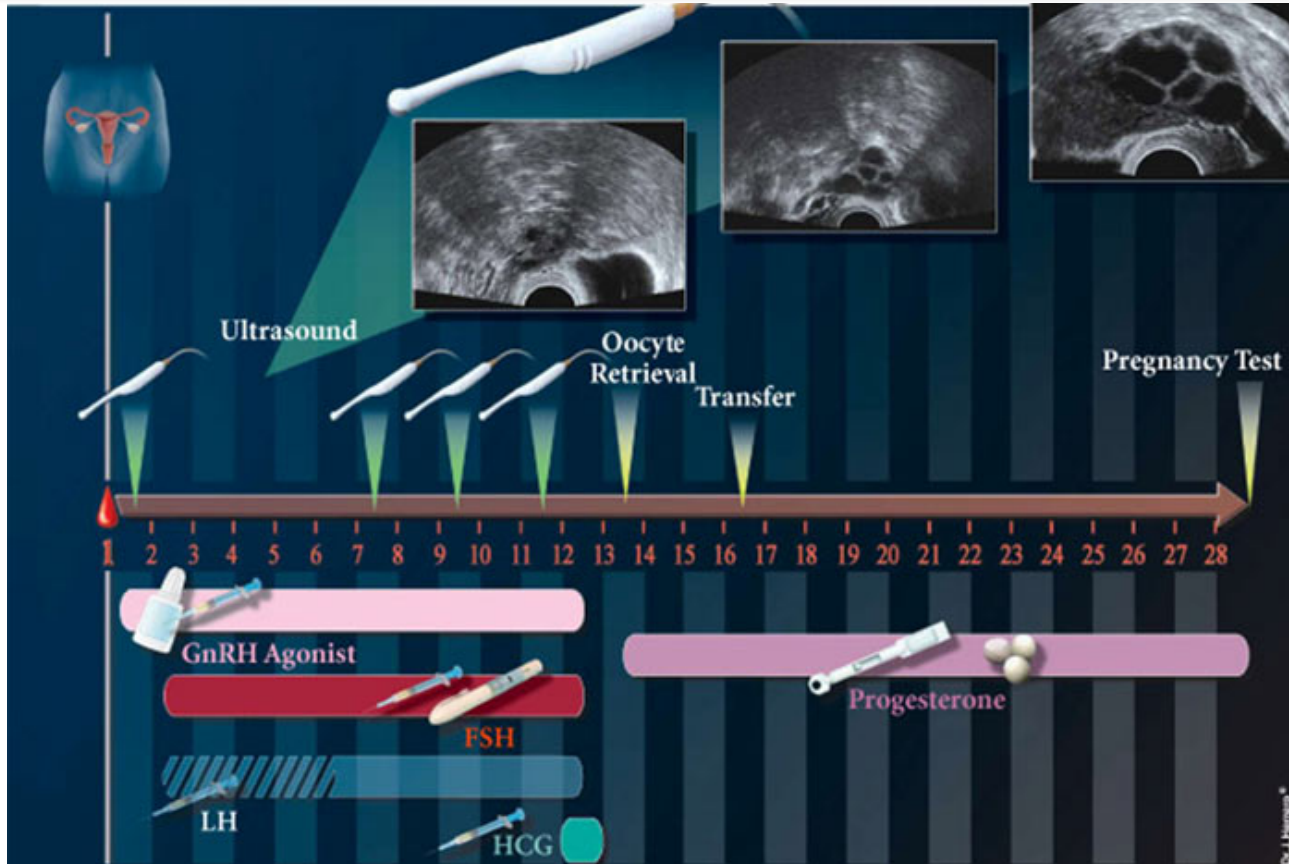


Stimolazione ovarica



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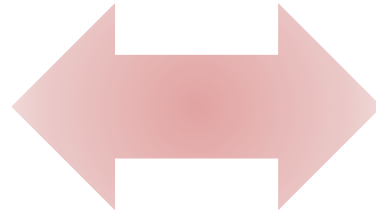
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Tiroide



PMA

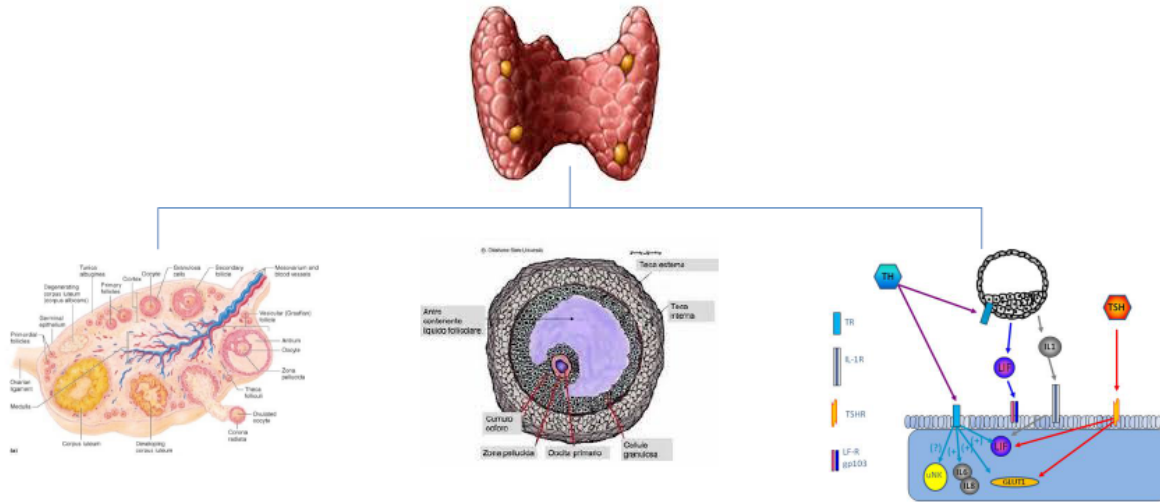


Tiroide → PMA



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Azione sinergica degli OT con FSH
 OT: esercitano **effetti stimolatori** diretti sulla funzione delle cellule della granulosa, come la differenziazione morfologica e la formazione del recettore LH/hCG

Aghajanova, 2009

Condivisione di Ag tra oocita e tiroide
 Zona pellucida: bersaglio di AbTg, AbTPO

Monteleone, 2010

A livello endometriale sono presenti recettori per ormoni tiroidei e TSH ed aumentano nella fase recettiva

OT: ruolo fondamentale durante l'impianto e i primi stages dello sviluppo embrionale

Stavreus, 2012

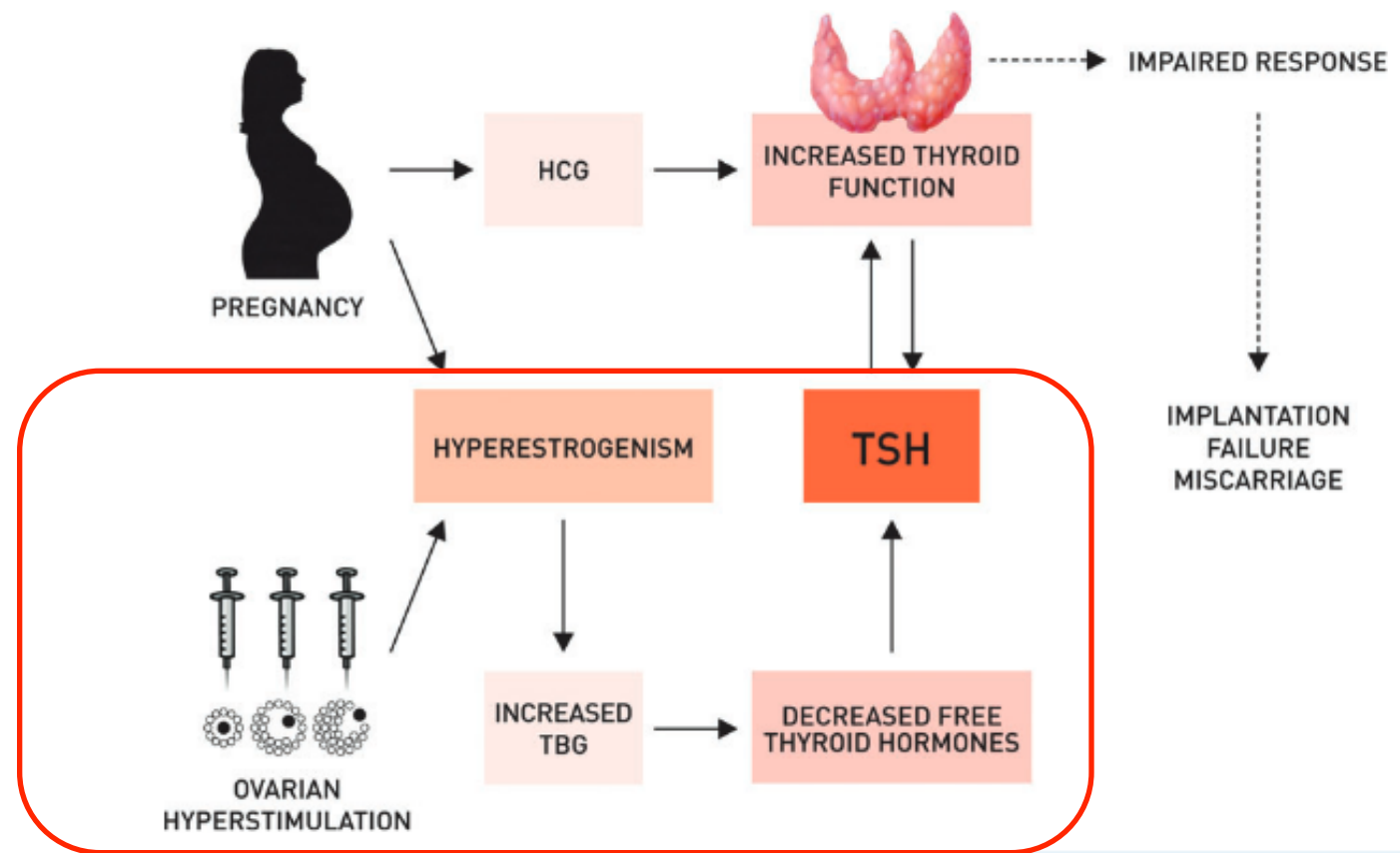


Tiroide ← PMA



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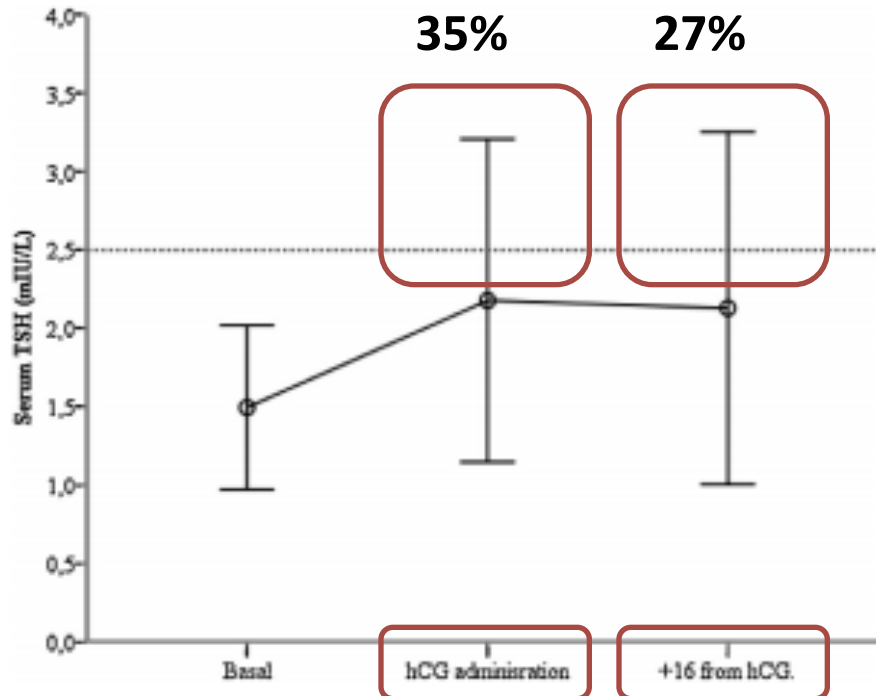
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Colicchia, 2014



Incidence of elevation of serum thyroid-stimulating hormone during controlled ovarian hyperstimulation for in vitro fertilization



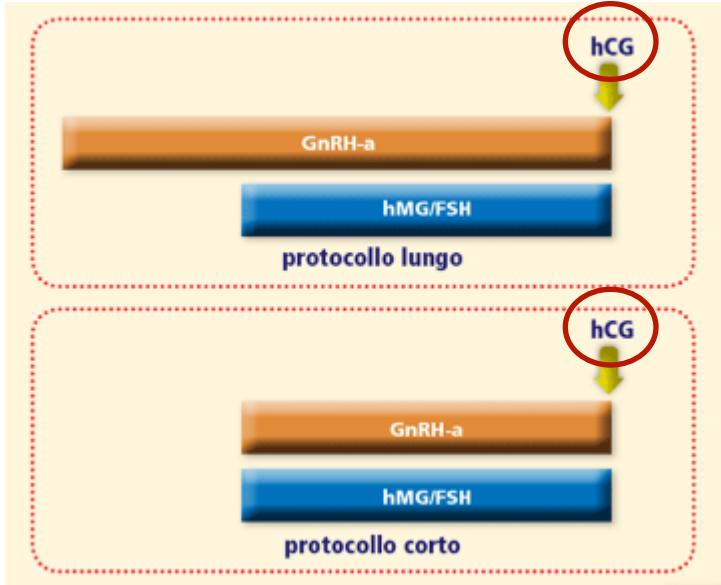


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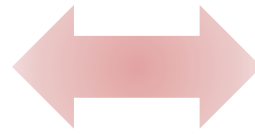
Elevata omologia strutturale CG -TSH



Riduzione dei livelli di TSH



Tiroide



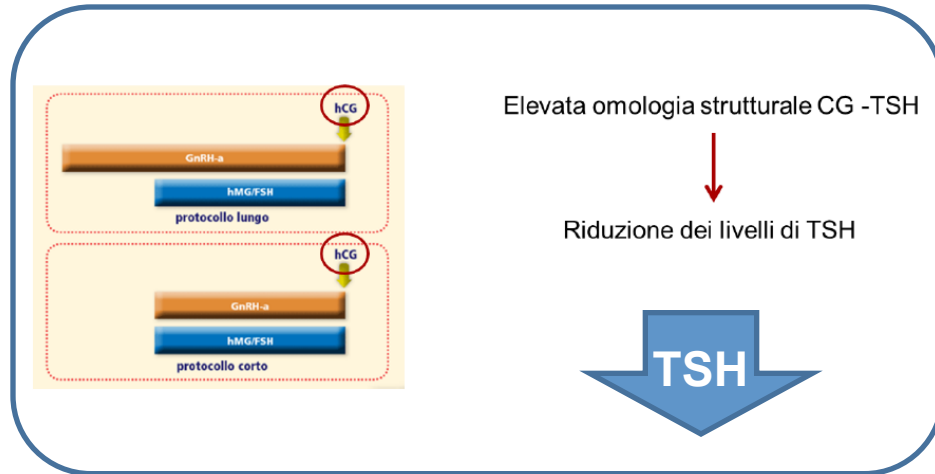
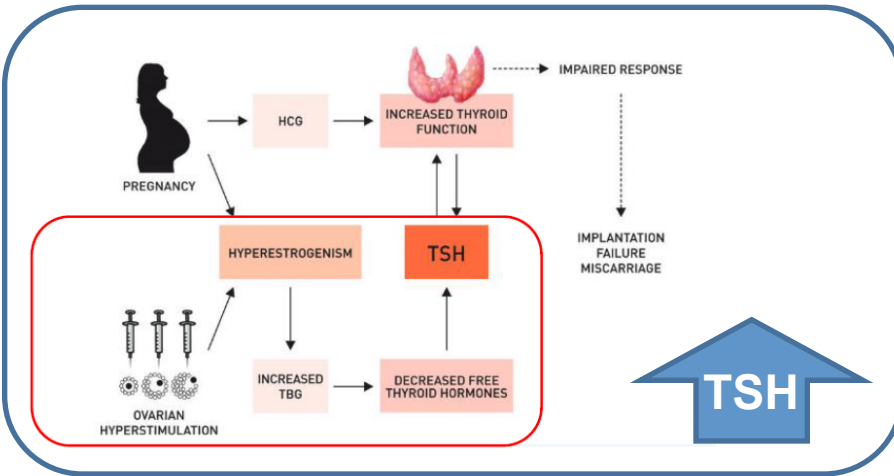
PMA



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In condizioni di eutiroidismo con Ab negativi ...



Effetto trascurabile della stimolazione ovarica

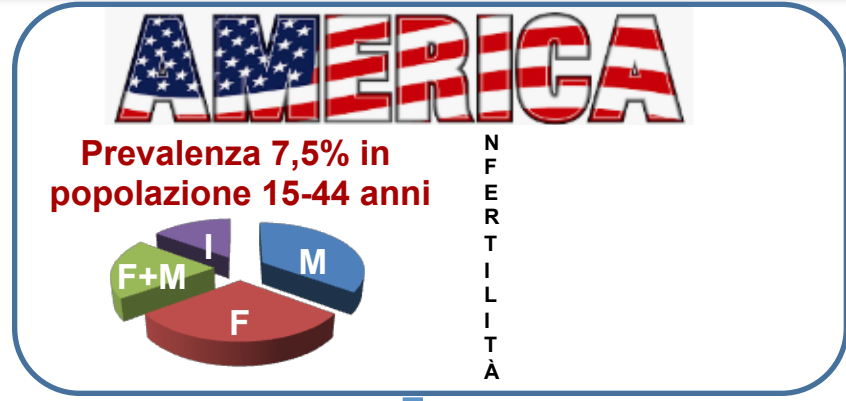
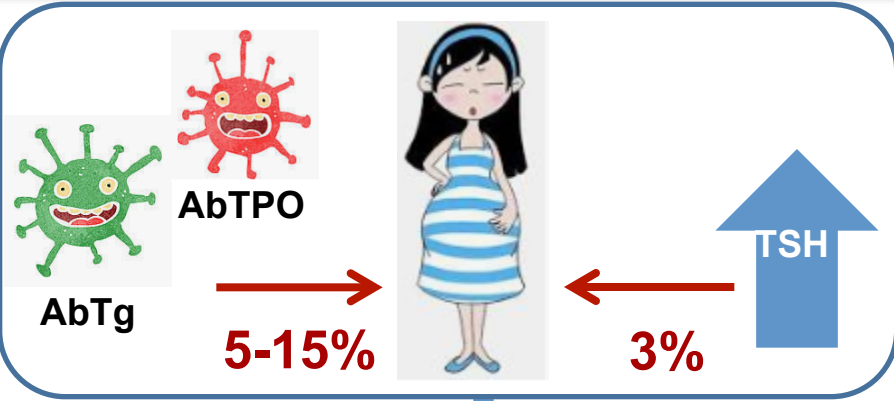


Numeri



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Elevata % di donne che si sottopongono a PMA sono affette da tireopatia

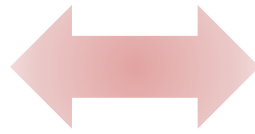
Thyroid autoimmunity, hypothyroidism and ovarian reserve: a cross-sectional study of 5000 women based on age-specific AMH values

**10% AbTPO+
4% ipotiroidismo subclinico o conclamato**

Nikolaos P. Polyzos^{1,2,*}, Evangelos Sakkas¹, Alberto Vaiarelli¹, Kris Poppe³, Michel Camus¹, and Herman Tournaye¹



Tiroide



PMA



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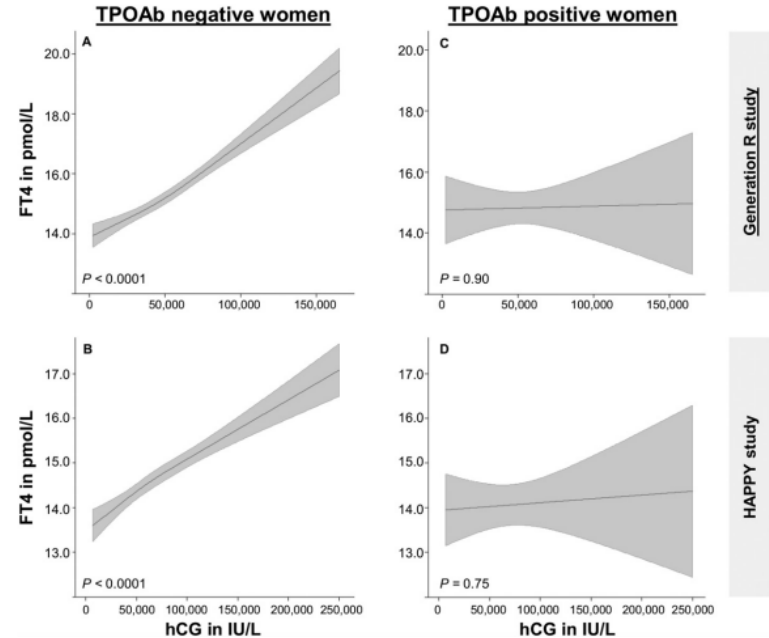
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In condizioni di tireopatia con AbTPO positivi...

Thyroid Autoimmunity Impairs the Thyroidal Response to Human Chorionic Gonadotropin: Two Population-Based Prospective Cohort Studies

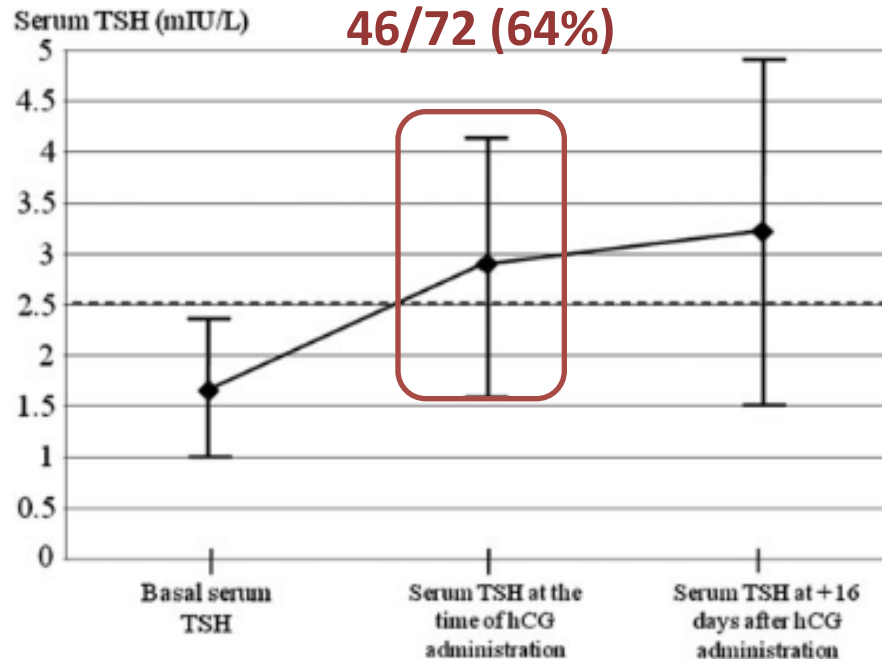
Tim I. M. Korevaar,^{1,2,8} Eric A. P. Steegers,³ Victor J. Pop,⁹ Maarten A. Broeren,¹⁰ Loyal Chaker,^{2,8} Yolanda B. de Rijke,⁴ Vincent W. V. Jaddoe,^{1,5,6} Marco Medici,^{1,2,8} Theo J. Visser,^{2,8} Henning Tiemeier,^{6,7} and Robin P. Peeters^{2,8}

2017





Thyroid Axis Dysregulation During *In Vitro* Fertilization in Hypothyroid-Treated Patients





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Clinical Study

A Busnelli and others

Levothyroxine adjustment in IVF pregnancies

173:4

417-424

Levothyroxine dose adjustment in hypothyroid women achieving pregnancy through IVF

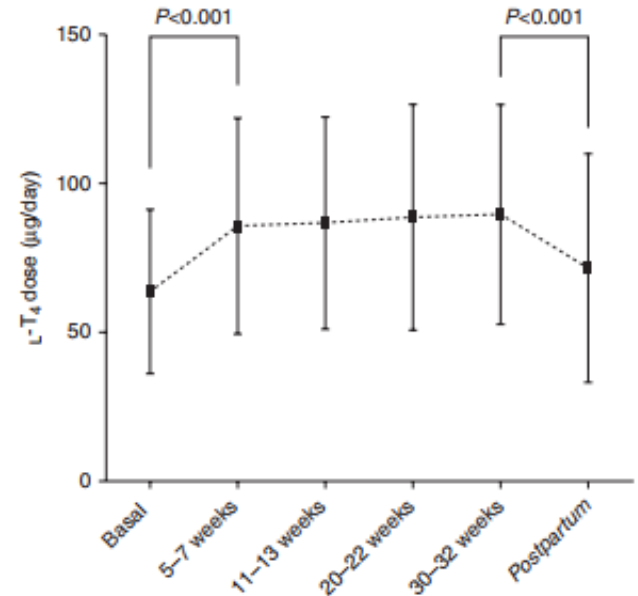
Andrea Busnelli^{1,2}, Guia Vannucchi¹, Alessio Paffoni¹, Sonia Faulisi^{1,2},
Laura Fugazzola^{1,2}, Luigi Fedele^{1,2} and Edgardo Somigliana¹

¹Infertility Unit, Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Via M. Fanti, 6, 20122 Milan, Italy and ²Università degli Studi, Milan, Italy

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84% delle donne ipotiroidee sottoposte a IVF necessitano di incremento della posologia precocemente (5°-7° settimana)

56% delle donne ipotiroidee con gravidanza spontanea necessitano di incremento della posologia precocemente





Tireopatia PMA



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2 ipotesi:

- 1. Una relativa insufficienza tiroidea, determinata in particolare dall'iperstimolazione ovarica**
- 2. Un ambiente sfavorevole nel quale l'autoimmunità tiroidea rappresenta un marker**



Autoimmunità tiroidea-PMA



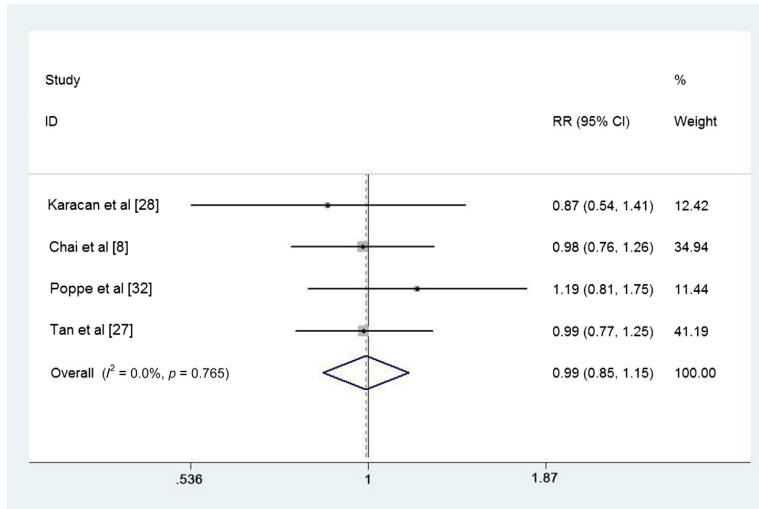
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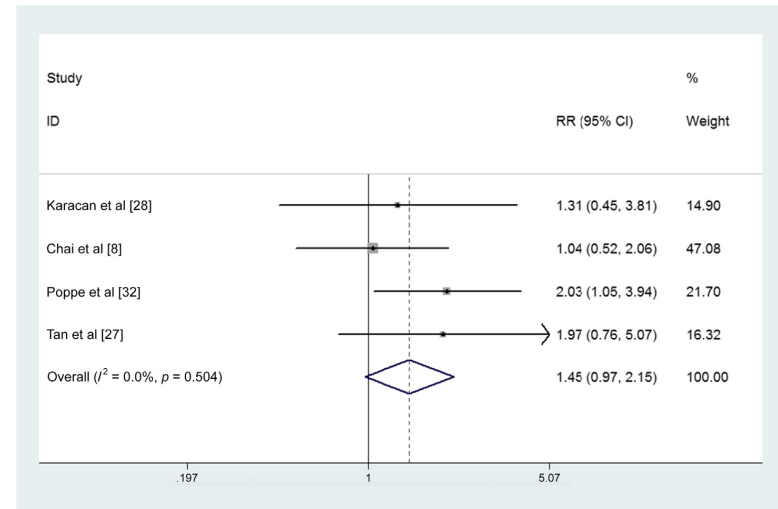
Original Article

Effect of thyroid autoimmunity *per se* on assisted reproduction treatment outcomes: A meta-analysis

Hui He ^{a, b}, Shuang Jing ^{a, b}, Fei Gong ^{a, b, c}, Yue Qiu Tan ^{a, b, c}, Guang Xiu Lu ^{a, b, c}, Ge Lin ^{a, b, c, *}



Clinical pregnancy rate



Miscarriage rate



Autoimmunità tiroidea-PMA



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Human Reproduction Update Advance Access published June 20, 2016

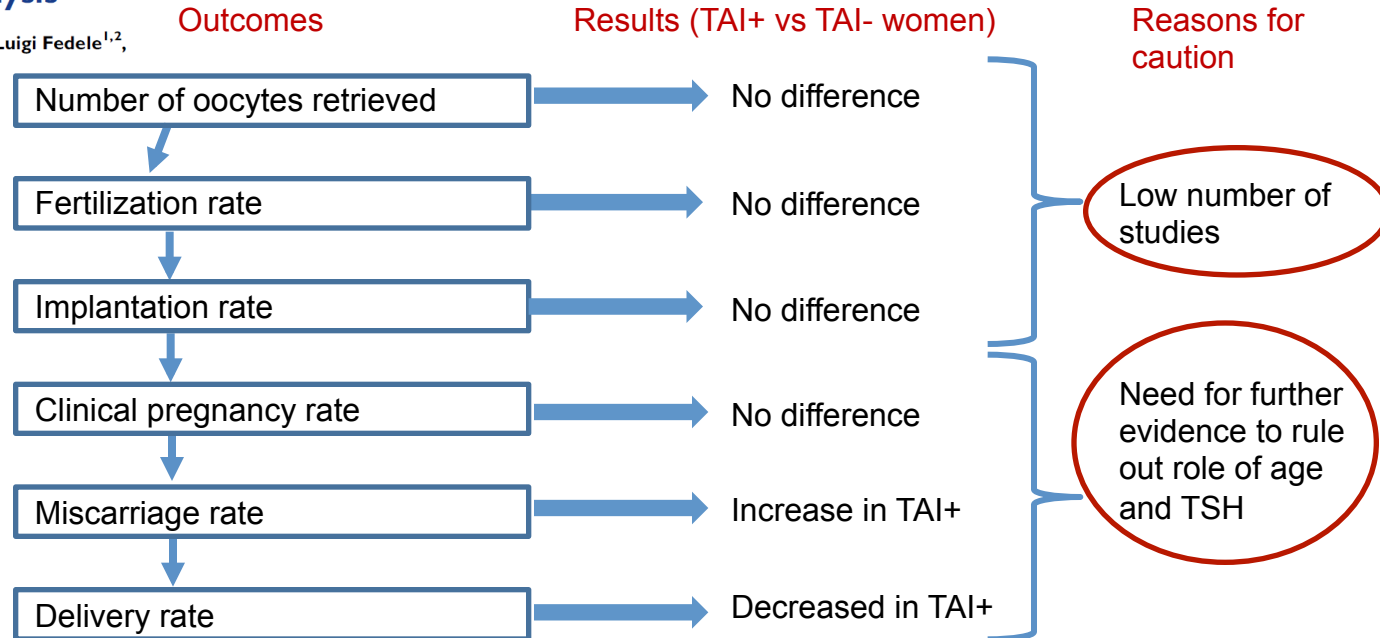
Human Reproduction Update, pp. 1-16, 2016

doi:10.1093/humupd/dmw019

human
reproduction
update

The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis

Andrea Busnelli^{1,2,*}, Alessio Paffoni¹, Luigi Fedele^{1,2}, and Edgardo Somigliana¹





Tiroide e IUI



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Table 2 Univariate and multivariate analysis

	Pregnancy (N = 37)	No pregnancy (N = 503)	Univariate analysis		Multivariate analysis	
			OR (95% CI) ^a	p	OR (95% CI) ^a	p
Age (years) ^b	30 (30-35)	34 (29-39)	0.92 (0.87;0.98)	0.015 ^d	0.94 (0.87;0.99)	0.049 ^d
Body mass index (kg/m ²) ^b	20.9 (19.9-27.0)	22.9 (20.4-26.0)	1.02 (0.93;1.07)	0.931	-	-
Primary infertility (vs. secondary infertility) ^c	19 (51.4)	258 (51.3)	1.00 (0.95;1.05)	0.861	-	-
Parity ^c	0 (0-1)	0 (0-0)	1.01 (0.60;1.71)	0.954	-	-
TSH (μIU/ml) ^b	1.6 (1.1-2.2)	1.9 (1.2-2.4)	0.89 (0.46;1.21)	0.556	-	-
TPO-Ab > upper level of normal ^f	0 (0)	61 (12.1)	0.07 (0.05;0.10)	0.015 ^d	0 (0;inf)	0.997
TG-Ab > upper level of normal ^f	2 (5.4)	105 (20.9)	0.22 (0.05;0.91)	0.037 ^d	0.87 (0.19;4.03)	0.861
Thyroid medication for overt hypothyroidism ^c	2 (5.4)	95 (18.9)	0.25 (0.06;1.04)	0.036 ^d	0.54 (0.12;2.47)	0.338
Thyroid medication TSH > 2.5 μIU/ml ^f	16 (43.2)	55 (10.9)	6.94 (3.60;13.40)	<0.001 ^d	3.31 (1.31;8.35)	0.009 ^d
Presence of PCO-S ^c	8 (21.6)	81 (16.1)	0.71 (0.31;1.60)	0.407	-	-
Metformin treatment ^b	3 (8.1)	31 (6.2)	1.34 (0.31;4.92)	0.500	-	-
Clomifen citrate stimulation ^c	19 (51.4)	146 (29.0)	0.39 (0.20;0.77)	0.006 ^d	0.77 (0.32;1.85)	0.629
Number of IUI treatment cycle ^b	1 (1-1)	1 (1-1)	0.90 (0.59;1.37)	0.638	-	-
Ovulation induction with HCG ^c	27 (73.0)	239 (47.5)	2.95 (1.40;6.22)	0.005 ^d	5.37 (1.72;16.69)	0.004 ^d
Endometrial thickness ^b	10 (8-11)	8 (9-10)	1.09 (0.91;1.31)	0.324	-	-
Male factor ^c	13 (35.1)	269 (53.5)	0.47 (0.23;0.95)	0.034 ^d	0.60 (0.27;1.03)	0.067



Tiroide e IUI



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Adjusted means of secondary outcomes by TSH group, for women undergoing IUI cycles at a fertility center.

Variable	Number of observations	TSH 0.40–2.49 mIU/L	TSH 2.50–4.99 mIU/L	P value
Total gonadotropin dose (units/ml)	2,860	902 (858–946)	888 (810–966)	.77
Peak estradiol (pg/ml, day before hCG)	1,427	347 (335–359)	360 (340–380)	.27
Peak estradiol (pg/ml, day of hCG)	1,274	510 (491–528)	507 (478–535)	.86
Number of preovulatory follicles (≥ 13 mm)	3,943	1.9 (1.9–2.0)	1.9 (1.8–2.0)	.67
Day of hCG trigger	3,975	11.3 (11.2–11.4)	11.3 (11.1–11.5)	.99
Endometrial lining thickness (mm)	3,930	8.2 (8.1–8.3)	8.2 (8.0–8.4)	.95

Note: Values are adjusted mean (95% CI) (adjusted for age, BMI, infertility diagnosis, cycle type [except when only FSH cycles are included]). For the first 3 variables listed, only FSH cycles were included.

Karmon. Preconceptional TSH and IUI outcomes. *Fertil Steril* 2015.



Ipotiroidismo/outcome PMA II° livello



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Table 2. Reproductive outcomes according to TSH concentrations

	All women	TSH ≤2.5 μIU/ml	TSH >2.5 μIU/ml	p value ¹
Number	158 (100)	120 (76)	38 (24)	
Oocytes retrieved	6 (6)	6 (6)	6 (6)	0.760
Oocytes 2PN	5 (6)	5 (6)	5 (5)	0.701
Embryos transferred	2 (2)	2 (2)	2 (1)	0.536
Biochemical pregnancy	69 (43.7)	54 (45.0)	15 (39.5)	0.55
Clinical pregnancy	60 (38.0)	46 (38.3)	14 (36.8)	0.869
Pregnancy loss	5 (3.2)	5 (4.2)	0 (0)	0.201
Live births	55 (34.8)	41 (34.2)	14 (36.8)	0.763

Mintziari, 2014



Data are given as medians with interquartile range in parentheses or as absolute numbers with percentages in parentheses.

¹ Baseline TSH ≤2.5 vs. >2.5 μIU/ml.

Chai, 2014

	TSH < 2.5 mIU/l (n = 508)	TSH ≥ 2.5 mIU/l (n = 119)	P-value	TSH < 3.5 mIU/l (n = 586)	TSH ≥ 3.5 mIU/l (n = 41)	P-value	TSH < 4.5 mIU/l (n = 602)	TSH ≥ 4.5 mIU/l (n = 25)	P-value
Clinical pregnancy rate per cycle initiated, %	45.7	42.0	NS	45.1	43.9	NS	45.2	40.0	NS
Miscarriage rate, %	19.4	10.0	NS	18.2	11.1	NS	17.6	20.0	NS
Live birth rate per fresh cycle, %	35.4	35.3	NS	35.2	39.0	NS	35.5	32.0	NS



Ipotiroidismo/outcome PMA II° livello



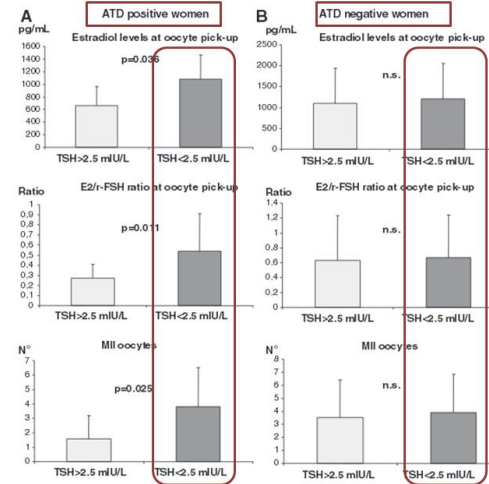
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Table III. Mean Hormone Levels by First Cycle Pregnancy Outcomes

	Number	Prolactin (ng/mL)		TSH (μ IU/mL)	
		Mean	SD	Mean	SD
Clinical pregnancy					
Yes	151	15.9	8.6	2.2	2.2
No	358	16.0	9.4	2.1	3.1
<i>p</i> value		0.78		0.21	
Detailed outcome					
Failed retrieval	50	14.8	9.4	1.8	1.2
Failed fertilization	22	17.2	8.2	5.1	11.6
Failed implantation	285	16.1	9.5	1.9	1.2
SAB	22	16.3	10.7	2.7	3.0
Liveborn	126	15.7	8.2	2.1	2.1
<i>p</i> value		0.721		0.004	
Fertilization rate					
<50%	141	16.6	8.6	2.5	4.7
\geq 50%	305	15.7	9.1	2.0	1.7
<i>p</i> value		0.23		0.05	

Cramer, 2003



Magri, 2013



Table III Birth outcome for 195 cycles in which a delivery has occurred

	TSH \leq 2.5 mIU/L (n = 150)	TSH > 2.5 mIU/L (n = 45)	All births (n = 195)
Singleton	(n = 93)	(n = 32)	(n = 125)
Gestational age	38.56 (32-41.5, 1.56)*	38.03 (27-41, 2.69)*	38.42 (27-41.5, 1.92)
Birth weight	7.33 (4.25-9.81, 1.09) [†]	6.78 (2.06-9.00, 1.38) [†]	7.19 (2.06-9.81, 1.19)
Twin	(n = 57)	(n = 13)	(n = 70)
Gestational age	36.08 (30-40, 2.01)*	34.65 (29-38.5, 3.66)*	35.81 (29-40, 2.43)
Birth weight	5.36 (2.75-7.69, 0.95) [‡]	4.83 (2.44-6.75, 1.42) [‡]	5.26 (2.44-7.69, 1.07)

Data are presented as the mean with the range and standard deviation in parentheses. The gestational age is the number of weeks at delivery. Birth weight is presented in pounds.

* *P* = .012 for TSH \leq 2.5 mIU/L compared with TSH > 2.5 mIU/L.

[†] *P* = .024.

[‡] *P* = .023.

Baker, 2006



Terapia con LT4 e PMA



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

Neeraj

Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women.

Raham 2010

Effect of levothyroxine treatment on in vitro pregnancy outcome in infertile women with subclinical hypothyroidism undergoing zona manipulation/intracytoplasmic sperm injection.

Kim 2011

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

Velkeniers 2013

[JAMA. 2017 Dec 19;318\(25\):2533-2541. doi: 10.1001/jama.2017.18249.](#)

Effect of Levothyroxine on Miscarriage Among Women With Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo Transfer: A Randomized Clinical Trial.

Wang 2017

RISULTATI NON CONCLUSIVI



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Alice 36 anni

nota per infertilità mista

Spermiogramma → quadro di oligospermia

componente ♀ → ridotta riserva ovarica

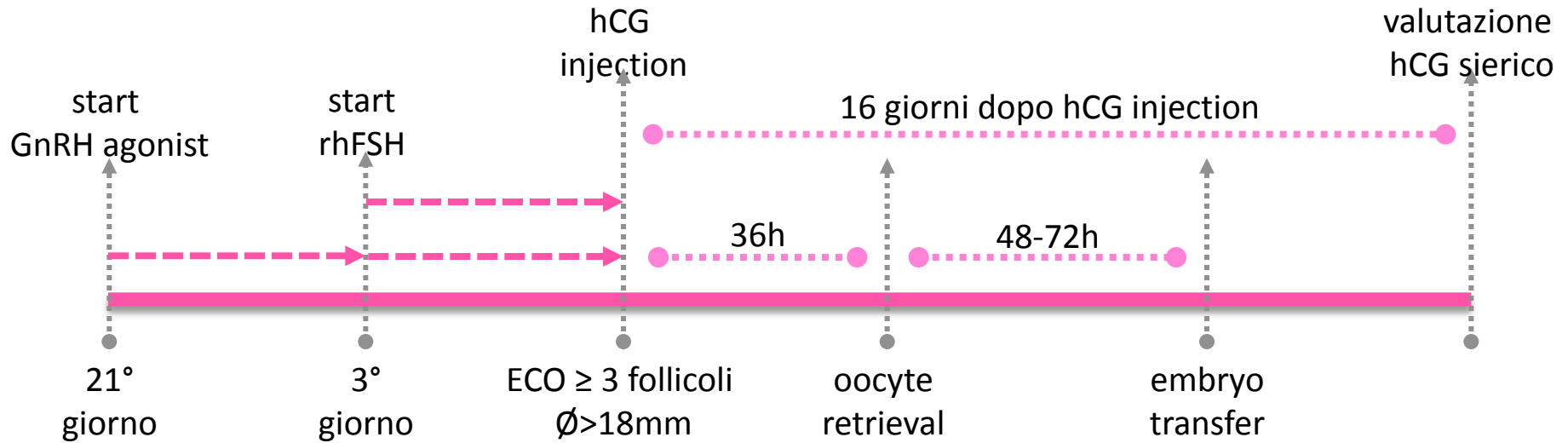
Familiarità positiva per tireopatia

Proposta ICSI



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Dosiamo il TSH prima della PMA in una paziente come Alice?



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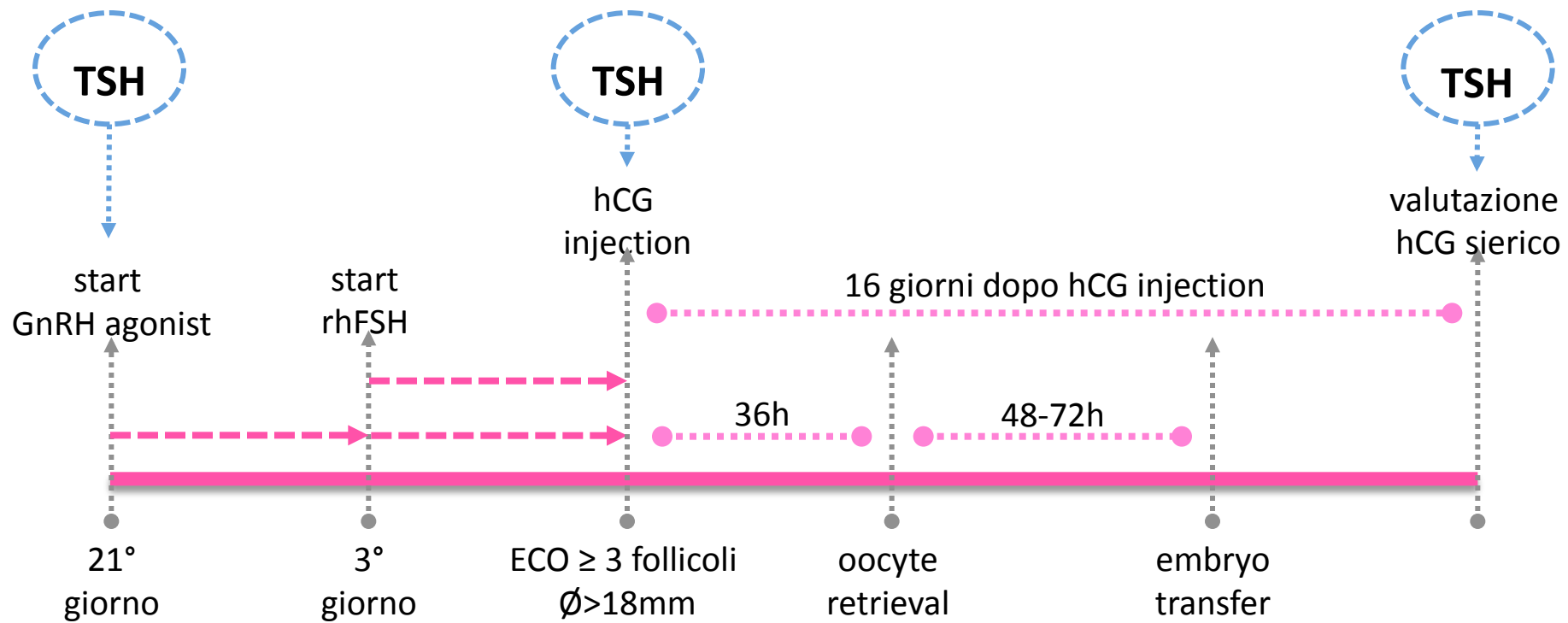
- Con età > 30 anni
- Con gozzo
- Con positività degli Ab (TPO)
- Con patologia nota in terapia con LT4
- Che vivano in aree di carenza iodica
- Con familiarità positiva per patologia tiroidea (incluso gozzo e autoimmunità)
- Con sintomi o segni suggestivi
- Con diabete mellito tipo 1 o altre malattie autoimmuni
- Con infertilità
- Con poliabortività
- Con precedenti trattamenti o irradiazione al collo

TSH basale 2.7 mU/L
AbTg e AbTPO negativi



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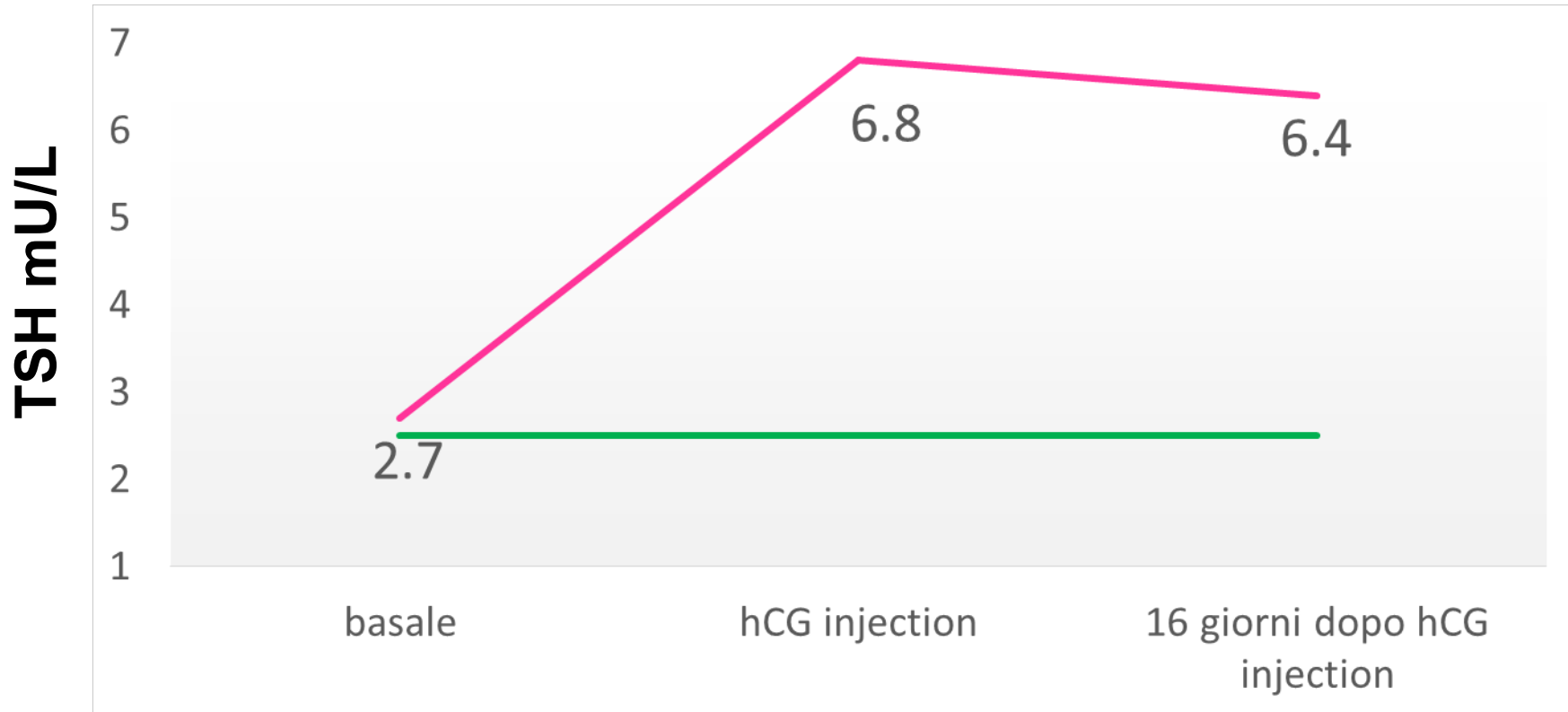


Andamento TSH



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Linee Guida 2017



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2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,^{1,*} Elizabeth N. Pearce,^{2,*} Gregory A. Brent,³ Rosalind S. Brown,⁴ Herbert Chen,⁵
Chrysoula Dosiou,⁶ William A. Grobman,⁷ Peter Laurberg,^{8,†} John H. Lazarus,⁹ Susan J. Mandel,¹⁰
Robin P. Peeters,¹¹ and Scott Sullivan¹²

VI. THE IMPACT OF THYROID ILLNESS UPON INFERTILITY AND ASSISTED REPRODUCTION

RECOMMENDATION 16: Evaluation of serum TSH concentration is recommended for all women seeking care for infertility.

RECOMMENDATION 17: LT4 treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy.



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	Eutir/Ab-	Eutir/Ab+	Ipo sub./Ab-	Ipo sub./Ab+	Ipo concl.
NON-IVF	-	No LT-4 (r.19)	LT-4* (r.18)	LT-4* (r.18)	LT-4
IVF	-	LT-4^S (r.21)	LT-4 (r.20)	LT-4 (r.20)	LT-4

Pre-fertilization TSH <2.5 mU/L (Ab+/Ab-)



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Alice 36 anni

nota per infertilità mista

Spermiogramma → quadro di oligospermia

componente ♀ → ridotta riserva ovarica

Familiarità positiva per tireopatia

TSH basale 1.8 mU/L

AbTg e AbTPO positivi

Proposta ICSI



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



	Eutir/Ab-	Eutir/Ab+	Ipo sub./Ab-	Ipo sub./Ab+	Ipo concl.
NON-IVF	-	No LT-4 (r.19)	LT-4* (r.18)	LT-4* (r.18)	LT-4
IVF	-	LT-4[§] (r.21)	LT-4 (r.20)	LT-4 (r.20)	LT-4

Trattamento con LT4 delle donne Ab+ che si sottopongono a PMA

[§]Insufficient evidence exists to determine whether LT4 therapy improves the success of pregnancy following ART in TPOAb-positive euthyroid women. However, administration of LT4 to TPOAb-positive euthyroid women undergoing ART may be considered given its potential benefits in comparison to its minimal risk.

*Insufficient evidence exist to determine if LT4 therapy improves fertility. LT4 may be considered to prevent progression to more significant hypothyroidism once pregnancy is achieved.

Monitoraggio TSH anche 1-2 settimane dopo la somministrazione di HCG per modificare tempestivamente la posologia di LT4 in donne in terapia



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



GRAZIE!