



Roma, 9-12 novembre 2017



ITALIAN CHAPTER



# Tireopatie e infertilità

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**Istituto Auxologico Italiano, Milano**



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# Disclosure statement



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**Nessun conflitto di  
interessi**

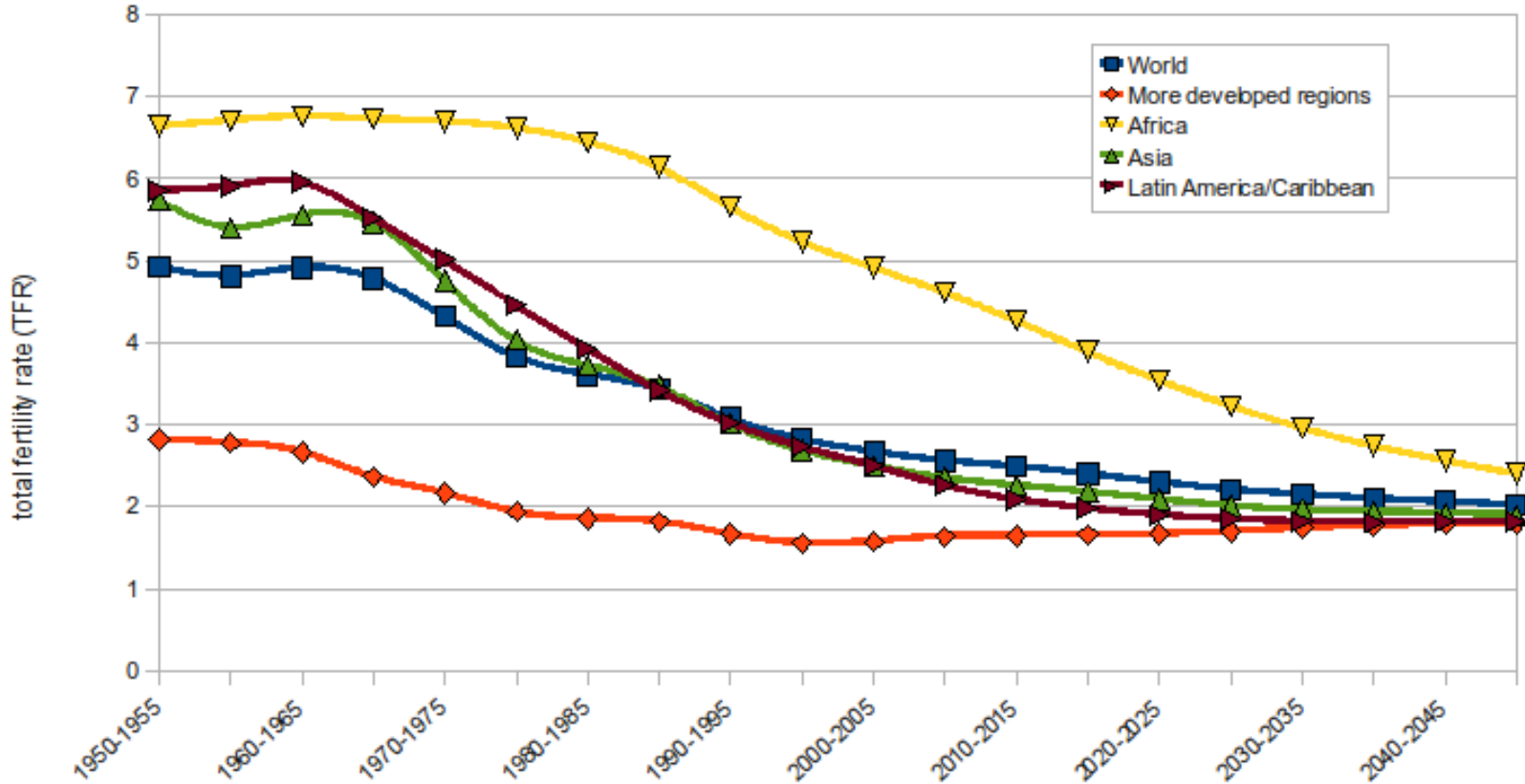


# Trend della fertilità totale 1950-2050



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# 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



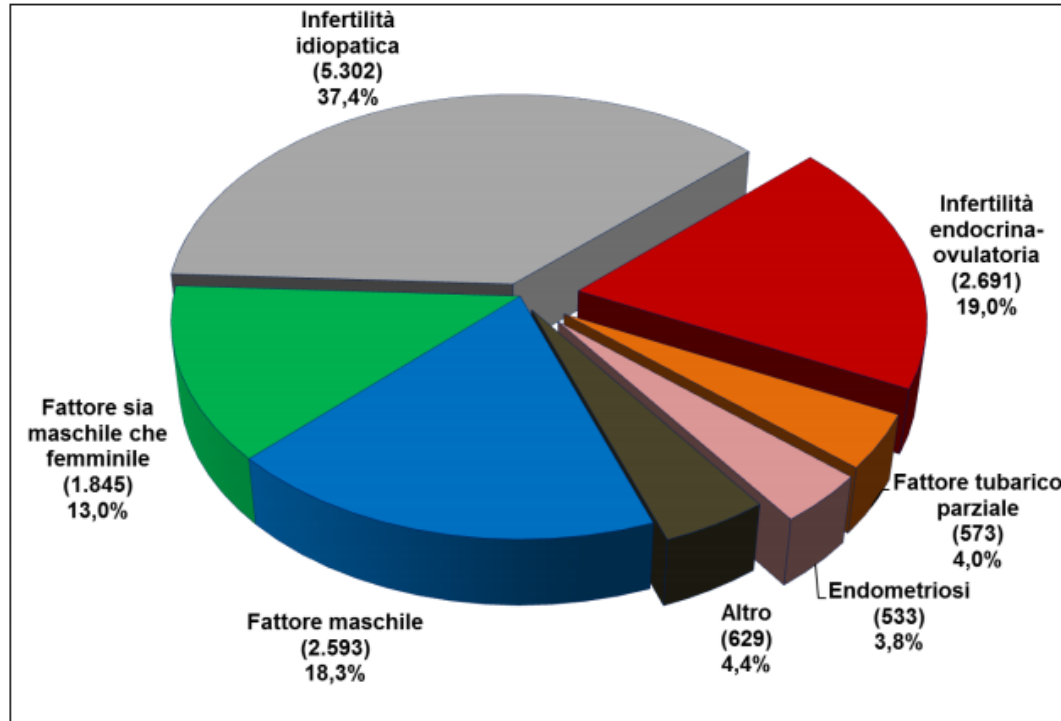
# Cause di infertilità



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Figura 3.2.1.: Distribuzione delle coppie trattate con Inseminazione Semplice senza donazione di gameti, secondo le cause di infertilità. Anno 2015. (in parentesi è espresso il numero di coppie in valore assoluto). **(14.166 coppie)**



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 Intra-uterina semplice** (HIUI homologous intra uterine insemination) con seme del partner

### Tecniche di secondo e terzo livello

**FIVET** (fecondazione in vitro embryo transfer)

**ICSI** (iniezione intra-citoplasmatica di un singolo spermatozoo)



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# Inseminazione intra-uterina: 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**



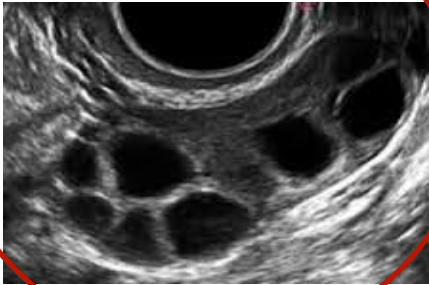
# INSEMINAZIONE IN VITRO: FIVET-ICSI



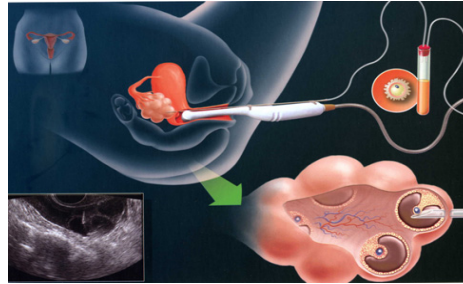
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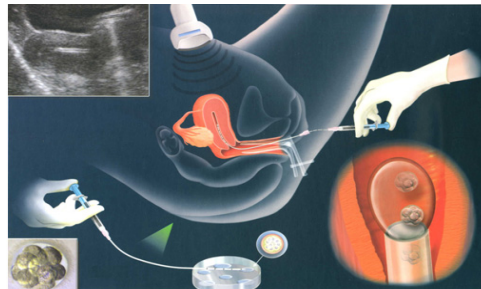
Stimolazione



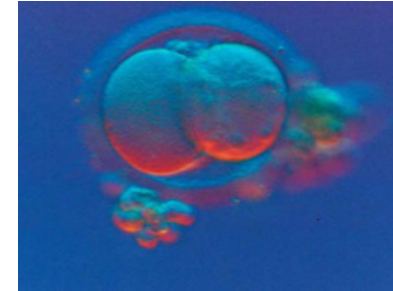
Pick-up oociti



Transfer dell'embrione



Coltura in vitro degli embrioni



Biopsia dell'embrione



Verifica dello stato di gravidanza



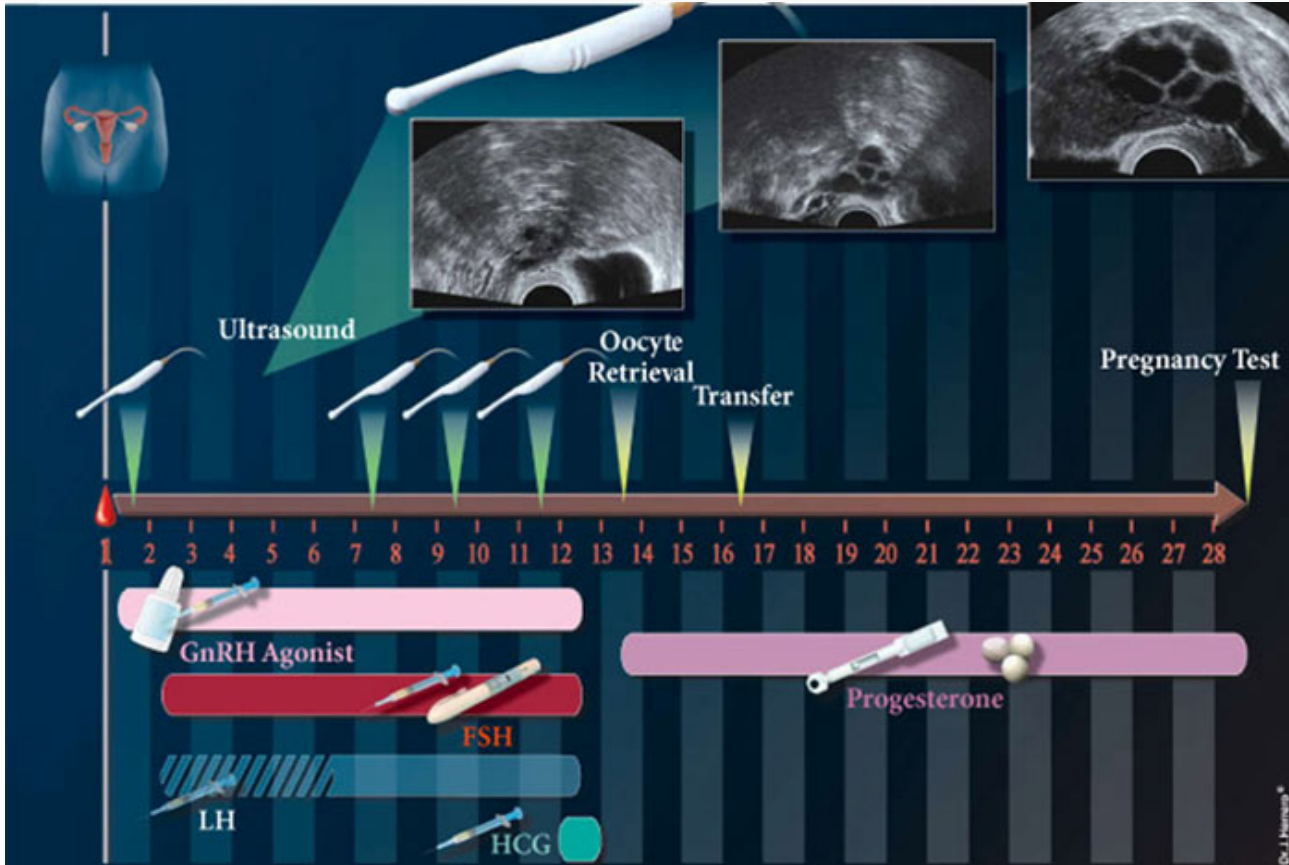


# Stimolazione ovarica



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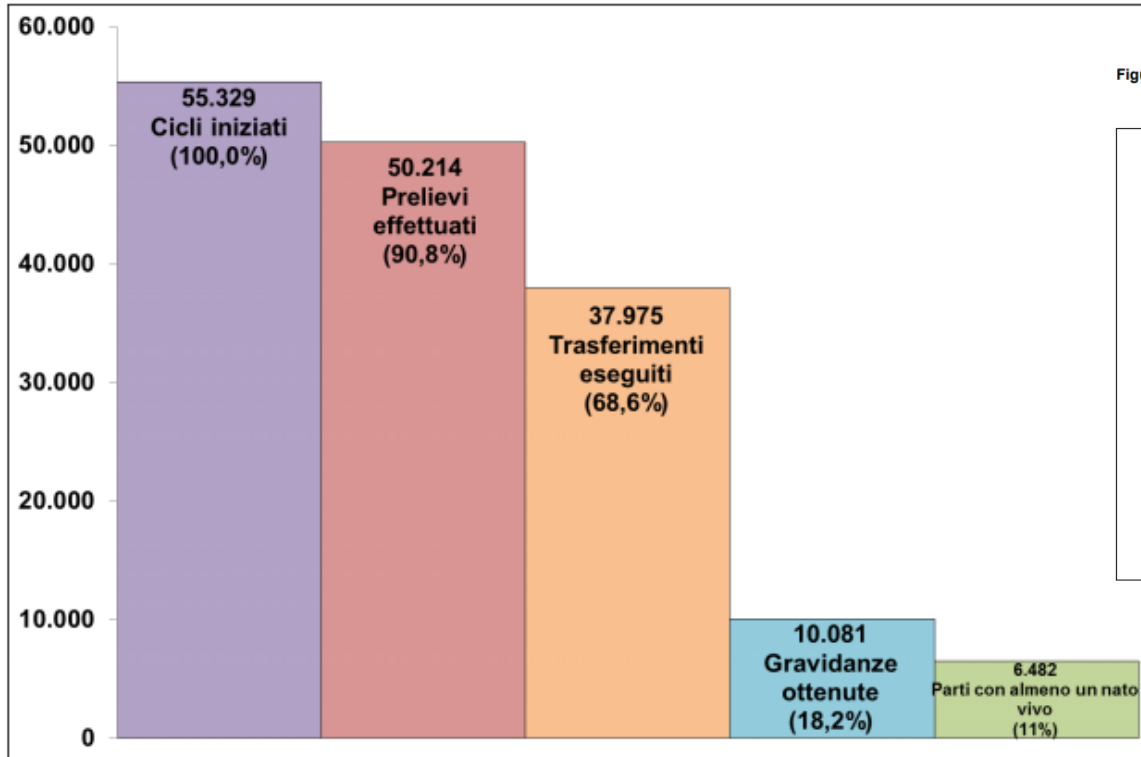
# Outcome



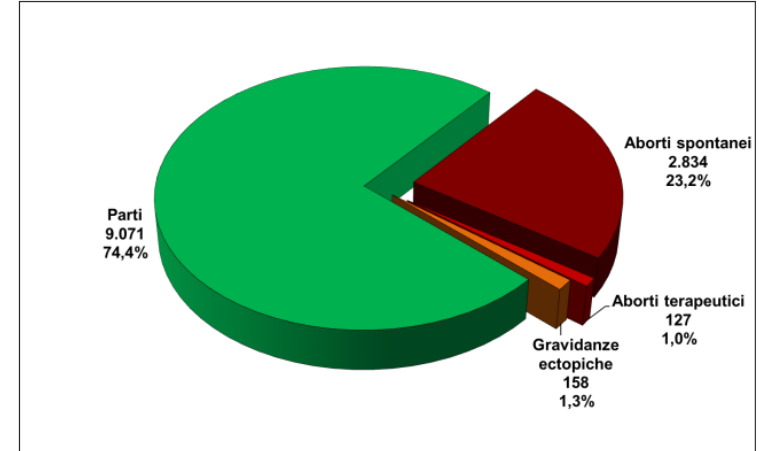
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**Figura 2: Cicli iniziati, prelievi effettuati, trasferimenti eseguiti e gravidanze ottenute, su tecniche a fresco di II e III livello (FIVET e ICSI) senza donazione di gameti nel 2015.**



**Figura 3.2.15: Esiti delle gravidanze monitorate ottenute da tecniche a fresco e da tecniche di scongelamento senza donazione di gameti, nell'anno 2015 (12.190 gravidanze monitorate).**





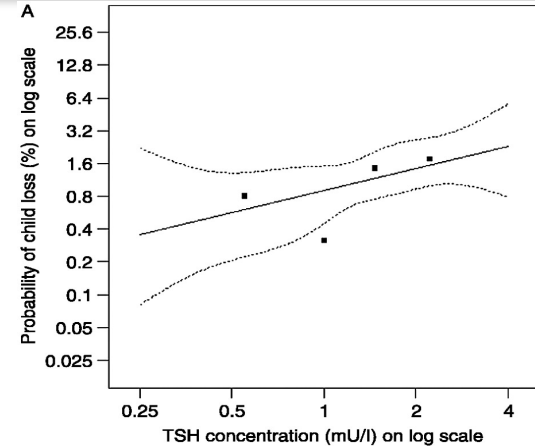
# Ipotiroidismo e aborto



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**Aumento del rischio di aborto del 60% per ogni raddoppiamento dei livelli di TSH**



**Benhadi , 2009**

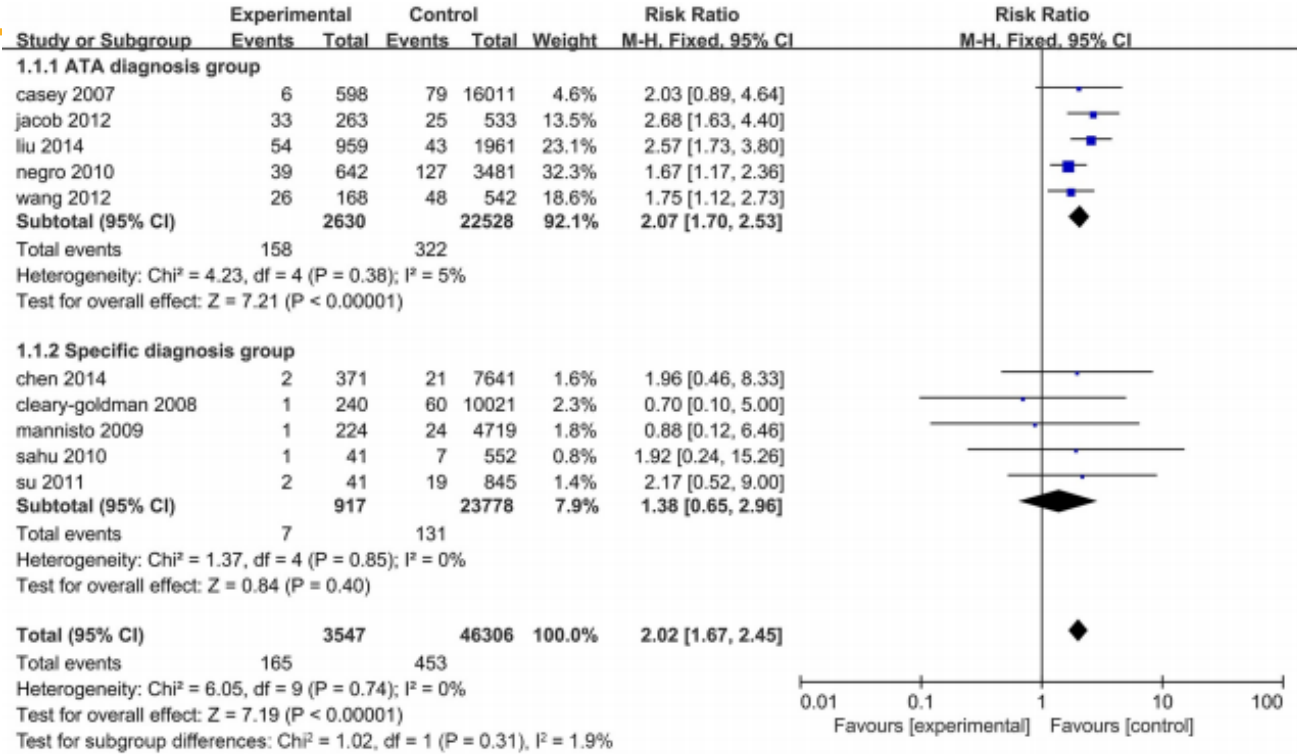
**TABLE 2.** Clinical characteristics of patients by group and miscarriage history

	TSH < 2.5 mU/L		TSH tra 2.5-5 mU/L	
	Group A (n = 3481)	Group B (n = 642)	Group A (n = 3481)	Group B (n = 642)
	Pregnancy loss (n = 127) (3.6%)	No pregnancy loss (n = 3354) (96.4%)	Pregnancy loss (n = 39) (6.1%)	No pregnancy loss (n = 603) (93.9%)
Age (yr)	31.7 ± 3.1	28.5 ± 5.0	31.3 ± 2.4	29.0 ± 5.2
Previous babies (n)	88 (69.3%)	2359 (70.3%)	28 (71.8%)	430 (71.3%)
Smoking (%)	1 (0.8%)	184 (5.5%) <sup>a</sup>	0 (0.0%)	38 (6.3%)
First gynecological visit (wk)	8.9 ± 1.5	8.8 ± 1.6	8.8 ± 1.5	8.9 ± 1.5
Week of pregnancy loss	11.7 ± 3.7		11.8 ± 3.6	
TSH first trimester (mIU/liter), median (interquartile range)	0.72 (0.30–1.33)	0.82 (0.36–1.40)	3.29 (2.79–3.61)	3.14 (2.79–3.43)
Free T <sub>4</sub> first trimester (pmol/liter)	12.4 ± 2.2	12.2 ± 2.1	9.9 ± 2.4	10.6 ± 2.1
Family history of thyroid disease (%)	13 (10.2%)	430 (12.8%)	7 (17.9%)	57 (9.4%)
Goiter (%)	0 (0%)	29 (0.9%)	0 (0%)	4 (0.7%)
Symptoms of hypo-/hyperthyroidism (%)	7 (5.5%)	260 (7.7%)	3 (7.7%)	42 (7%)
Type 1 diabetes/autoimmune disease (%)	0 (0%)	34 (1%)	0 (0%)	6 (1%)
Irradiation (%)	0 (0%)	1 (0.03%)	0 (0%)	1 (0.2%)
Previous miscarriage/preterm deliveries (%)	3 (2.4%)	47 (1.4%)	0 (0%)	9 (1.5%)

**Negro, 2010**

Demographic information, pregnancy history, clinical information, thyroid function tests, and mean week of pregnancy loss are broken down by group and whether pregnancy loss occurred. Group A TSH levels are below 2.5 mIU/liter; group B TSH levels are between 2.5 and 5.0 mIU/liter.

<sup>a</sup> P < 0.05 for comparison between miscarriage and no miscarriage subgroups within group).



Aumento del rischio di aborto di 1.9 volte se TSH > 2.5 mU/L



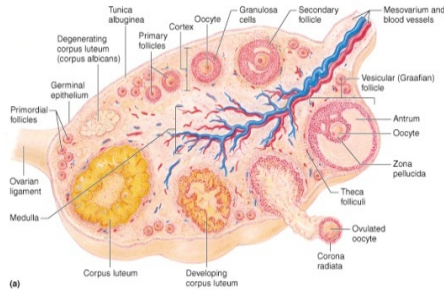
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**Tiroide**  **PMA**

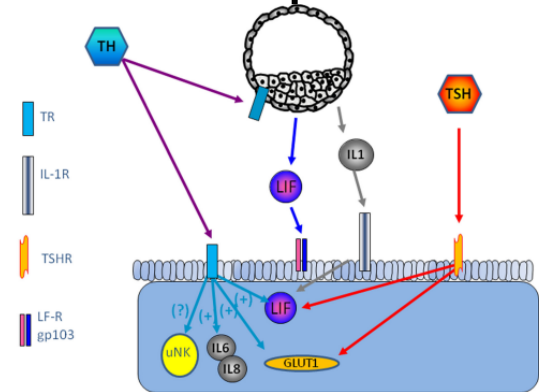


### Azione sinergica degli OT con FSH

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

Aghajanova, 2009

Stavreus, 2012



**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**



# 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) <sup>a</sup>	p	OR (95% CI) <sup>a</sup>	p
Age (years) <sup>b</sup>	30 (30-35)	34 (29-39)	0.92 (0.87;0.98)	0.015 <sup>d</sup>	0.94 (0.87;0.99)	0.049 <sup>d</sup>
Body mass index (kg/m <sup>2</sup> ) <sup>b</sup>	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) <sup>c</sup>	19 (51.4)	258 (51.3)	1.00 (0.95;1.05)	0.861	-	-
Parity <sup>c</sup>	0 (0-1)	0 (0-0)	1.01 (0.60;1.71)	0.954	-	-
TSH (μIU/ml) <sup>b</sup>	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 <sup>f</sup>	0 (0)	61 (12.1)	0.07 (0.05;0.10)	0.015 <sup>d</sup>	0 (0;inf)	0.997
TG-Ab > upper level of normal <sup>f</sup>	2 (5.4)	105 (20.9)	0.22 (0.05;0.91)	0.037 <sup>d</sup>	0.87 (0.19;4.03)	0.861
Thyroid medication for overt hypothyroidism <sup>c</sup>	2 (5.4)	95 (18.9)	0.25 (0.06;1.04)	0.036 <sup>d</sup>	0.54 (0.12;2.47)	0.338
Thyroid medication TSH > 2.5 μIU/ml <sup>f</sup>	16 (43.2)	55 (10.9)	6.94 (3.60;13.40)	<0.001 <sup>d</sup>	3.31 (1.31;8.35)	0.009 <sup>d</sup>
Presence of PCO-S <sup>c</sup>	8 (21.6)	81 (16.1)	0.71 (0.31;1.60)	0.407	-	-
Metformin treatment <sup>b</sup>	3 (8.1)	31 (6.2)	1.34 (0.31;4.92)	0.500	-	-
Clomifen citrate stimulation <sup>c</sup>	19 (51.4)	146 (29.0)	0.39 (0.20;0.77)	0.006 <sup>d</sup>	0.77 (0.32;1.85)	0.629
Number of IUI treatment cycle <sup>b</sup>	1 (1-1)	1 (1-1)	0.90 (0.59;1.37)	0.638	-	-
Ovulation induction with HCG <sup>c</sup>	27 (73.0)	239 (47.5)	2.95 (1.40;6.22)	0.005 <sup>d</sup>	5.37 (1.72;16.69)	0.004 <sup>d</sup>
Endometrial thickness <sup>b</sup>	10 (8-11)	8 (9-10)	1.09 (0.91;1.31)	0.324	-	-
Male factor <sup>c</sup>	13 (35.1)	269 (53.5)	0.47 (0.23;0.95)	0.034 <sup>d</sup>	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 ( $\geq 13$ 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



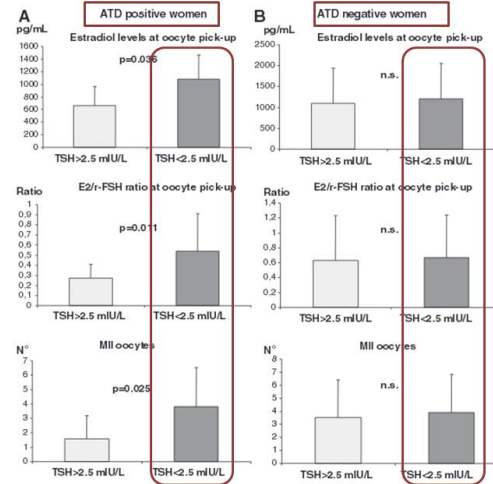
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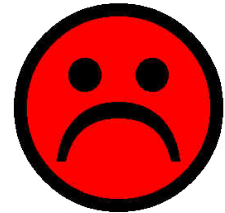
**Table III.** Mean Hormone Levels by First Cycle Pregnancy Outcomes

	Number	Prolactin (ng/mL)		TSH ( $\mu$ 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) <sup>†</sup>	6.78 (2.06-9.00, 1.38) <sup>†</sup>	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) <sup>‡</sup>	4.83 (2.44-6.75, 1.42) <sup>‡</sup>	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.

<sup>†</sup> *P* = .024.

<sup>‡</sup> *P* = .023.

Baker, 2006



# 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 <sup>1</sup>
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.

<sup>1</sup> 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



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# Autoimmunità tiroidea/infertilità



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**Autoimmunità aumenta il rischio di sviluppare ipotiroidismo, soprattutto in pazienti sottoposta a PMA (Koppe, 2008)**

**Autoimmunità tiroidea è espressione di autoimmunità generale**

**Associazione con Ab anti-cardiolipina (Toulis 2010)**

**Associazione con endometriosi (Poppe 2002, Abalovich 2007, Gerhard 1991)**

**Associazione con PCO (Janssen 2004, Kachuei 2011)**

**Associazione con POF (Abalovich 2007)**



# Autoimmunità tiroidea/infertilità



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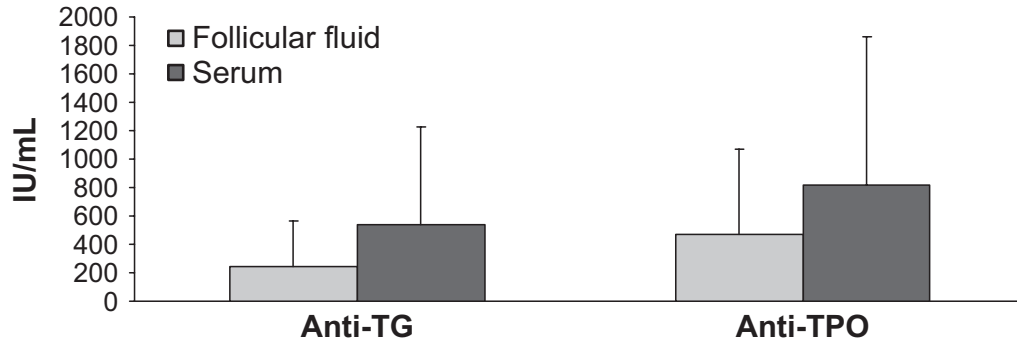
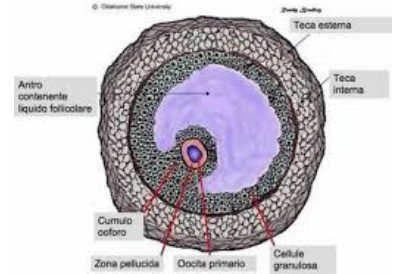
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## Female Infertility Related to Thyroid Autoimmunity: The Ovarian Follicle Hypothesis

Patrizia Monteleone<sup>1</sup>, Donatella Parrini<sup>1</sup>, Pinuccia Faviana<sup>2</sup>, Elena Carletti<sup>1</sup>, Elena Casarosa<sup>1</sup>, Alessia Uccelli<sup>1</sup>, Vito Cela<sup>1</sup>, Andrea Riccardo Genazzani<sup>1</sup>, Paolo Giovanni Artini<sup>1</sup>

<sup>1</sup>Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa, Pisa, Italy;

<sup>2</sup>Department of Surgery, Division of Pathology, University of Pisa, Pisa, Italy



Condivisione di Ag tra oocita e tiroide

Zona pellucida: bersaglio di AbTg, AbTPO



# Autoimmunità tiroidea/infertilità



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Human Reproduction Update Advance Access published June 20, 2016

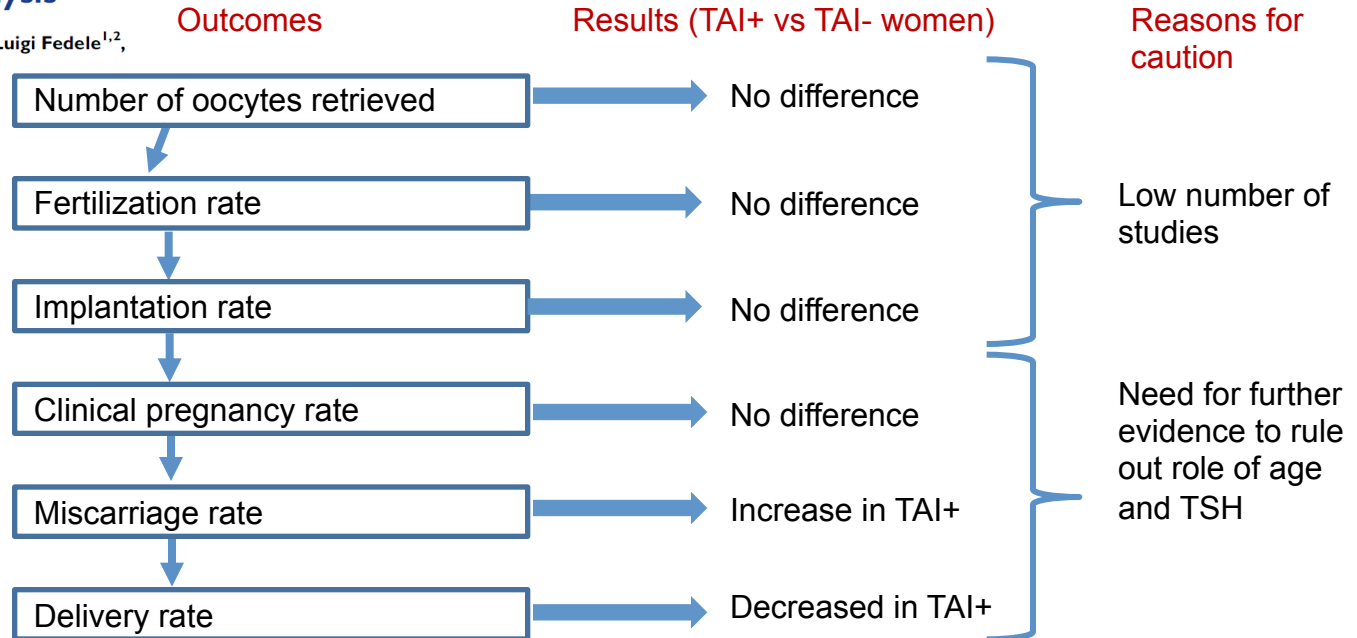
Human Reproduction Update, pp. 1-16, 2016

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<sup>1,2,\*</sup>, Alessio Paffoni<sup>1</sup>, Luigi Fedele<sup>1,2</sup>, and Edgardo Somigliana<sup>1</sup>





# Autoimmunità tiroidea/infertilità



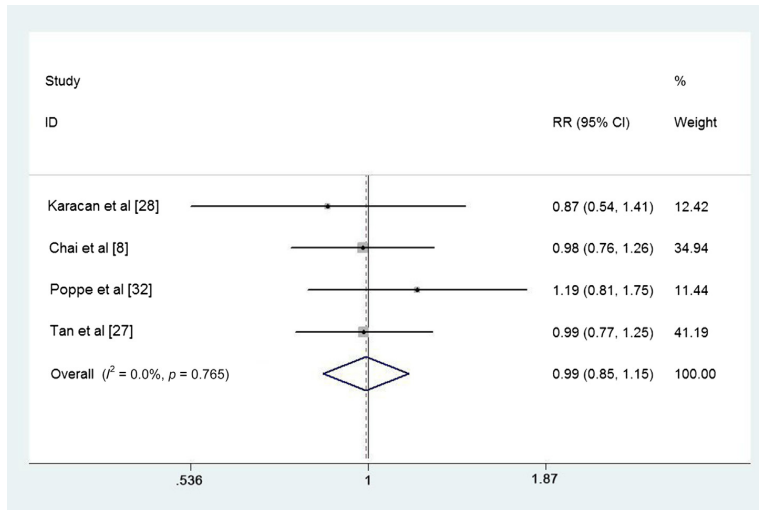
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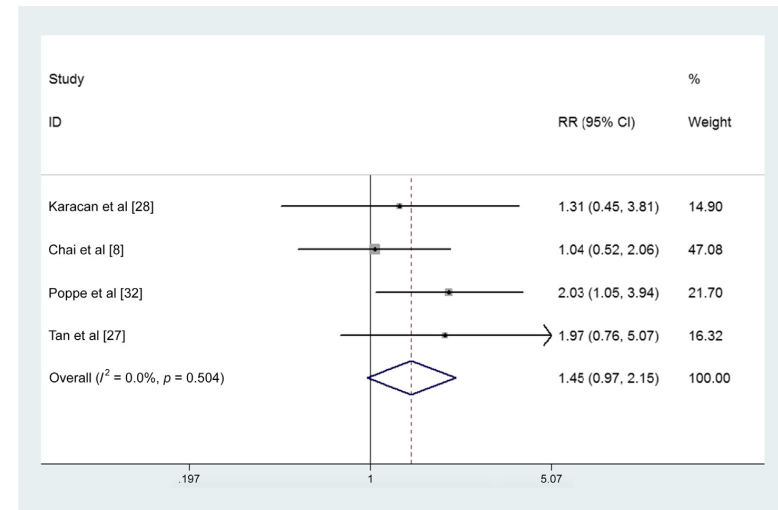
Original Article

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

Hui He <sup>a, b</sup>, Shuang Jing <sup>a, b</sup>, Fei Gong <sup>a, b, c</sup>, Yue Qiu Tan <sup>a, b, c</sup>, Guang Xiu Lu <sup>a, b, c</sup>, Ge Lin <sup>a, b, c, \*</sup>



Clinical pregnancy rate



Miscarriage rate



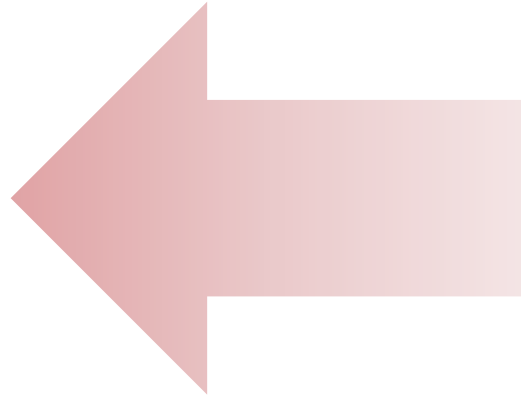
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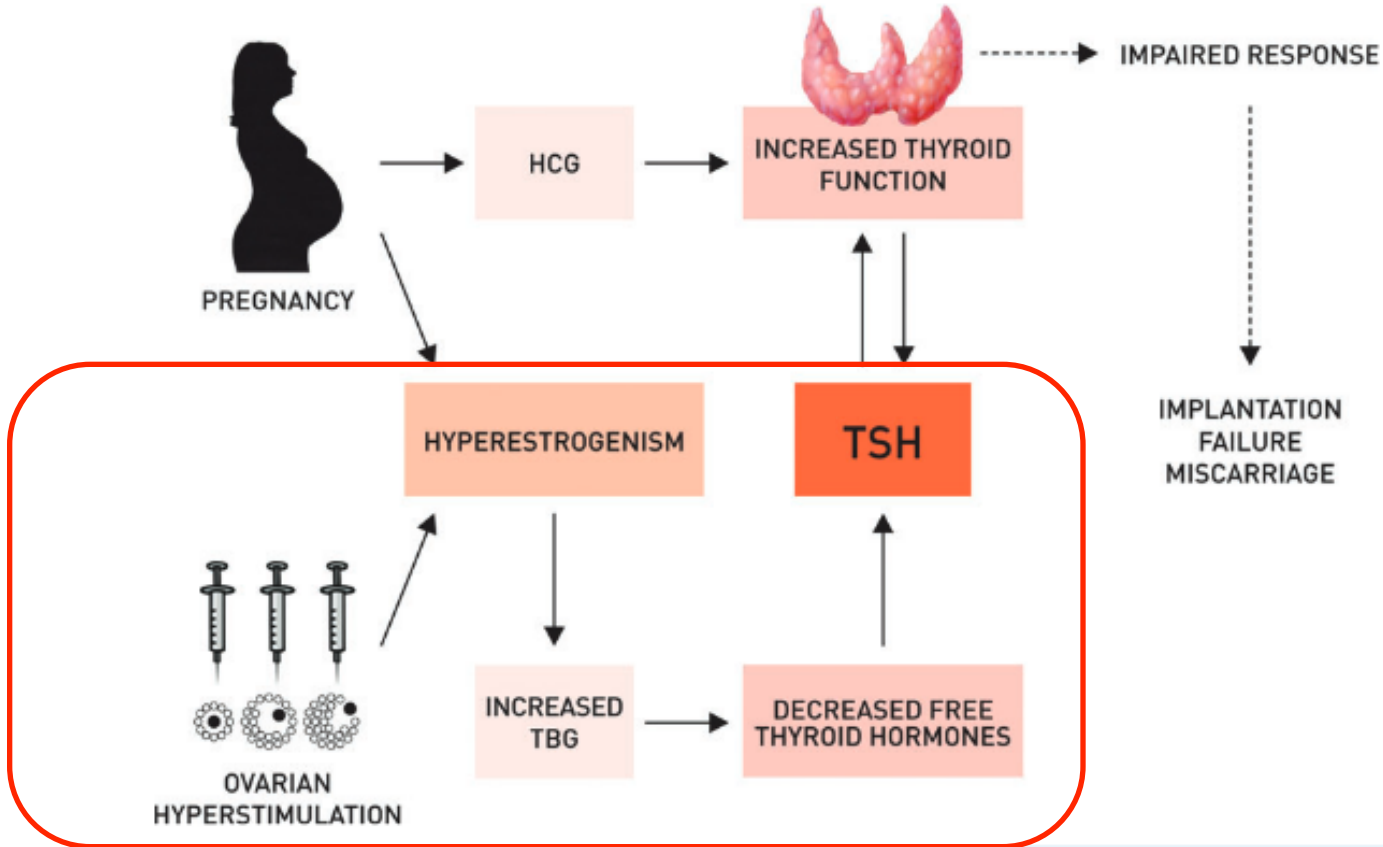
ITALIAN CHAPTER



**Tiroide**



**PMA**







# La stimolazione ovarica per IVF ha un impatto importante sull'omeostasi endocrina, in particolare sull'asse ipotalamo-ipofisi-tiroide (Muller 2000; Poppe, 2004; Poppe 2005, Mintziori 2011; Gracia 2012; Reinblatt 2013)

**TABLE 1**

Studies of thyroid function during assisted reproduction techniques.

ID	First author, year (reference)	Setting, country	Study characteristic	OS protocol
1.	Muller, 2000 (1)	Academic center, the Netherlands	Retrospective study	GnRH analog and hMG
2.	Poppe, 2004 (2)	Academic center, Belgium	Prospective study First ART cycle	GnRH agonist and hMG or hrFSH
3.	Poppe, 2005 (11)	Academic center, Belgium	Prospective study First ART cycle	GnRH agonist and hMG or hrFSH
4.	Haller, 2006 (14)	Private center, Estonia	Prospective study	GnRH agonist (n = 7, 5.4%) or GnRH antagonist (n = 122,

**Aumento del TSH a livelli superiori rispetto al cut-off suggerito per primo trimestre di gravidanza (2,5 mU/L)**

7.	Monteleone, in press (13)	Academic center, Italy	Prospective study	GnRH-antagonist and hrFSH
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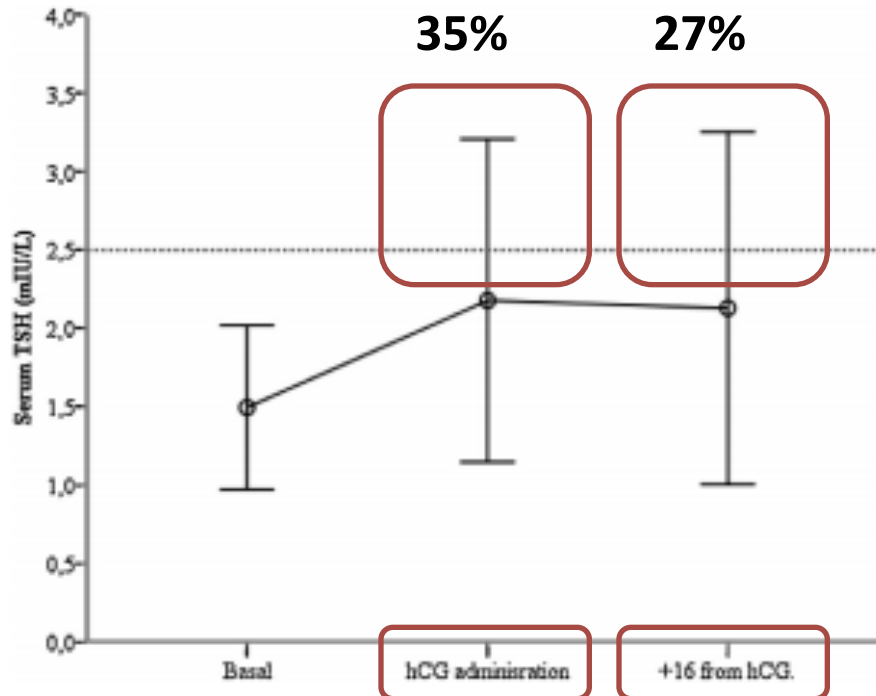
Note: hrFSH = human recombinant FSH.

Mintziori. Thyroid function during ovarian stimulation. Fertil Steril 2011.

**Mintziori, 2011**

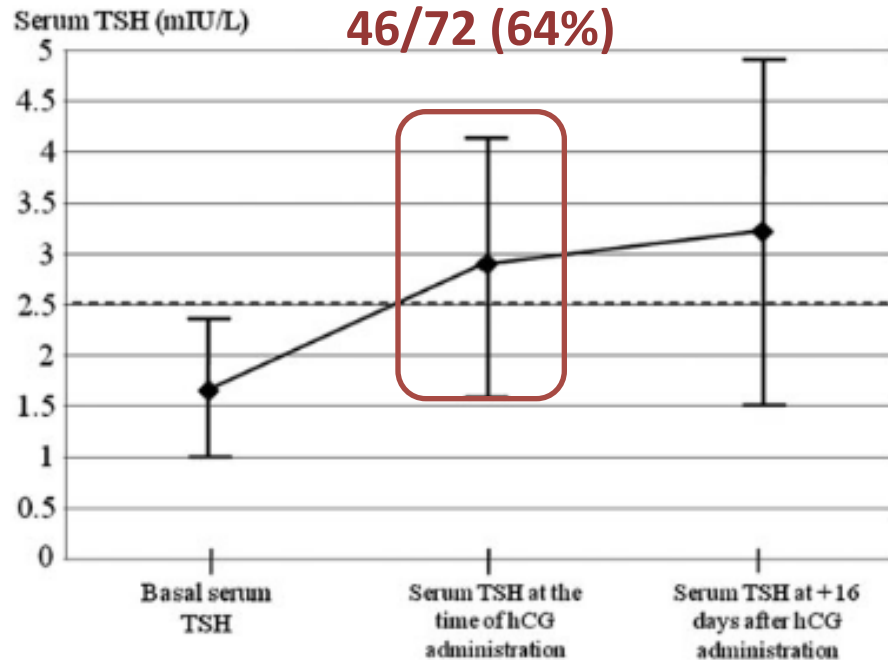


## Incidence of elevation of serum thyroid-stimulating hormone during controlled ovarian hyperstimulation for in vitro fertilization





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





ITALIAN CHAPTER

Roma, 9-12 novembre 2017

**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

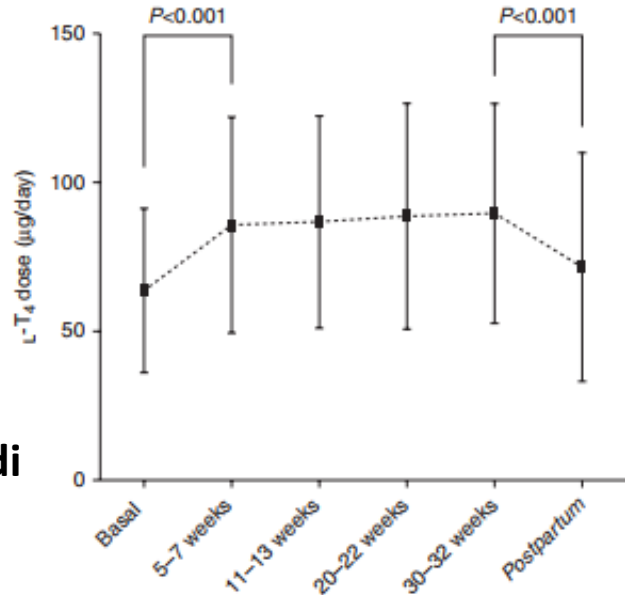
Andrea Busnelli<sup>1,2</sup>, Guia Vannucchi<sup>1</sup>, Alessio Paffoni<sup>1</sup>, Sonia Faulisi<sup>1,2</sup>, Laura Fugazzola<sup>1,2</sup>, Luigi Fedele<sup>1,2</sup> and Edgardo Somigliana<sup>1</sup>

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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**





# Terapia con LT4 e PMA



ITALIAN CHAPTER

Roma, 9-12 novembre 2017

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

**Negro 2005**

*In Vitro* Fertilization Pregnancy Rates  
in Levothyroxine-Treated Women With Hypothyroidism

**RISULTATI NON DEFINITIVI**

**Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/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**



# Linee Guida 2017



ITALIAN CHAPTER

Roma, 9-12 novembre 2017

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

Erik K. Alexander,<sup>1,\*</sup> Elizabeth N. Pearce,<sup>2,\*</sup> Gregory A. Brent,<sup>3</sup> Rosalind S. Brown,<sup>4</sup> Herbert Chen,<sup>5</sup>  
Chrysoula Dosiou,<sup>6</sup> William A. Grobman,<sup>7</sup> Peter Laurberg,<sup>8,†</sup> John H. Lazarus,<sup>9</sup> Susan J. Mandel,<sup>10</sup>  
Robin P. Peeters,<sup>11</sup> and Scott Sullivan<sup>12</sup>

## 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.



	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 <sup>§</sup> (r.21)	LT-4 (r.20)	LT-4 (r.20)	LT-4

**\*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.**

**§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.**

**RECOMMENDATION 24. In women who achieve pregnancy following controlled ovarian hyperstimulation, TSH elevations should be treated according to the recommendations outlined in Section VII. In nonpregnant women with mild TSH elevations following controlled ovarian stimulation, serum TSH measurements should be repeated in 2–4 weeks because levels may normalize.**



Roma, 9-12 novembre 2017



ITALIAN CHAPTER



**Human Reproduction**, pp. 1–7, 2017

doi:10.1093/humrep/dex240

human  
reproduction

OPINION

# Routine serum thyroid-stimulating hormone testing—optimizing pre-conception health or generating toxic knowledge?

Abha Maheshwari<sup>1,\*</sup>, Priya Bhide<sup>2</sup>, Jyotsna Pundir<sup>3</sup>,  
and Siladitya Bhattacharya<sup>4</sup>





Roma, 9-12 novembre 2017



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# GRAZIE !

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