Hypogonadism Hypogonadotropic Treatment

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And Metabolic Diseases

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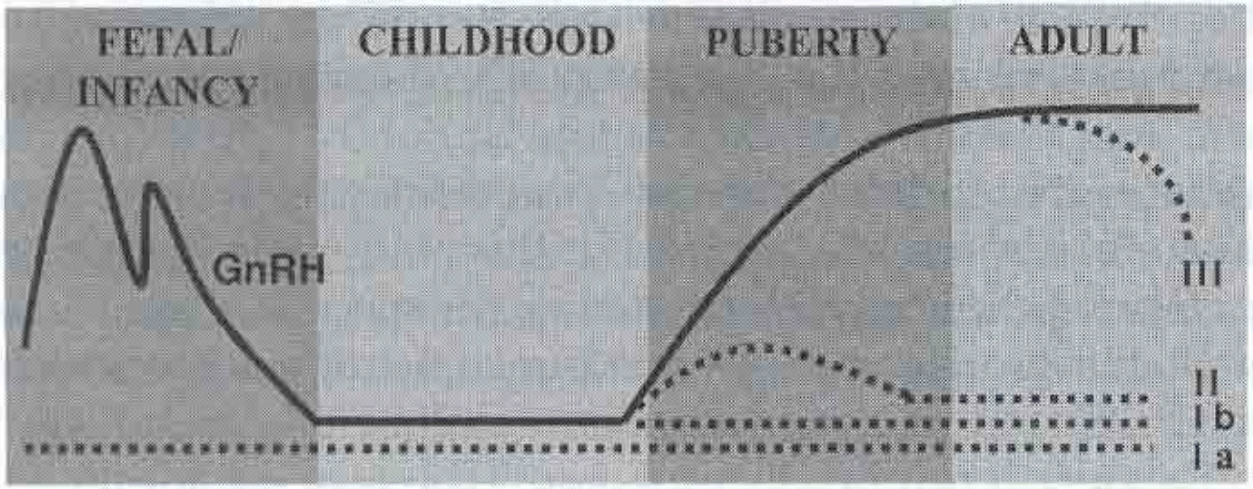
Key points

- Pathophysiology
- Gentic aspects
- Fragility and Resilience
- Medical Treatment and its outcomes: Gn and/or T

HPG AXIS ACROSS THE LIFE CYCLE AMONG NORMAL AND HH MALES

(Pitteloud et al JCEM 2002)



AGING ?

GnRH deficiency	Complete		Partial	Adult-onset
	Ia	Ib	II	III
Testicular development	-	-	+	+ + +
Cryptorchidism	+/-	-	-	-
Microphallus	+/-	-	-	-
Inhibin B level	+/-	+	+ + +	++
MIS level	+ + +	+ + +	-	-

Obesity?

LOH ?

Table 1. Causes of Hypogonadism

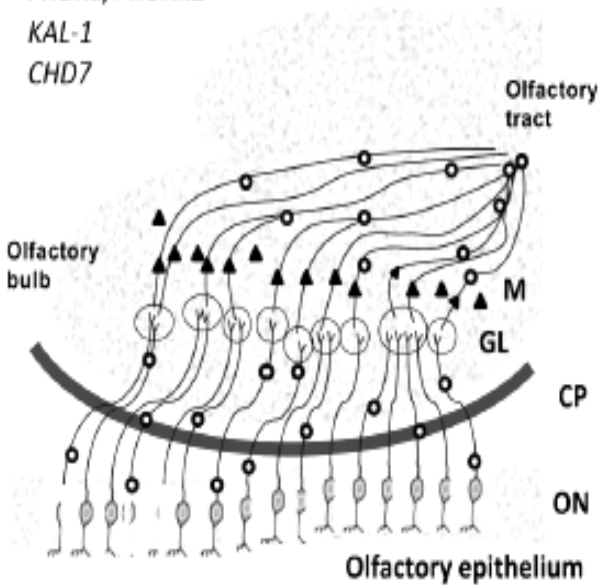
Type	Congenital Causes	Acquired Causes
Primary (testicular)	- Klinefelter's Syndrome - Anorchia (bilateral) - Cryptorchidism - Y microdelection - Sertoli –cell-only syndrome - Gonadal disygenesia - Myotonic dystrophy - Enzymatic defects in Testosterone syntesis - Leydig cell aplasia - Noonan's syndrome - XX 46 male syndrome - XYY syndrome	- Chemotherapy/radiation therapy - Acquired Anorchia - Testicular infections (mumps, echovirus, flavivirus) - Testicular Tumors - High doses of certain drugs (cimetidine, spironolactone, ketoconazole, flutamide, cyproterone)
Secondary (hypothalamic-pituitary)	- Kallmann's syndrome - Hydiopathic Hypogonadotropic Hypogonadism - Prader-Willi syndrome - Dandy-Walker malformation - Isolated LH deficiency (Pasqualini syndrome) - Isolated FSH deficiency - Biologically inactive LH and FSH	- Any acute systemic illness - Hypopituitarism (tumor, infarction, infiltrative disease, infection, trauma, radiation-induced) - Hyperprolactinemia - Hemochromatosis - Certain drugs (estrogens, psychoactives, metoclopramide, opioids, leuprolide) - Cushing's syndrome - Cirrhosis - Morbid obesity - Idiopathic
Mixed primary and secondary		- Late-onset Hypogondism (LOH) - Alcoholism - Systemic disease (uremia, liver failure, AIDS, sickle cell disease) - Drugs (ethanol, corticosteroids)
Androgen target organs resistance	- Complete Androgen Insensitivity syndrome. - Partial Androgen Insensitivity syndrome. - 5α reducatase Deficiency - Estrogen deficiency or resistance	

< 5%

VA Giagulli et al Curr. Pharmacol. Dis, 2011

Migration

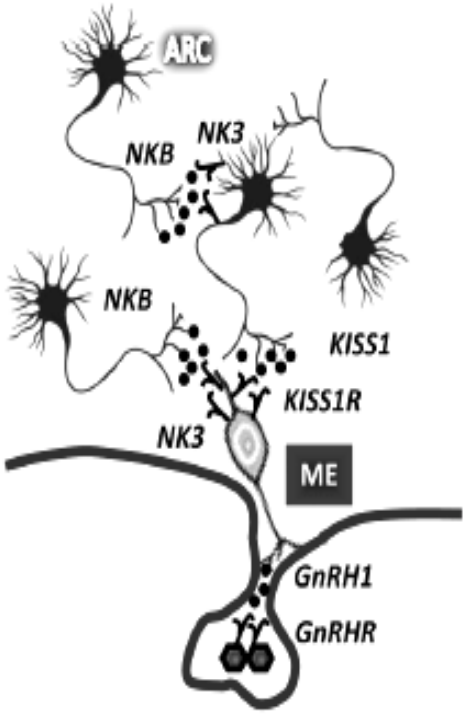
PROK2/PROKR2
KAL-1
CHD7



GnRH neuron genesis

FGF8/FGFR1
HS6ST1
NELF

Upstream signals



GnRH synthesis/action

Bonomi et al AJA,2012

REPORTED DIGENITIC CASES OF SUBJECTS WITH NORMOSMOTIC CONGENITAL HYPOGONADOTROPIC HYPOGONADISM

Patient	Sex	Gene 1	No. of alleles	Gene 2	No. de alleles	Reference
1	M	*FGFR1*	2[b]	*FGF8*	2[c]	Falardeau *et al.*, [15]
2	M	*FGFR1*	1	*FGF8*	1	Falardeau *et al.*, [15]
3	F	*FGFR1*	1	*GNRHR*	2	Pitteloud *et al.*, [21]
4	M	*WDR11*	1	*KAL1*	1	Quaynor *et al.*, [23]
5	M	*WDR11*	1	*GNRHR*	1	Quaynor *et al.*, [23]
6	F	*FGFR1*	1	*GNRHR*	2	Raivio *et al.*, [41]
7	F	*FGFR1*	1	*PROKR2*	1	Raivio *et al.*, [41]
8	F	*FGFR1*	1	*KAL1*	1	Sykiotis *et al.*, [42]

[a]Siblings described in this study; [b]compound heterozygous; [c] homozygous.

Information taken from Quaynor et al., [23].

Ipogonadismo ipogonadotropo

Ipogonadismo ipogonadotropo isolato

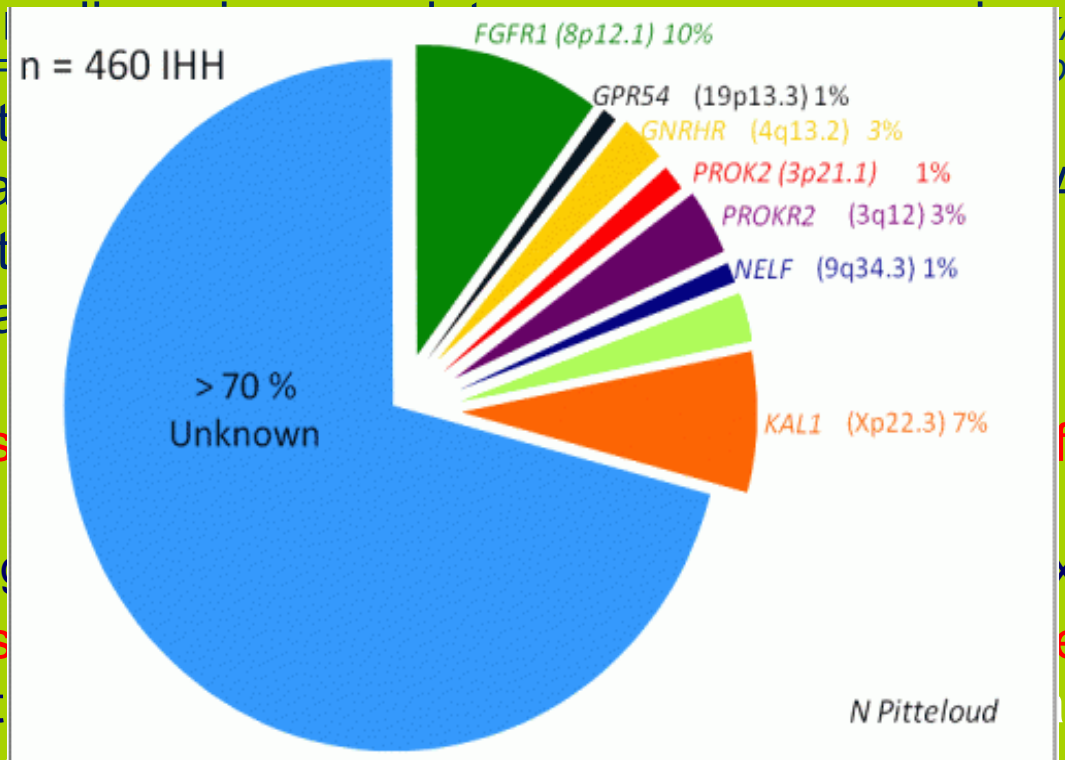
- sindrome di Kallmann, *KAL1, FGFR1,PROK2, PROKR2, FGF8, HS6ST1, CHD7)*
- ipogo… *…AL1, GNRHR, GNRH1*
  GPR54, F… …07)
- deficit…
- ipopla… …AX-1
- deficit…
- S. Pra…

Ipogonadis… …fisari multipli

Mutazione … …x2, Sox3

Ipogonadis… …el SNC

tumori, t… …o chemiote…olari, infettive, infiammatorie



Reversal and Relapse of Hypogonadotropic Hypogonadism: Resilience and Fragility of the Reproductive Neuroendocrine System

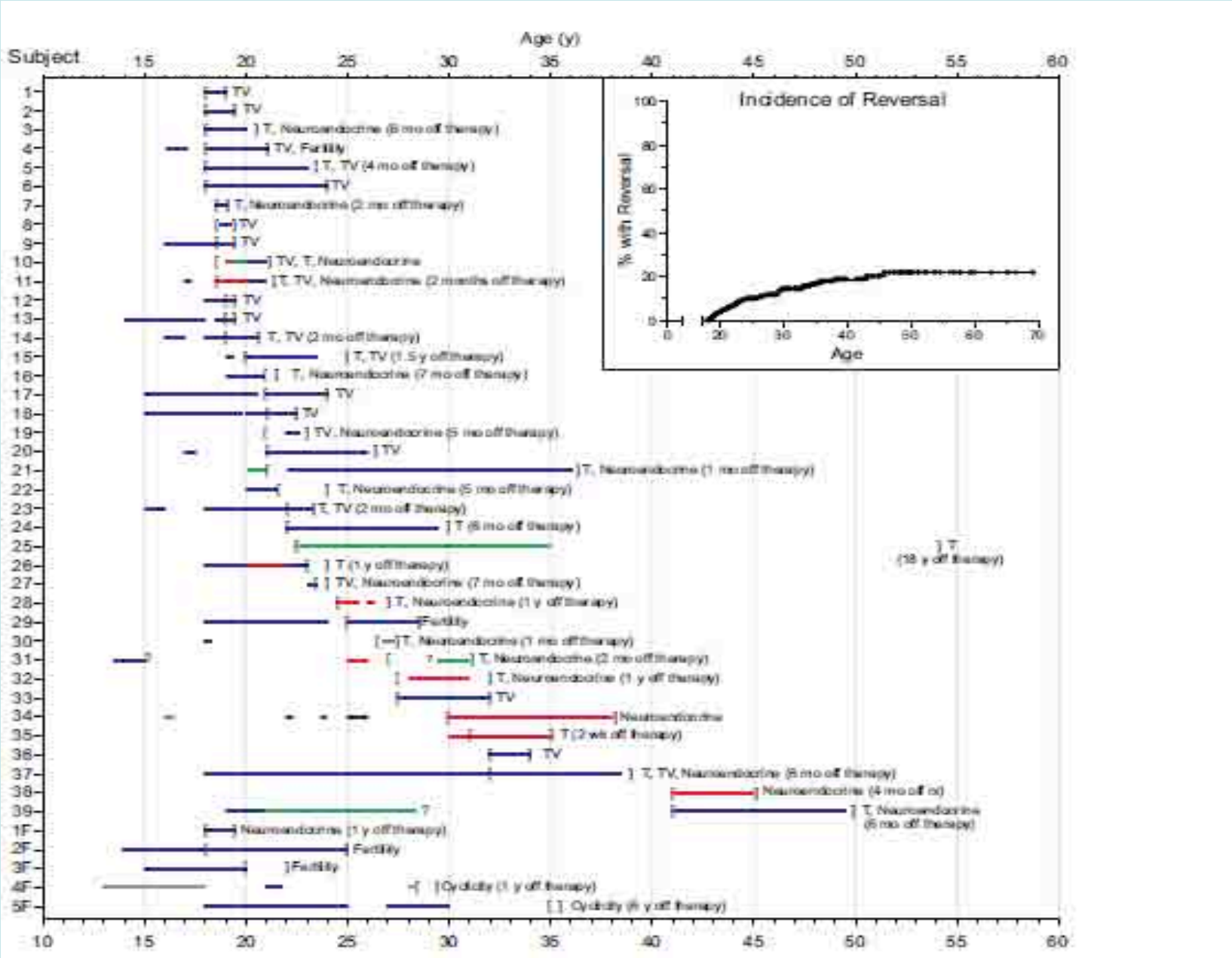
Valerie F. Sidhoum, Yee-Ming Chan, Margaret F. Lippincott, Ravikumar Balasubramanian, Richard Quinton, Lacey Plummer, Andrew Dwyer, Nelly Pitteloud, Frances J. Hayes, Janet E. Hall, Kathryn A. Martin, Paul A. Boepple, and Stephanie B. Seminara

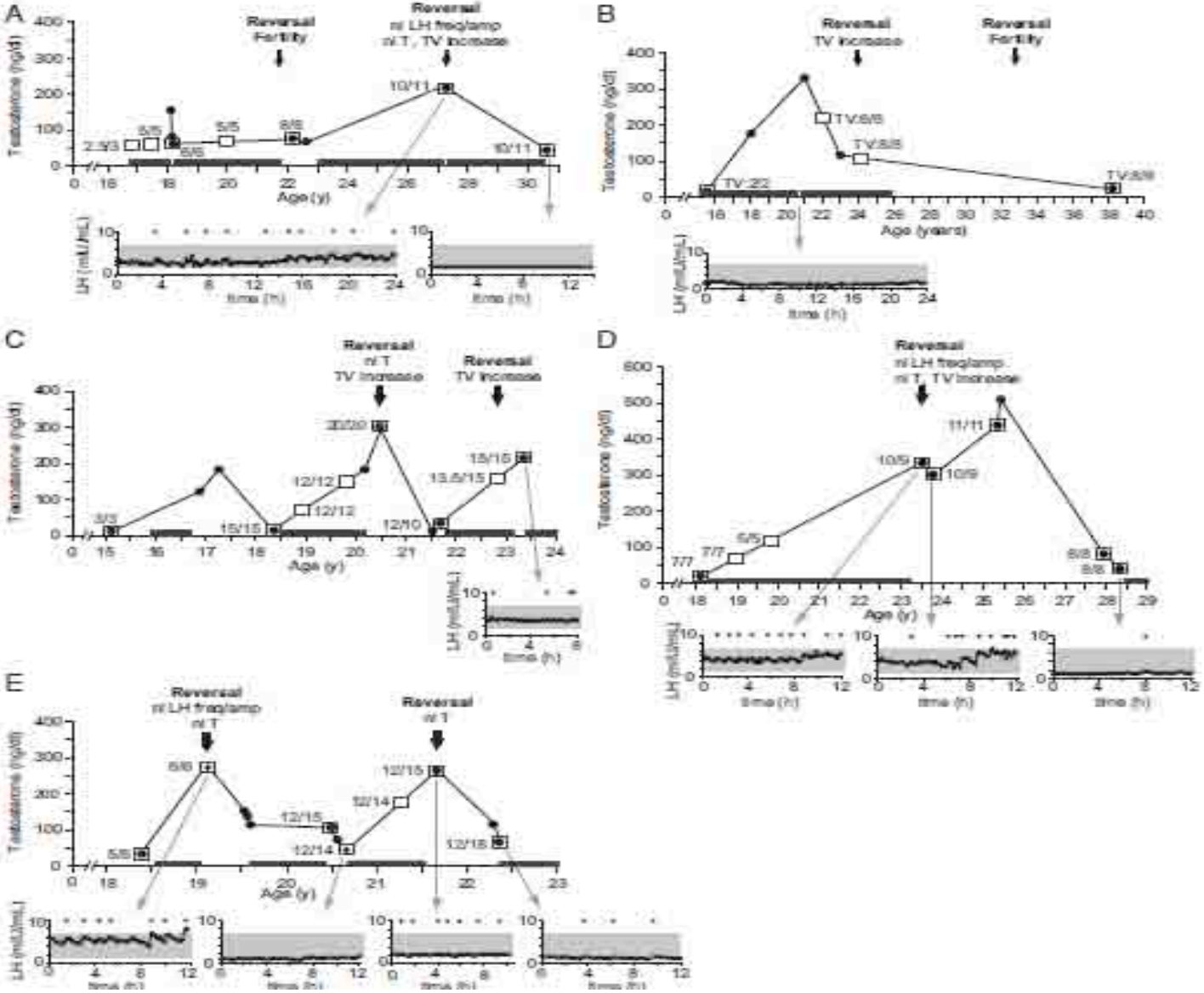
JCEM, 93,861, 2014

Table 1. Clinical Characteristics of Patients who Achieved Reversal of IHH

	Men		Women	
	% or Mean (range)	N	% or Mean (range)	n
Kallmann syndrome	31%	12/39	20%	1/5
Normosmic IHH	69%	27/39	80%	4/5
Age at last evidence for hypogonadotropism, y	23.8 (18–41.5)	39	24.0 (18–35)	5
Age at first evidence for reversal, y	28.3 (19.1–53.6)	39	26.5 (19.5–35.5)	5
Duration of therapy before reversal, y	4.4 (0.5–21)	32	6.7 (0.4–11)	4
Micropenis	27%	9/33	—	
Cryptorchidism	15%	6/39	—	

—, not applicable.


Subject
Age (y)
Incidence of Reversal
% with Reversal
Age


A
Reversal
Fertility
Reversal
n/ LH freq/amp
n/ T , TV increase
Testosterone (ng/dl)
Age (y)
LH (mIU/mL)
time (h)
B
Reversal
TV increase
Reversal
Fertility
TV:6/6
TV:6/6
TV:22
TV:6/6
Age (years)
C
Reversal
n/ T
TV increase
Reversal
TV increase
3/3
15/15
12/12
12/12
20/20
12/10
15/15
15.5/15
D
Reversal
n/ LH freq/amp
n/ T , TV increase
7/7
7/7
5/5
10/9
10/9
11/11
6/6
6/6
E
Reversal
n/ LH freq/amp
n/ T
Reversal
n/ T
5/5
6/6
12/15
12/14
12/14
12/15
12/16

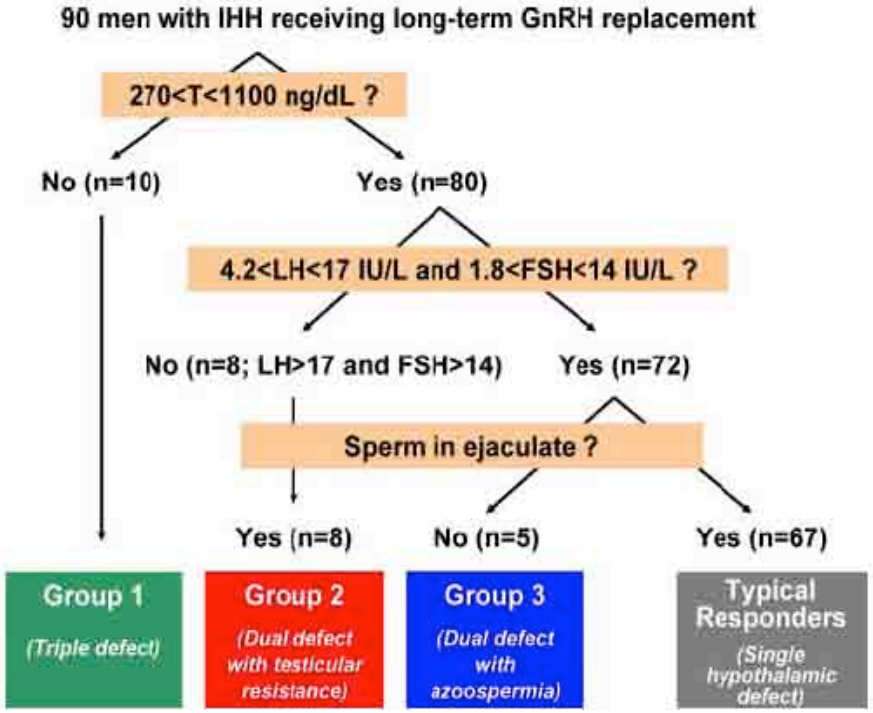
ORIGINAL ARTICLE
Endocrine Research

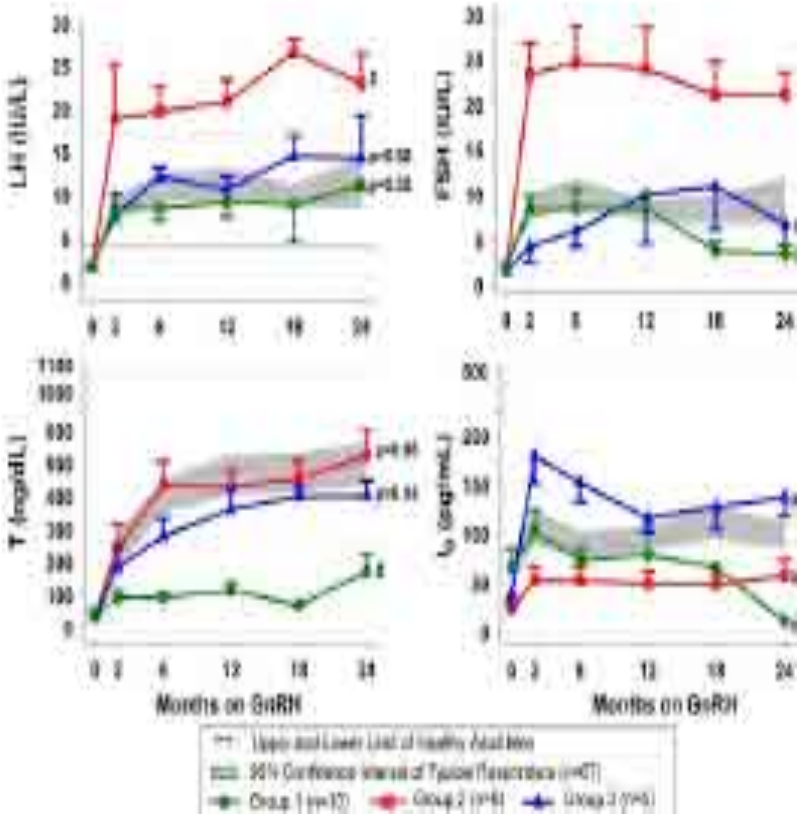
Congenital Idiopathic Hypogonadotropic Hypogonadism: Evidence of Defects in the Hypothalamus, Pituitary, and Testes

JCEM, 2009

Gerasimos P. Sykiotis,* Xuan-Huong Hoang,* Magdalena Avbelj, Frances J. Hayes, Apisadaporn Thambundit, Andrew Dwyer, Margaret Au, Lacey Plummer, William F. Crowley, Jr., and Nelly Pitteloud

Harvard Reproductive Endocrine Sciences Center and the Reproductive Endocrine Unit of the Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts 02114





Medical therapies

Main outcomes of hypogonadism therapy

1)Pubertal development and sex characteristics induction

2)Maintain normal androgenization

3)Prevent co-morbidities (obesity, diabetes mellitus, ostoeporosis, etc)

4)Induction spermatogenesis (fertility)

Nevertheless, there have been no guidilenes so far

Evidence-based Medicine Update on Testosterone Replacement Therapy (TRT) in Male Hypogonadism: Focus on New Formulations

V.A. Giagulli[1,*], V. Triggian[1]i, G. Corona[2], D. Carbone[3*], B. Licchelli[1], E. Tafaro[1], F. Resta[4], C. Sabbà[4], M. Maggi[2] and E. Guastamacchia[1]

[1]*Endocrinology and Metabolic Diseases, University of Bari "Aldo Moro"*; [2]*Andrology Unit, Department of Clinical Physiopathology, University of Florence*; [3]*Institute of Clinical and Hormonal Research, Foggia*; [4]*Geriatric Unit and Rare Diseases Center*; [*]*Biomedical Research Association "Guglielmo Telesforo", Foggia, Italy*

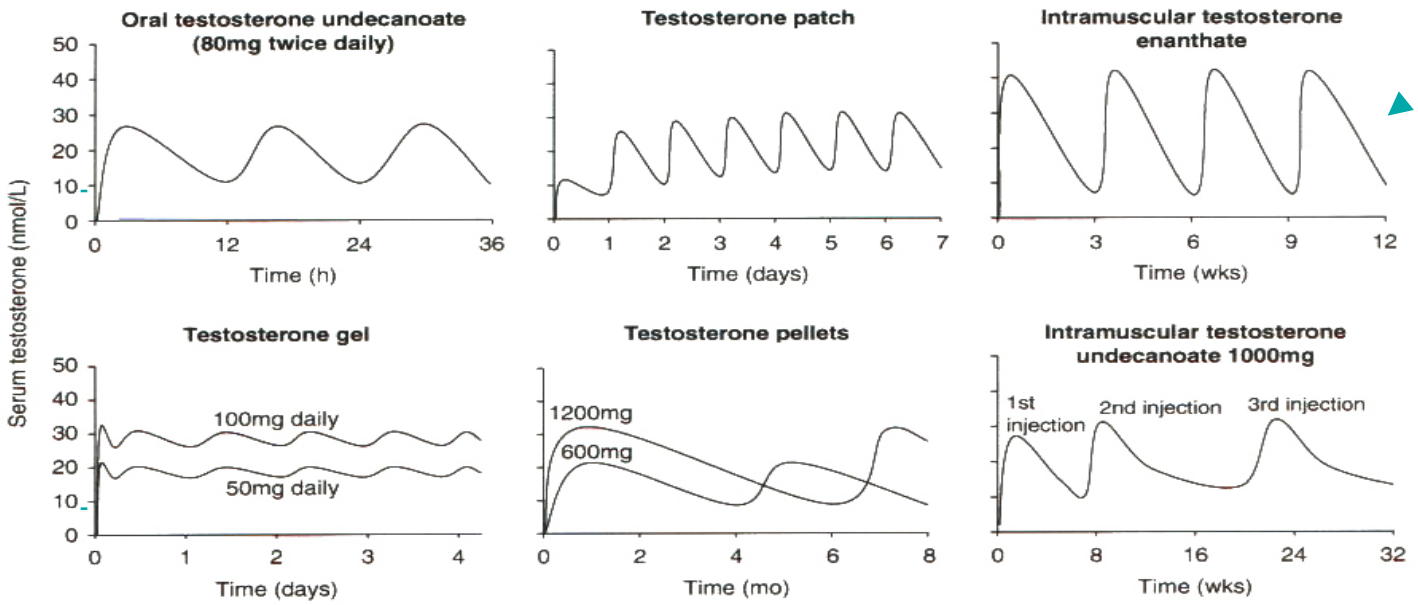
Abstract: Until the 2000s Testosterone (T) Replacement Therapy (TRT) was not very satisfactory for male hypogonadic patients because the available T formulations were not able to reproduce the physiological pattern of T secretion in man. In fact, oral formulations (oral undecanoate T) showed very short half-life (<24 hours), requiring the administration of several daily doses, whereas the old injection products (T esters) were characterized by very long half-life (>7 days) because of their adipose tissue storage, requiring to be administered every 2-3 weeks but determining remarkable and quick fluctuations (in 2-3 weeks) of the testosteronemia with variations in a few days from over-physiological levels (> 2000 ng/dl) to very low levels (< 200 ng/dl). Nowadays, several compounds can attain the standards of suitability and effectiveness of TRT in hypogonadal men. Both transcutaneous (gel) T and long-acting injectable formulations are the most modern preparations that can satisfy the criteria of an ideal chronic replacement therapy. In fact, they keep the serum T levels in the physiological range imitating its circadian rhythm, leading to the development and/or the preservation of male sexual characteristics and, finally, positively influencing bone mass, skeletal muscle and adipose tissue distribution. In particular, the availability and use of long-acting injectable undecanoate T can really improve the patients' compliance as requested for a life-long treatment. However, definitive and conclusive evidence regarding the main end-points, such as the diminished recurrence of falls in elderly men, the decrease in fractures in osteoporotic subjects, the reduction in disabling conditions and the extension of life, have not been reached so far. Therefore, the aim of this review is to sum up the most important evidence that has been collected regarding TRT, highlighting in particular those concerning both transcutaneous and long-acting injectable T compounds.

Clinical and biochemical characteristics for Testosterone compounds

a) Lead to circulating T levels strictly close to the physiological ones;
b) Warrant a daily release of T similar to the daily production of the steroid by the testis (3-10 mg/day);
c) Give a normal serum T that must be converted at sensitive tissues level either into DHT by the 5α reductase activity (30-80 ng/dl), and into 17β-estradiol by the aromatase activity (20-50 pg/ml);
d) Reproduce the T circadian rhythm;
e) Have little or absent negative effects on the prostate, the liver, the lipid profile and the cardiovascular system;
f) Represent a convenient and satisfying mean of replacement treatment for patients who can manage the therapy autonomously.

Giagulli et al Curr. Pharm. Des, 2011

Serum T in different forms of T application



L J.G.Gooren and M.C.M. Bunck
Drugs 64,2004

Current Testosterone Formulations on Market

	Generic name	Commercial name	Doses
INJECTABLE	*Testosterone propionate*	Testovis®	100 mg every 2-4 weeks
	Testosterone enantate	Testoviron® Dep.	200-400 mg every 2-4 weeks
	Testosterone undecanoate	Nebid®	1000 mg every 10-14 weeks
ORAL	*Testosterone undecanoate*	Andriol®	120-240 mg /day
TRANS-DERMAL	*Testosterone patch*	Androderm® Testopatch®	2.5-5 mg/day 1.8-2.4 mg/day
	Testosterone gel	Testogel® Androgel® Testim®	50-100 mg/day
		Tostrex®	60-80 mg/day
BUCCAL	*Buccal Testosterone*	Striant®	30 mg 2 times a day

Giagulli et al Curr.Pharm.Design,2011

Properties of Different T preparations

	T over 24 hours	E_2	DHT	Convenience	Dose Flexibility
Injectable T esters	–	±	±	±	–
Oral TU	±	+	±	+	+
Scrotal T patch	+	+	–	–	–
Nonscrotal T patch	+	+	+	±	–
T gel	+	+	+	+	+
T implants	+	+	+	+	±
Injectable TU	+	+	+	+	–

DHT = 5α-dehydrotestosterone; **E_2** = 17β-estradiol; **TU** = testosterone undecanoate; **+** indicates favourable; ± indicates reasonable; – indicates faulty.

L.J.G. Gooren and M.C.M. Burck
Drugs 64,2004

Adequacy of T replacement:
Clinical and Biochemical endpoints

- **Clinical Signs and Symptom:**

  - Subjective parameters: Sexual desire and activity, well-being and mood.

  -Objective parameters: Heamoglobin and Heamatocrit (quicker sign); BMD (slower sign)

- **Biochemical Parameters:**

  DHT, Estradiol, SHBG, LH and T

The Role of Long-Acting Parenteral Testosterone Undecanoate Compound in the Induction of Secondary Sexual Characteristics in Males with Hypogonadotropic Hypogonadism

Vito A. Giagulli, MD, PhD,*† Vincenzo Triggiani, MD,* Maria D. Carbone, MD,†‡ Giovanni Corona, MD, PhD,§ Emilio Tafaro, MD,* Brunella Licchelli, MD,* and Edoardo Guastamacchia, MD*

*Endocrinology and Metabolic Diseases, University of Bari "Aldo Moro," Bari, Italy; †Biomedical Research Association "Guglielmo Telesforo," Foggia, Italy; ‡Institute of Clinical and Hormonal Research, Foggia, Italy; §Sexual Medicine and Andrology Unit, Department of Clinical Physiopathology, University of Florence and Endocrinology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy

Table 1 Clinical characteristics, hormonal levels, and number of CAG repeats of patients and controls

Groups	Diagnosis	Case no.	Age (years)	BMI (kg/m²)	Testis (volume)	Penis length (cm)	CAG no.	FSH (IU/L)	LH (IU/L)	T (ng/dL)	SHBG (nM/L)	FT (ng/dL)	BioT (ng/dL)
CG	Normospermic men	15	19.5 ± 1.0	23.9 ± 1.1	22.3 ± 1.5	12.7 ± 2.0	19.8 ± 1.0	6.6 ± 2.5	7.5 ± 2.5	645.5 ± 79.5	41.8 ± 3.9	12.5 ± 1.9	275 ± 61
HHG	Idiopathic	1	18	23	4	4.5	19	1.5	1.0	120	60	1.49	35.1
	Idiopathic	2	17	24	4	4.5	25	1.8	1.2	100	59	1.25	29.3
	Idiopathic	3	17	26	6	5.5	21	0.9	1.7	130	56	1.71	40.2
	Idiopathic	4	17	23	6	4.8	20	1.6	1.1	89	53	1.21	28.4
	Idiopathic	5	19	24	4	3.8	27	2.1	0.9	92	49	1.31	31.1
	Idiopathic	6	17	25	4	4.8	22	1.8	0.9	132	50	1.88	44.1
	Intermediate BT	7	20	24	8	3.5	25	2.2	1.5	141	54	1.91	44.9
	Major BT	8	21	25	6	4.5	20	2.4	1.1	180	59	2.31	54.1
	Major BT	9	20	24	10	5.8	18	1.50	1.2	160	52	2.23	53.4
			18.50 ± 1.50	24.22 ± 1.31	5.78 ± 2.71**	4.7 ± 0.7**	21.89 ± 2.92	1.78 ± 0.43**	1.19 ± 0.27**	127.2 ± 29.2**	53.7 ± 3.8**	1.7 ± 0.39**	40.01 ± 9.27**

*$P < 0.01$; **$P < 0.001$ (Mann–Whitney U-test).
BT = β-thalassemia; BioT = biologically active testosterone; BMI = body mass index; CAG = cytosine-adenine-guanine; CG = control group; FSH = follicle-stimulating hormone; FT = testosterone-free fraction; HHG = hypogonadotropic hypogonadic group; LH = lutainizing hormone; SHBG = sex hormone binding globulin; T = total testosterone.

Table 2 Height, centile, and midparent target height in hypogonadal subjects in basal condition and after 1 and 2 years of parenteral testosterone undecanoate therapy

Diagnosis	Case no. (age [years])	Basal height (cm)	Centile	Height (cm) at 1 year	Centile	Height (cm) at 2 years	Centile	MPTH (cm)
Idiopathic	1 (18)	168.5	20	172	35	174	50	170
Idiopathic	2 (17)	170	25	174	50	176.5	60	172
Idiopathic	3 (17)	173	50	177	75	180	80	182
Idiopathic	4 (17)	170.5	25	174	50	177	60	169
Idiopathic	5 (19)	174	50	178.5	75	182	80	183
Idiopathic	6 (17)	177	70	181.5	80	183	85	185
Intermediate β-thalassemia	7 (20)	168	20	169.5	<50	171	<50	174
Major β-thalassemia	8 (21)	166	10	168	<50	169.5	<50	172
Major β-thalassemia	9 (20)	166.5	10	168	<50	169	<50	174

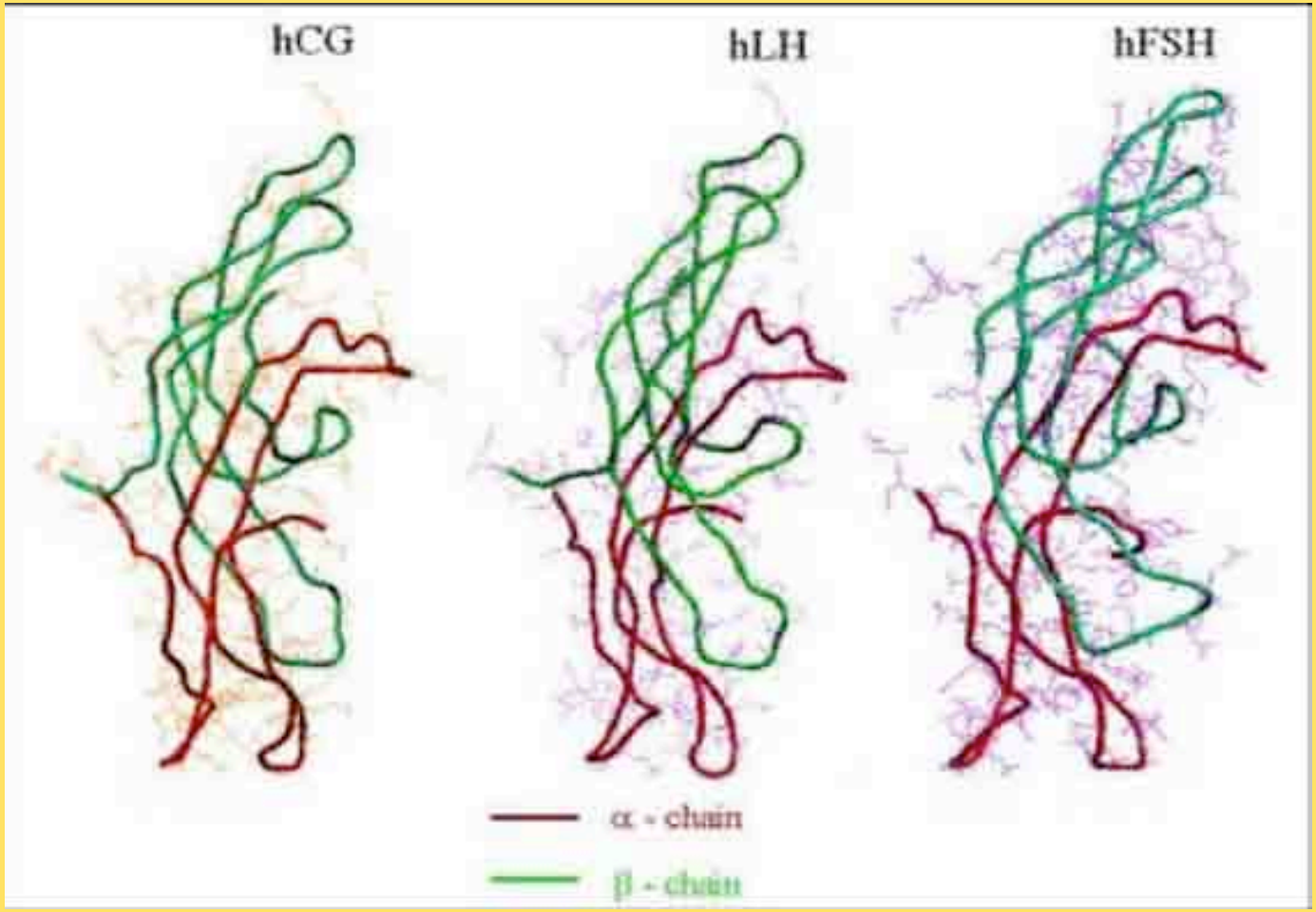
Calculated centile according to Italian cross-sectional growth charts.
MPTH = Midparental target height.

Spermatogensis induction

Scopo del trattamento dell'infertilità maschile

- Ottenere gravidanze spontanee
- Sopperire alla necessità di tecniche di fecondazione assistita (ART)
- Ridurre il livello della ART per superare la causa maschile
- Incrementare la pregnancy rate durante le tecniche di ART

Struttura terziaria di hCG,LH e FSH



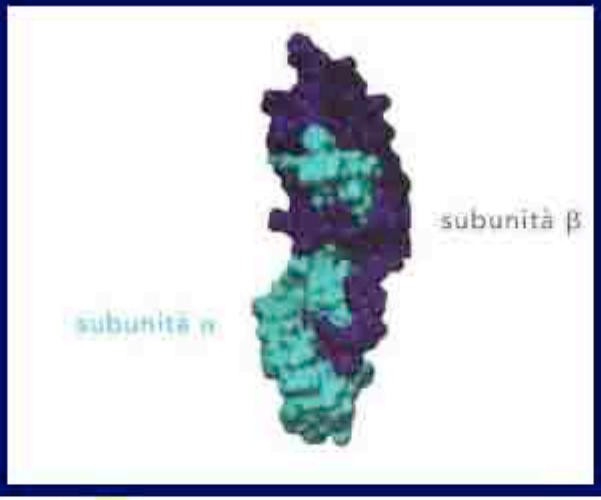
FSH

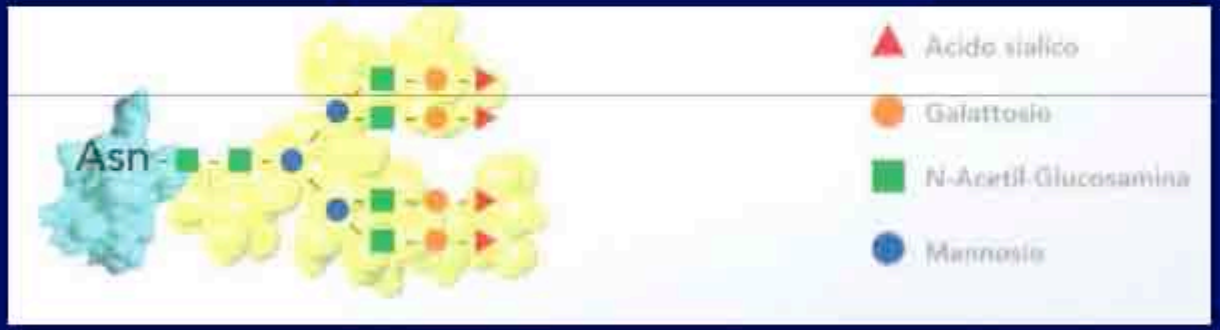
- Prodotto e secreto in forme molecolari multiple

- Le isoforme differiscono nella struttura oligosaccaridica, che ne determina un particolare comportamento *in vivo* e *in vitro*

- Il contenuto di acido sialico nella catena oligosaccaridica è direttamente correlato all'emivita

- La minor emivita delle forme a minor contenuto di acido sialico è compensata da una maggior bioattività.



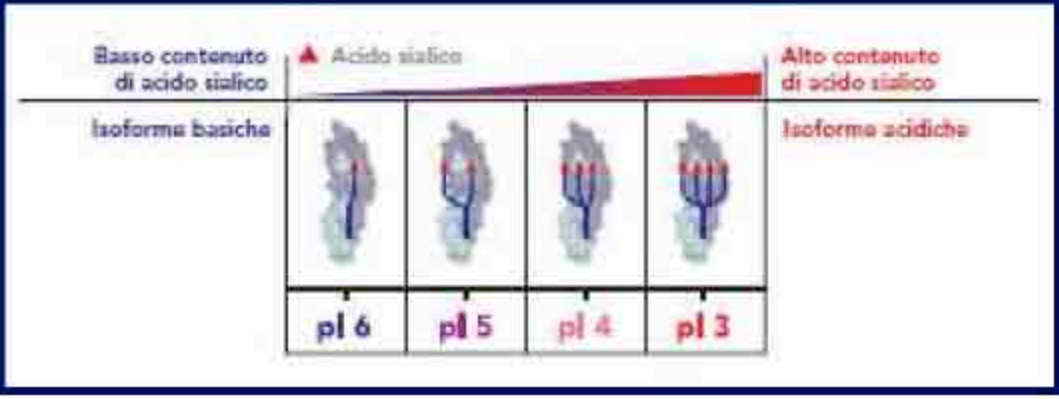


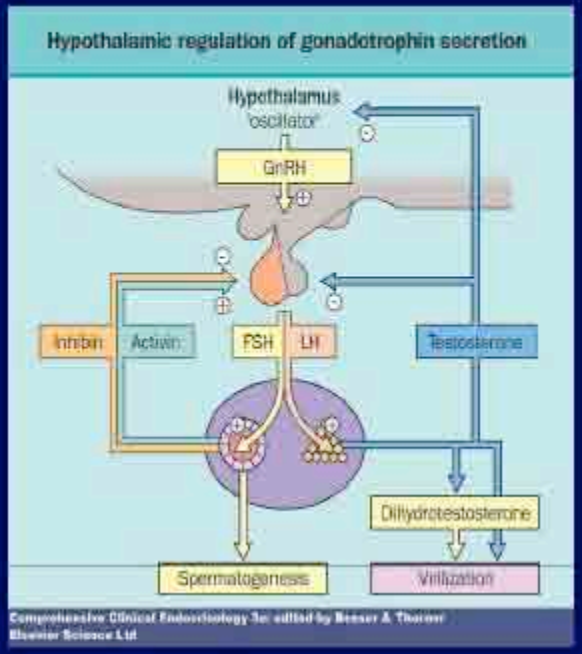
Ogni subunità di FSH possiede due siti di glicosilazione su cui si legano catene di oligosaccaridi

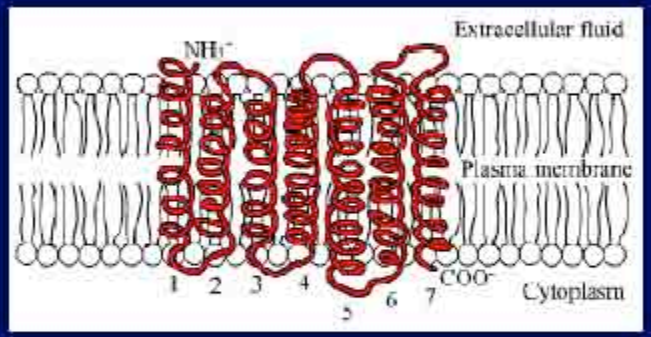
Ciascuna catena è composta da differenti tipi di monosaccaridi che possono o non possono terminare con una molecola di ac. sialico

ISOFORME DELL'FSH A DIVERSA ATTIVITA' BIOLOGICA

- Si distinguono per PI e pH
- L'ac. sialico terminale della catena dei carboidrati determina la clearance metabolica e di conseguenza la sua attività
- Molecole molto glicosilate con ac. sialico sono metabolizzate più lentamente ma hanno meno affinità per il recettore





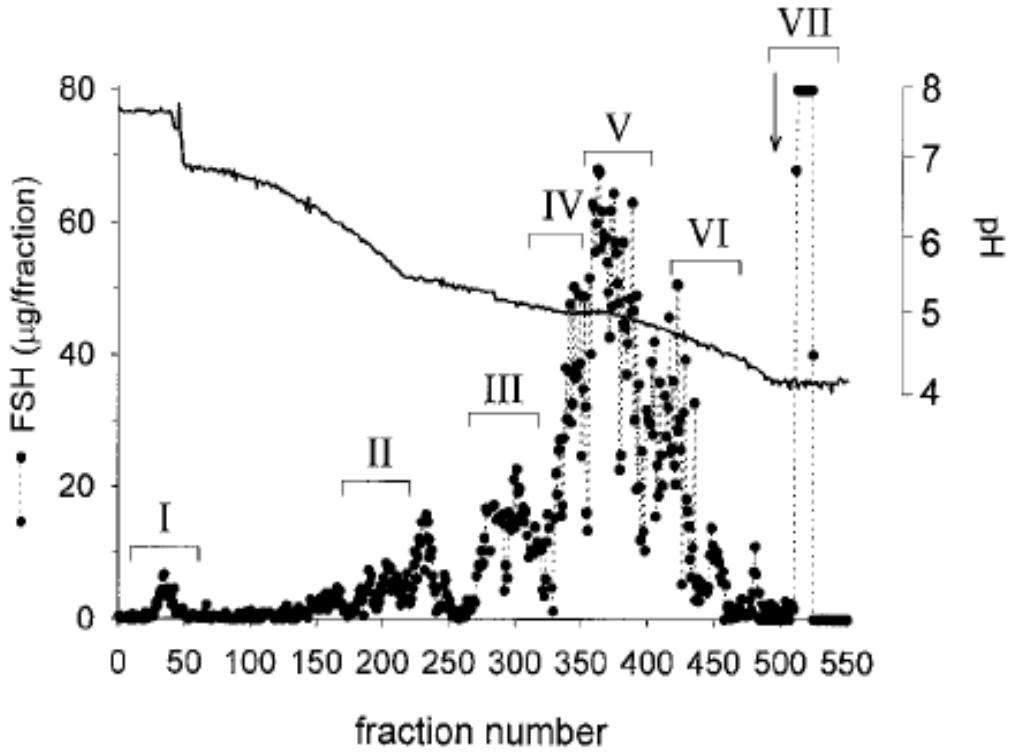


- **Alterazioni nel profilo delle isoforme dell'FSH**
- Mutazioni nella sequenza aminoacidica del recettore per l'FSH

Differential effects of the charge variants of human follicle-stimulating hormone

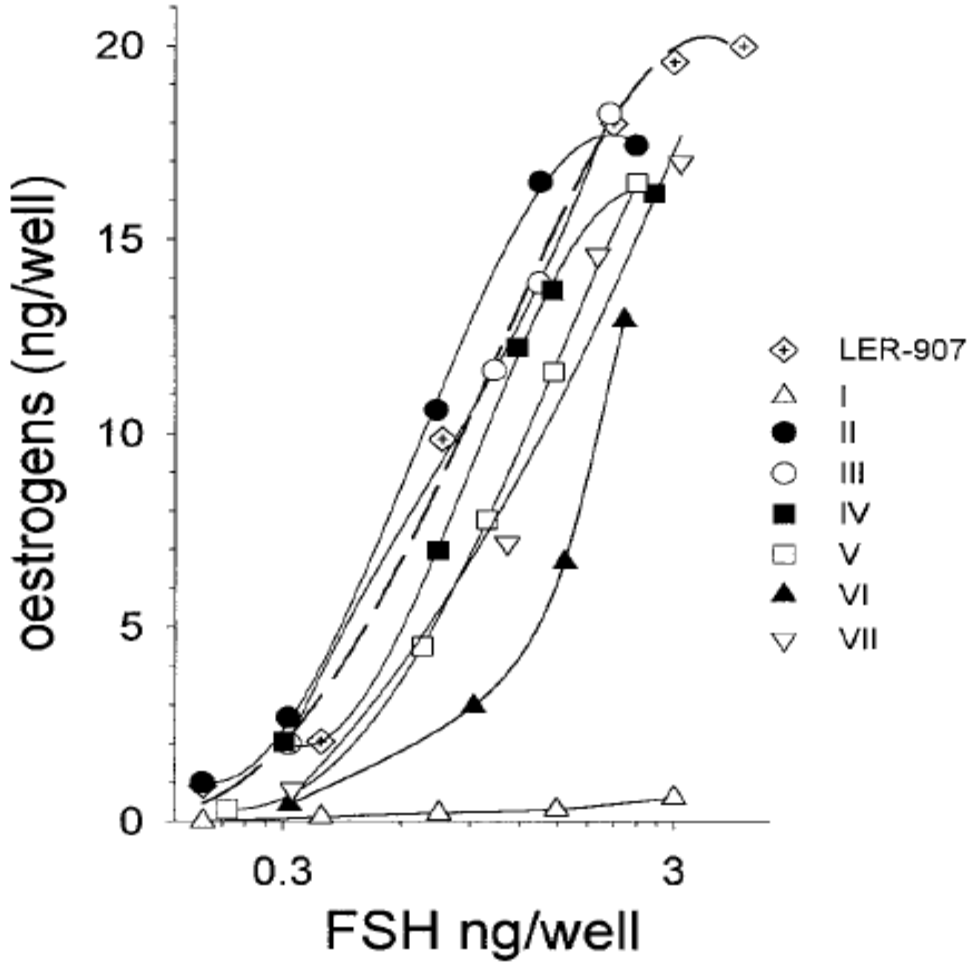
C M Timossi[1,2], J Barrios-de-Tomasi[2], R González-Suárez[3], M Celeste Arranz[3], V Padmanabhan[4], P M Conn[5] and A Ulloa-Aguirre[2,5]

J Endocrinol, 2000



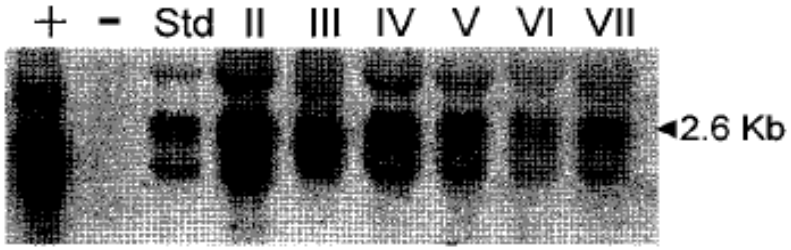
	Isoform						
	I	II	III	IV	V	VI	VII
pH	>7·10	6·60–6·20	5·47–5·10	5·06–4·60	4·76–4·12	4·05–3·82	<3·80
B/I	—	1·24[a]	0·90[b]	0·76[c]	0·62[d]	0·37[e]	0·49[f]
S.D.		0·05	0·04	0·02	0·04	0·04	0·03

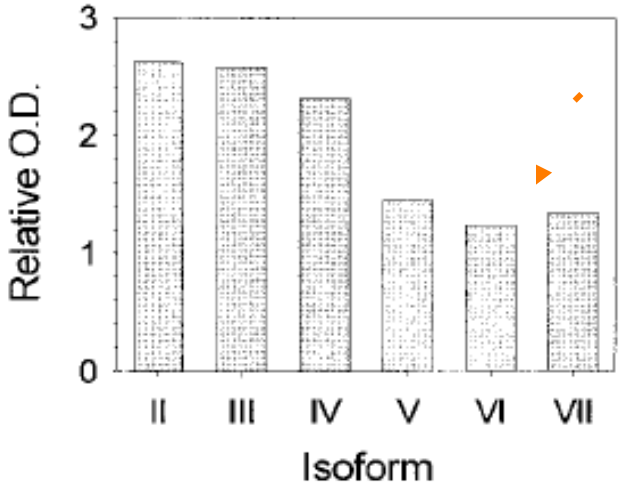
[a–f]Significant differences ($P<0·05$) among isoforms (one-way analysis of variance and Bonferroni protected t tests).



A

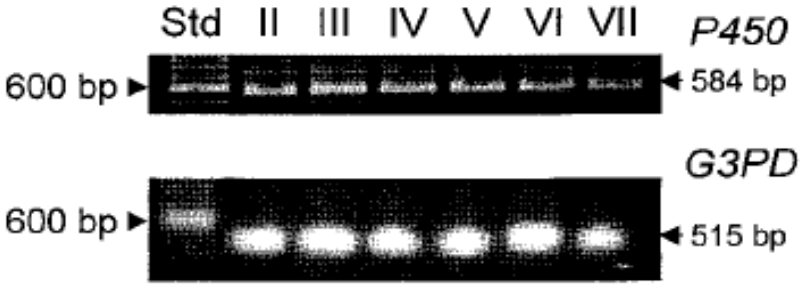
Cytch P450 mRNA expression

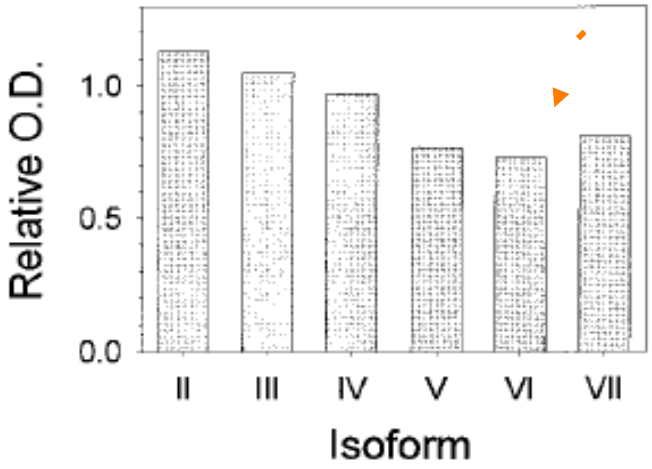


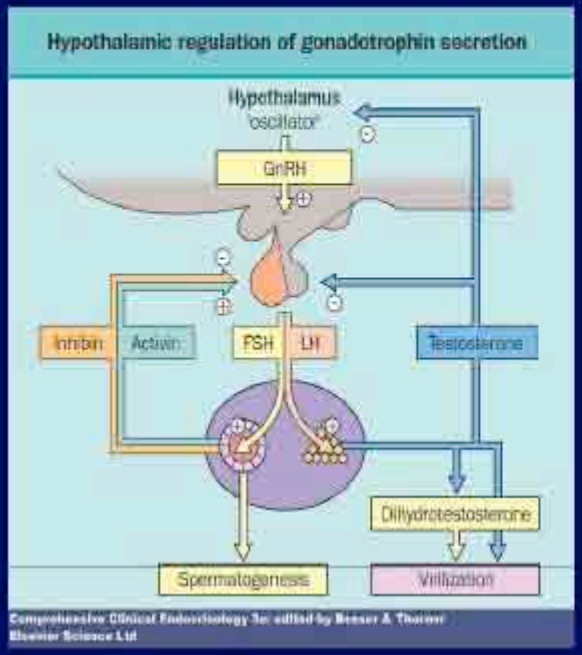


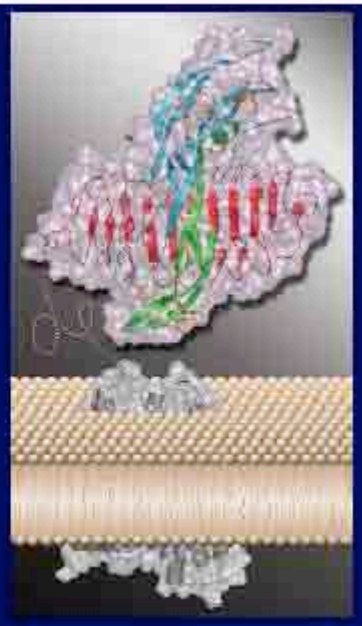
B

Cytch P 450 and G3PD PCR expression



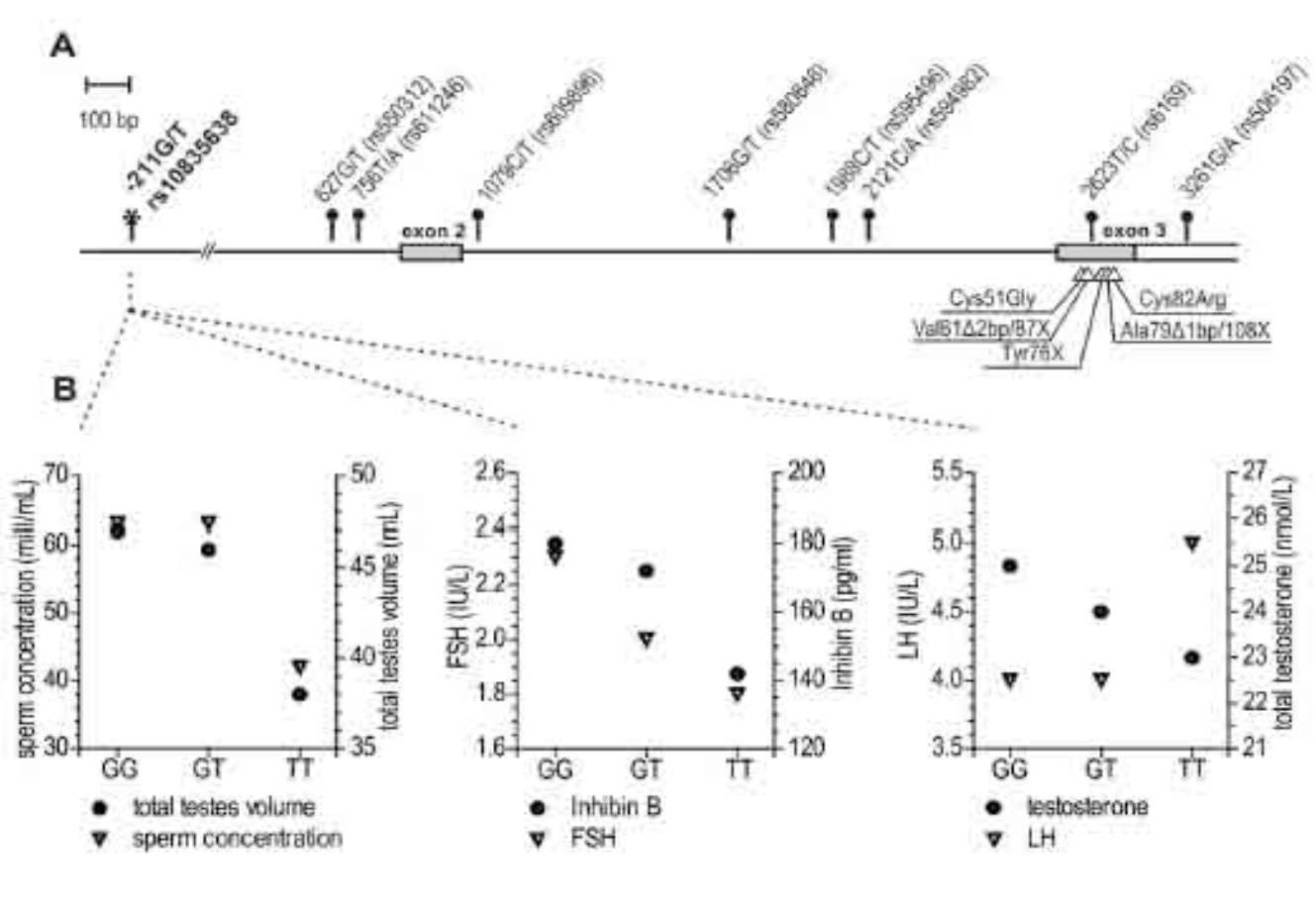




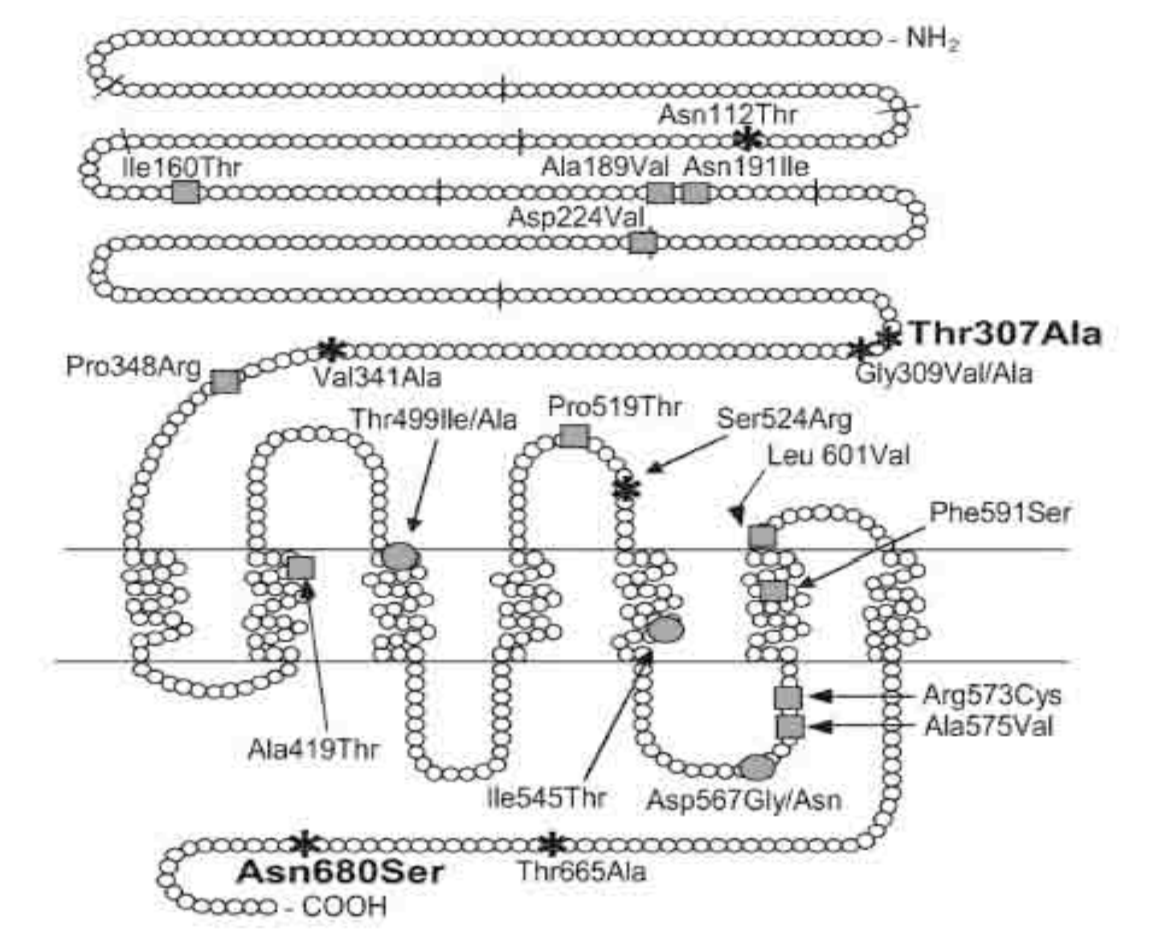


- Mutazioni nella sequenza aminoacidica dell'FSH
- **Mutazioni nella sequenza aminoacidica del recettore per l'FSH**

Genetic variation in the FSHB gene



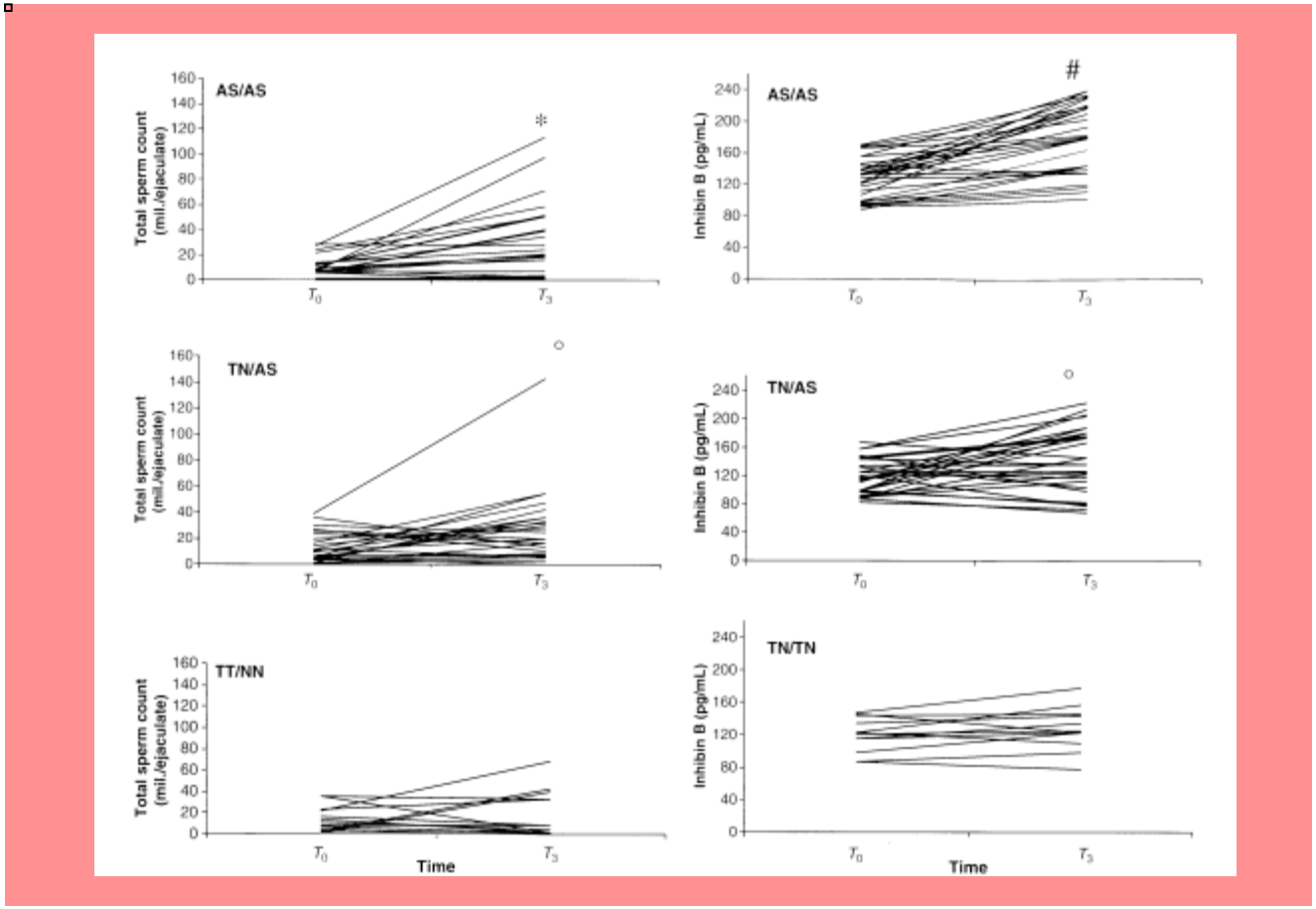
Ferlin A Fert Steril 2011



The distribution of currently known functional polymorphisms, and activating and inactivating mutations across the human FSHR gene. The FSHR exon boundaries are marked with short bars striking through the protein sequence. **Greycircles** depict the activating, **greysquares** inactivating mutations, and the **asterisks** the polymorphisms. The two polymorphisms Thr307Ala and Asn680Ser with currently known pharmacogenetic significance and exhibiting linkage disequilibrium in most populations are marked in bold. An additional polymorphism that has been indiated to have pharmacogenetic potential is FSHR–29G/A located in 5′-untranslated region and thus, not presented in this figure.

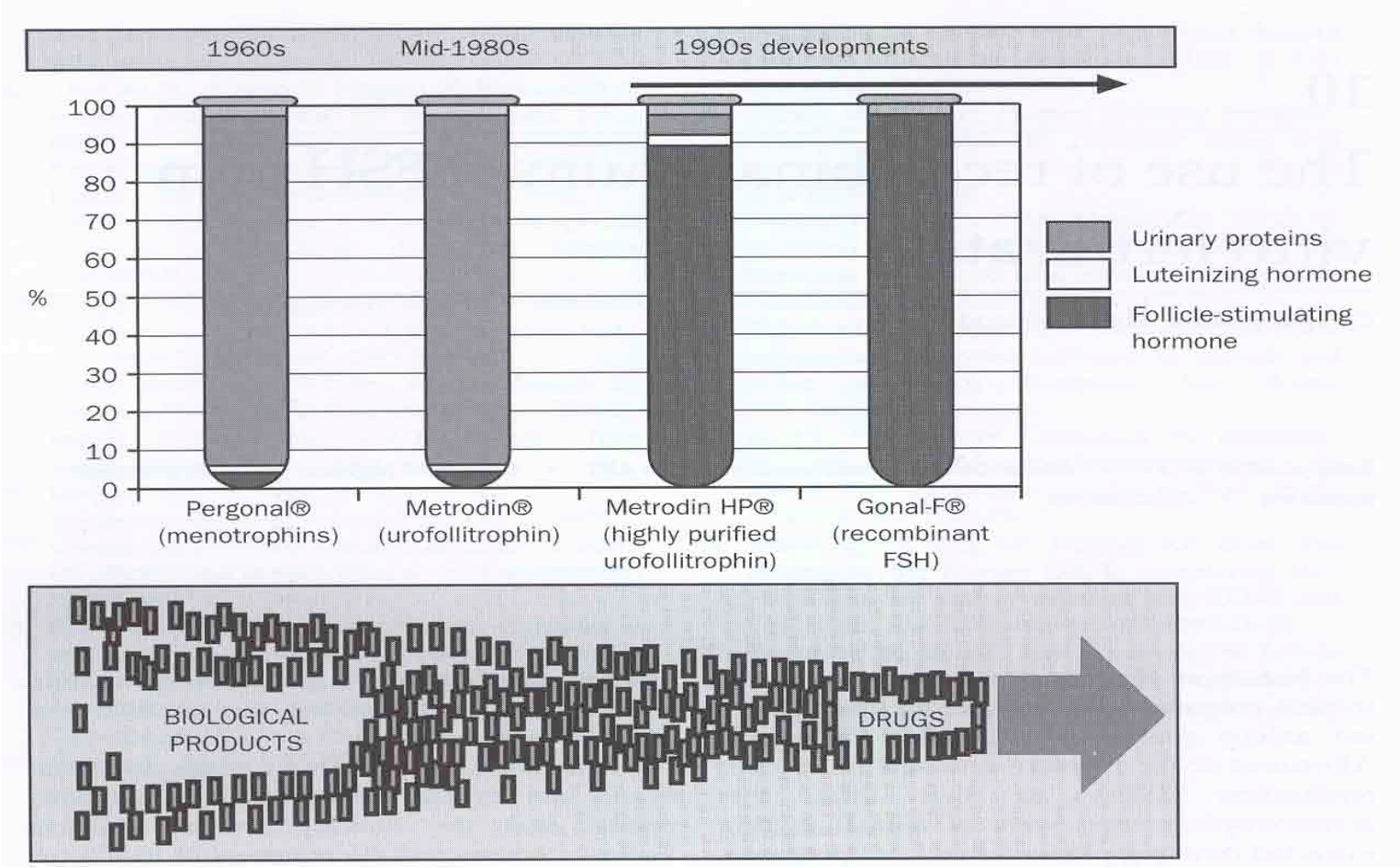
La differente risposta alla terapia con FSH dei pazienti oligozospermici con polimorfisomo del recettore FSH e normali livelli sierici di FSH

(Selice R et al IJA, 2011)



*p< 0.005;# p>0.001; °p>0.05

THE EVOLUTION OF FSH PREPARATIONS



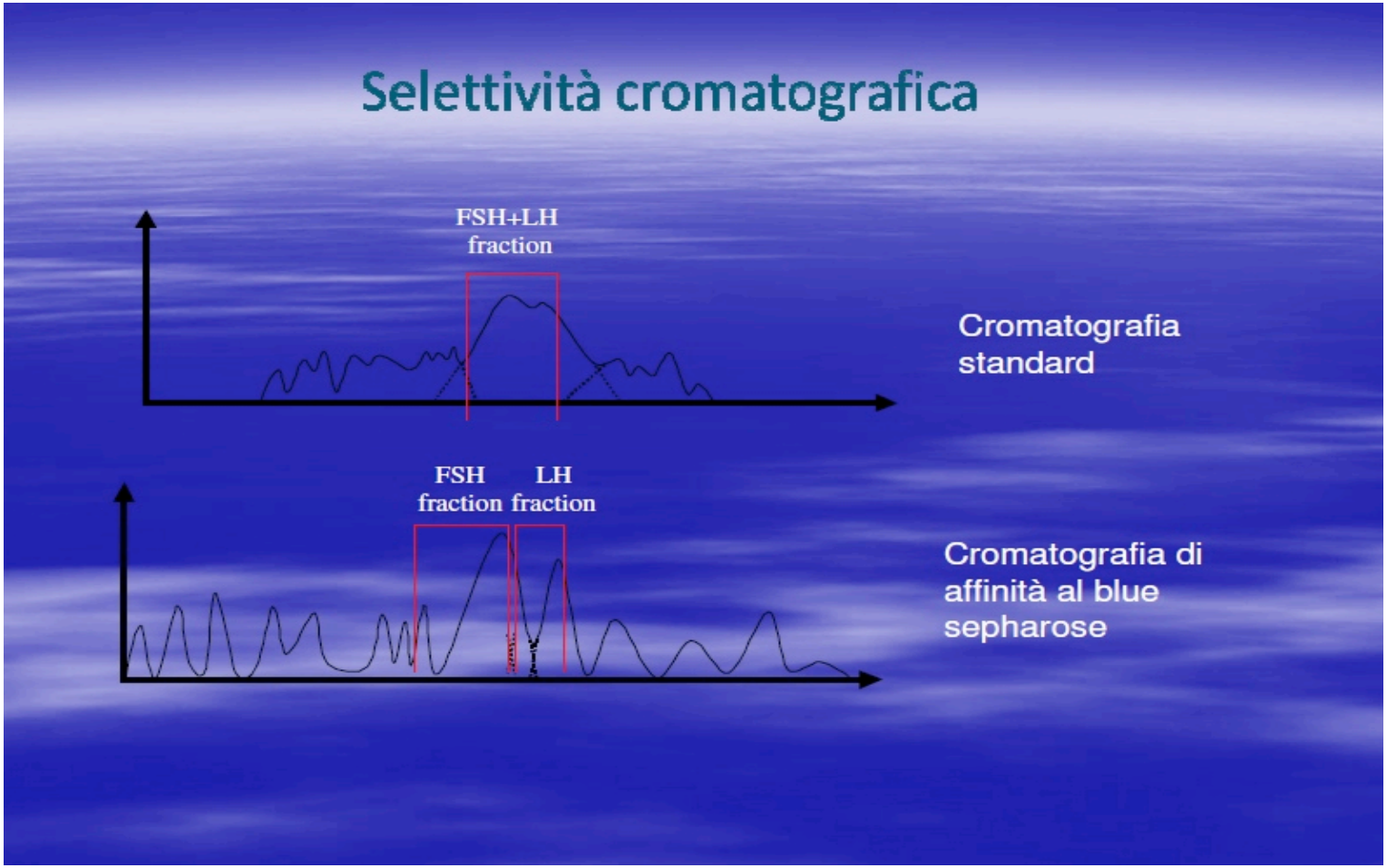
Il Mercato

PRODOTTO	AZIENDA	CONTENUTO	MOLECOLA	DATA DI LANCIO	PREZZO €
GONAL F	MERCK SERONO	75 UI rFSH 150,300,450,900,1050	FOLLITROPINAα DA DNA RICOMBINANTE	Ottobre '95	40,61 .. 564,86
PUREGON	SCHERING PLOUGH ORGANON	50 UI rFSH 100,300,600	FOLLITROPINAβ DA DNA RICOMBINANTE	Maggio '96	27,50 … 489,30
MEROPUR	FERRING	75UI FSH + 75 UI LH 10 FIALE	MENOTROPINA	Aprile 2006	279,71

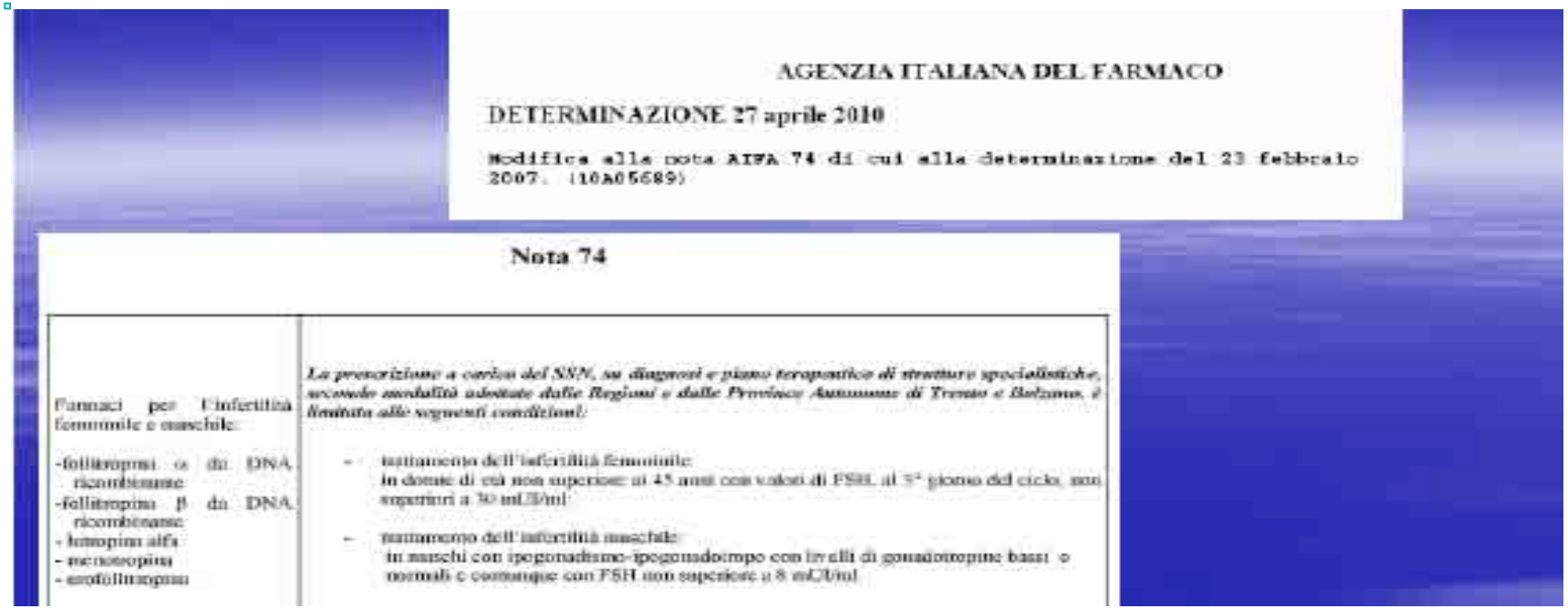
FSH-HP

Fostimon 10 fiale 75 UI FSH: € 145.22

FSH-HP (Fostimon-IBSA)



FSH e Prescrivibilità



AGENZIA ITALIANA DEL FARMACO

DETERMINAZIONE 27 aprile 2010

Modifica alla nota AIFA 74 di cui alla determinazione del 23 febbraio 2007. (10A05689)

Nota 74

Farmaci per l'infertilità femminile e maschile: -follitropina α da DNA ricombinante -follitropina β da DNA ricombinante - lutropina alfa - menotropina - urofollitropina	*La prescrizione a carico del SSN, su diagnosi e piano terapeutico di strutture specialistiche, secondo modalità adottate dalle Regioni e dalle Province Autonome di Trento e Bolzano, è limitata alle seguenti condizioni:* – trattamento dell'infertilità femminile: in donne di età non superiore ai 45 anni con valori di FSH al 3° giorno del ciclo non superiori a 30 mUI/ml – trattamento dell'infertilità maschile: in maschi con ipogonadismo-ipogonadotropo con livelli di gonadotropine basse o normali e comunque con FSH non superiore a 8 mUI/ml

Gli studi ci confronto tra FSH ricombinante o urinario, sono stati soggetti a meta-analisi e di farmaco-economia con risultati non conclusivi

(3 crit di appropiratezza terapia andrologica Quaderni del Ministero della Salute, 2012)

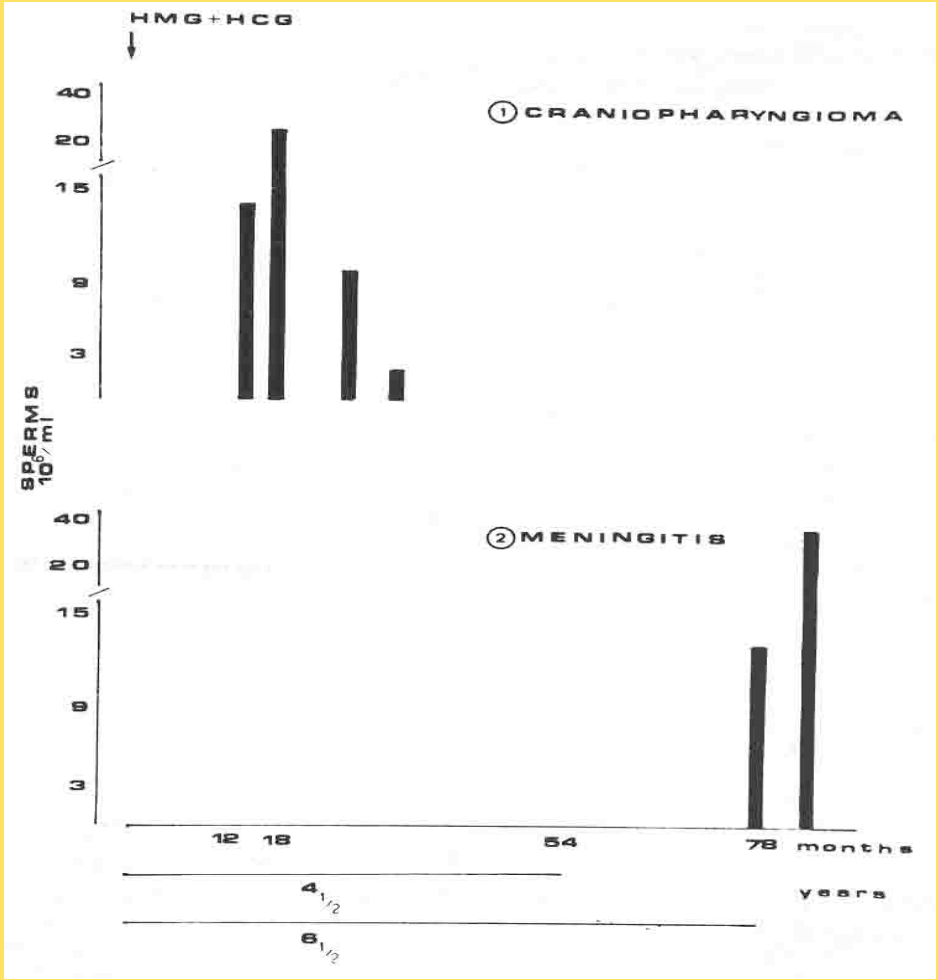
Beta HCG in commercio

- **Gonasi** (gonadotropina di sintesi) con fiale da 250, 1000, 2000, 5000 e 10000 UI;
- **Pregnyl** (gonadotropina estrattiva) con fiale di 1500 e 5000 UI.
- **Ovitrelle** (HCG ricombinante; 250 mcgr/fl) ha un costo più elevato e (come da scheda tecnica) non ha indicazioni nel maschio.

Fattori prognostici di fertilità

RECOVERY OF FERTILITY IN HYPOGONADOTROPIC MEN

(Abbaticchio G. et al, 1985)

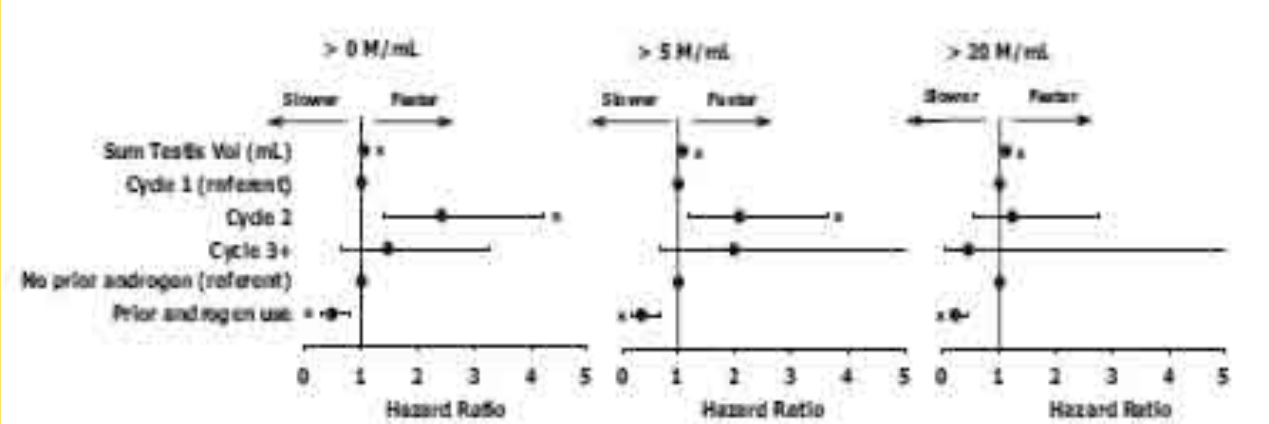


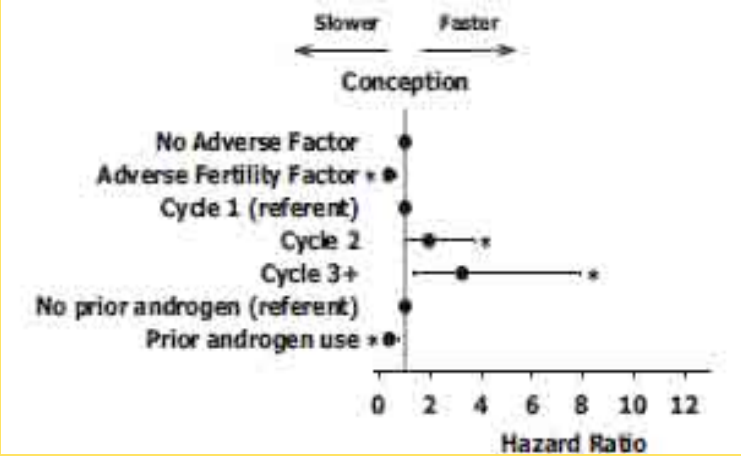
ORIGINAL ARTICLE
Endocrine Care

Induction of Spermatogenesis and Fertility during Gonadotropin Treatment of Gonadotropin-Deficient Infertile Men: Predictors of Fertility Outcome

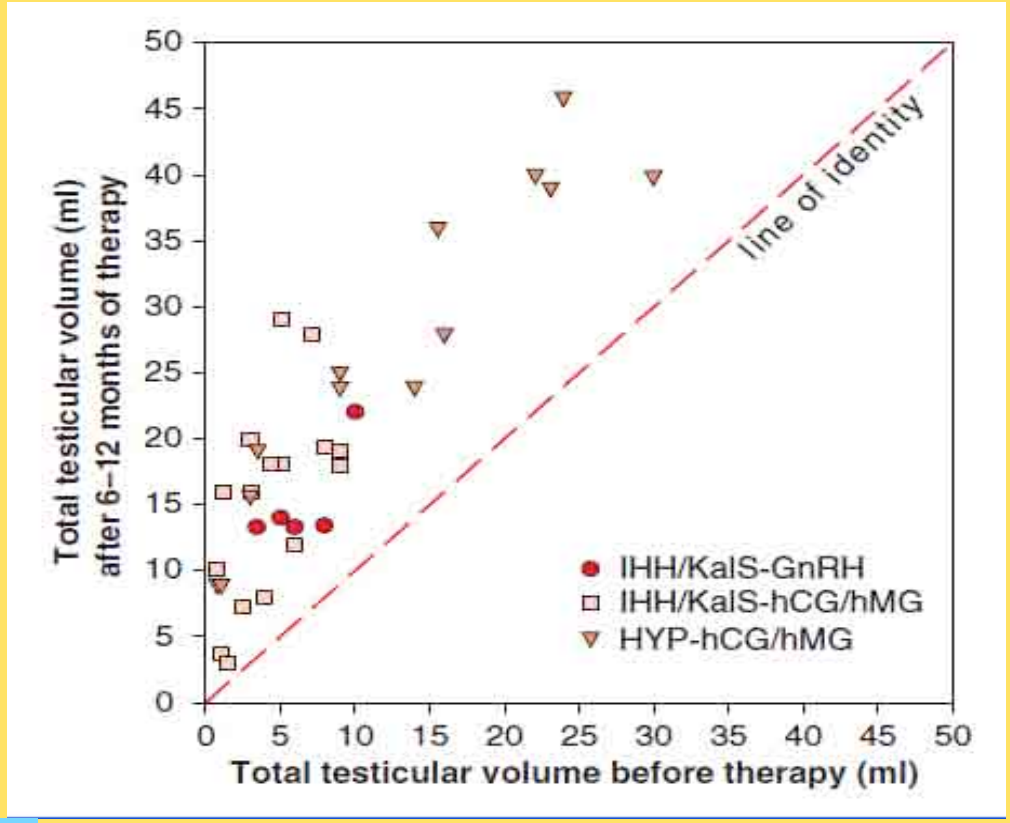
JCEM,2009

Peter Y. Liu, H. W. Gordon Baker, Veena Jayadev, Margaret Zacharin, Ann J. Conway, and David J. Handelsman





Relazione tra volume testicolare iniziale e volume raggiunto dopo la terapia con BHCG/FSH



H.M. Behre et al. 2010

J Assist Reprod Genet 2014
DOI 10.1007/s10815-014-0221-4

GENETICS

Could androgen receptor gene CAG tract polymorphism affect spermatogenesis in men with idiopathic infertility?

V. A. Giagulli · M. D. Carbone · G. De Pergola · E. Guastamacchia · F. Resta · B. Licchelli · C. Sabbà · V. Triggiani

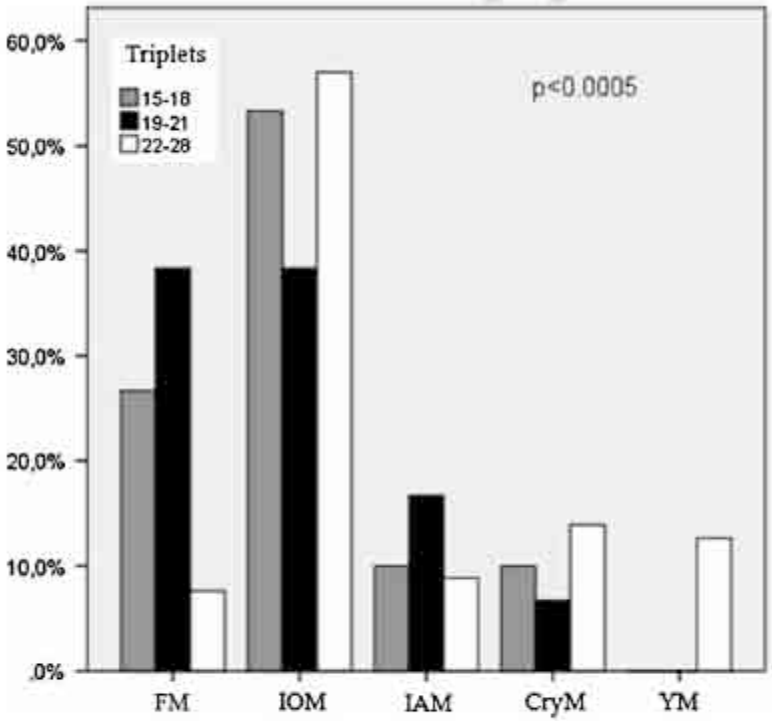


Fig. 1 The distribution frequency of fertile participants (FM), idiopathic oligozoospermic men (IOM), idiopathic azoospermic male(IAM), ex-cryptorchid men (CryM) and subjects with Yq microdeletions (YM). $P=<0.0005$ from chi-square test

Table 3 Different subgroups of CAG repeats length versus clinical characteristics, seminal parameters and endocrine plasma levels in all of fertile and infertile men with idiopathic infertility taken together

	Fertile subjects and men with idiopathic infertility			
CAG length	n 15–18 (n 37)	n 19–21 (n 72)	n 22–28 (n 62)	*p value*
Età (yrs)	33.3±7.2	33.5±6.6	33.2±6.7	0.97
TS (ml)	16.4±3.5	17.2±3.6	15.5±2.8	**<0.05**
SV (ml)	2.9±0.5	3.2±0.6	3.1±0.7	0.23
SpC (10^6×ml)	13.5±20.2	19.9±20.2	8.2±11.3	**<0.005**
PM %	8.8±7.9	9.9±7.9	5.8±5.7	**<0.01**
IM %	60.8±31.1	55.2±29.3	65.3±30.6	0.15
FSH (mU/l)	10.1±9.0	8.5±6.3	10.5±7.8	0.30
LH (mU/l)	6.3±2.6	6.6±3.0	7.1±3.0	0.39
T (nMol/l)	16.6±3.3	17.8±3.3	16.7±3.7	0.12
InhB (pg/ml)	129.6±60.1	149.7±57.3	104.6±45.8	**<0.005**
T/LH	3.1±1.7	3.6±2.5	3.0±2.2	0.33
InhB/FSH	28.6±34.1	31.9±9.1	18.9±24.7	**<0.05**

p value from ANOVA test on different subgroups of CAG repeats length. Statistically significant *p* values are in bold. Legenda: see Tables 1 and 2

Effectiveness of Gonadotropin administration for spermatogenesis induction in hypogonadotropic hypogonadism: a possible role of Androgen Receptor CAG repeat polymorphism and therapeutic measures

Tab n.1 Clinical characteristics, sperm, biological and hormonal parameters in PRHH, PSHH and CG

Clinical characteristics	CG (n 35)	PRHH (n 12)	PSHH (n 11)
Age* (yrs)	36 (32-43)	28 (24-34)^c	36 (34-46)
BMI* (kg/m^2)	26(24-28)	24 (23-26)	26(25-29)
TS* (ml)	20 (18-22)	5 (4-6)^c	16(13-16)^b
Sperm parameters			
Volume (ml)	3.3±0.5	0.3±0.2^c	0.8±0.5^c
Count (10^6/ml)	46.2±11.5	0.00	0.00
Biological and hormonal parameters			
CAG* n	20 (9-22)	21(20-25)	21(20-23)
FSH (UI/L)	7.4±1.8	1.0±0.39^c	1.51±0.5^c
LH (UI/L)	6.5±1,5	1.5±1.16^c	1.2±0.5^c
IB (pg/ml)	212,2±30.5	51.8±23.4^c	86.4±36.7^c
T (nM/L)	20.25±3,5	3.0±1.1^c	3.5± 0.9^c

Entries are means ± SD or * medians (interquartile 25th - 75th percentile) for normally or non-normally distributed variables, respectively.
Refer to the test for biological, hormonal parameters and subject groups abbreviations.
a =p < 0.05; b= p < 0.01; c = p < 0.001 compared to CG.

Giagulli et al, EMID-DT,2011

Effectiveness of Gonadotropin Administration for Spermatogenesis Induction in Hypogonadotropic Hypogonadism: A Possible Role of Androgen Receptor CAG repeat Polymorphism and Therapeutic Measures

V.A. Giagulli[1,#,*], V. Triggiani[1], G. Corona[2,§], M.D. Carbone[3,#], E. Tafaro[1], B. Licchelli[1], F. Resta[4], C. Sabbà[4], M. Maggi[2] and E. Guastamacchia[1]

[1]*Endocrinology and Metabolic Diseases, University of Bari;* [2]*Andrology Unit, Department of Clinical Physiopathology, University of Florence;* [3]*Institute of Clinical and Hormonal Research, Foggia;* [4]*Rare Diseases Center, University of Bari;* [5]*Biomedical Research Association "Guglielmo Telesforo", Foggia;* [§]*Endocrinology Unit, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy*

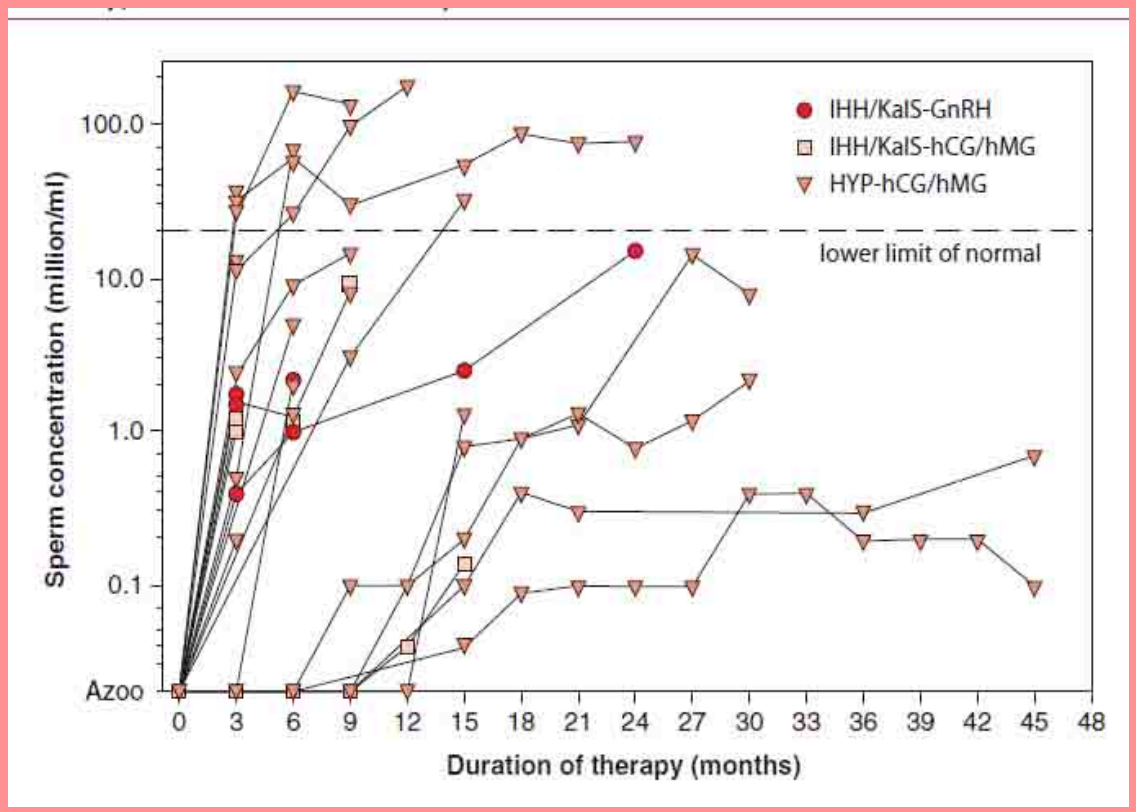
Table 4. **Age, testis size (TS), CAG number and hormonal parameters of HH men subdivided in 2 groups according to the months' time for reaching complete spermatogenesis (C-Sp).**

	C-Sp < 12 Months (n 11)	C-Sp > 12 Months (n 12)
Age * (years)	35,5 (32-40)	27 (22-44,5)
TS* (ml)	16 (12-16)	12 (10,5-14,5)[a]
CAG* n	20 (19-22)	23 (20-25)[a]
T (nM/L)	15.1±3.6	15.9±2.9
IB (pg/ml)	178.4±25.5	157.6±16.8

Entries are means ± SD or * medians (interquartile 25th - 75th percentile) for normally and non-normally distributed variables, respectively. Refer to tests and tab. n1 for hormonal abbreviations.

a = $p < 0.05$ compared to HH group who obtained the C-Sp within 12 months.

Induzione della spermatogenesi in HH in rapporto alla durata della terapia



H.M. Behre et al. 2010

Prepubertal hypogonadotropic hypogonadism Conclusions

Gn secretion:
-fetal, postneonatal, prepuberal
-Permanent or temporany
- stressful event
-Metabolic factors

Diversity of:
- pathophysiology
-clinical aspects

Testis responsiveness

Different therapeutic approaches and responsiveness


Thank you for bearing with me!!