IL RITARDO DI SVILUPPO PUBERALE NEL MASCHIO

Follow up e preservazione della fertilità

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ROMA
9__11
NOVEMBRE
2012

1° CORSO NAZIONALE DI AGGIORNAMENTO

Associazione Medici Endocrinologi

I PER[CORSI]AME

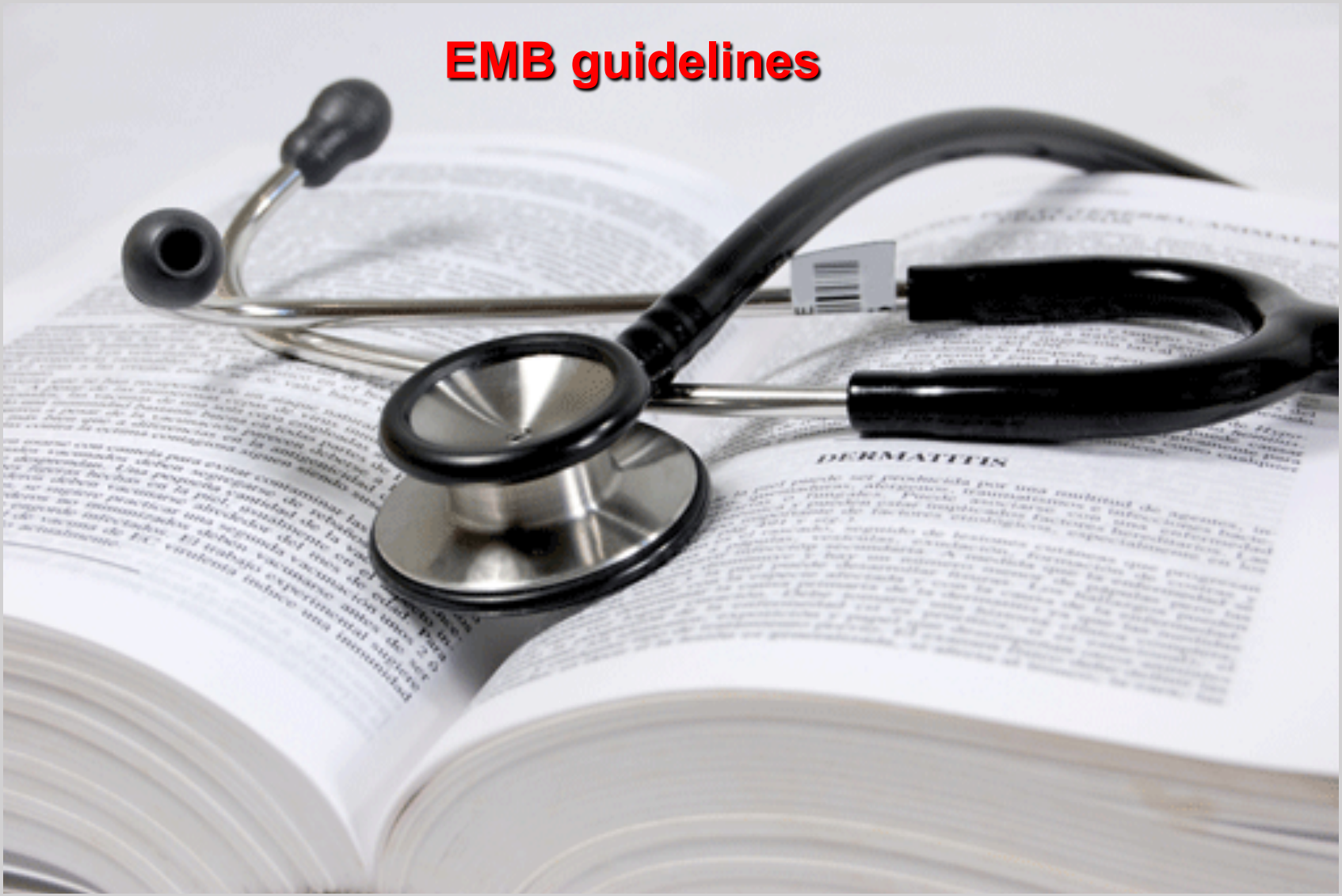
Il Ritardo Puberale

Table 2 Causes of male delayed puberty

- **Reversible** (functional)
  - **Systemic illnesses and other reversible conditions**
    - **Systemic illness**
      - Cystic fibrosis
      - Asthma
      - Inflammatory bowel disease
      - Celiac disease
      - Juvenile rheumatoid arthritis
      - Sickle cell disease
      - Thalassemia
      - Hemosiderosis
      - Chronic renal disease
      - AIDS
      - Malignancies
    - **Excessive energy expenditure, exercise**
    - **Emotional deprivation**
    - **Malnutrition**
    - **Endocrinopathies**
      - Diabetes mellitus
      - Hypothyroidism
      - Hyperprolactinemia
      - Growth hormone deficiency
      - Cushing syndrome
      - Obesity
  - **Constitutional delay of puberty**
  - **Hypogonadotropic (secondary) hypogonadism (10%)**
- **Irreversible** (permanent)
  - **Hypogonadotropic (secondary) hypogonadism (90%)**
  - **Hypergonadotropic (primary) hypogonadism (100%)**

Linee guida ???

Roma,
9-11 novembre 2012



Flow Chart

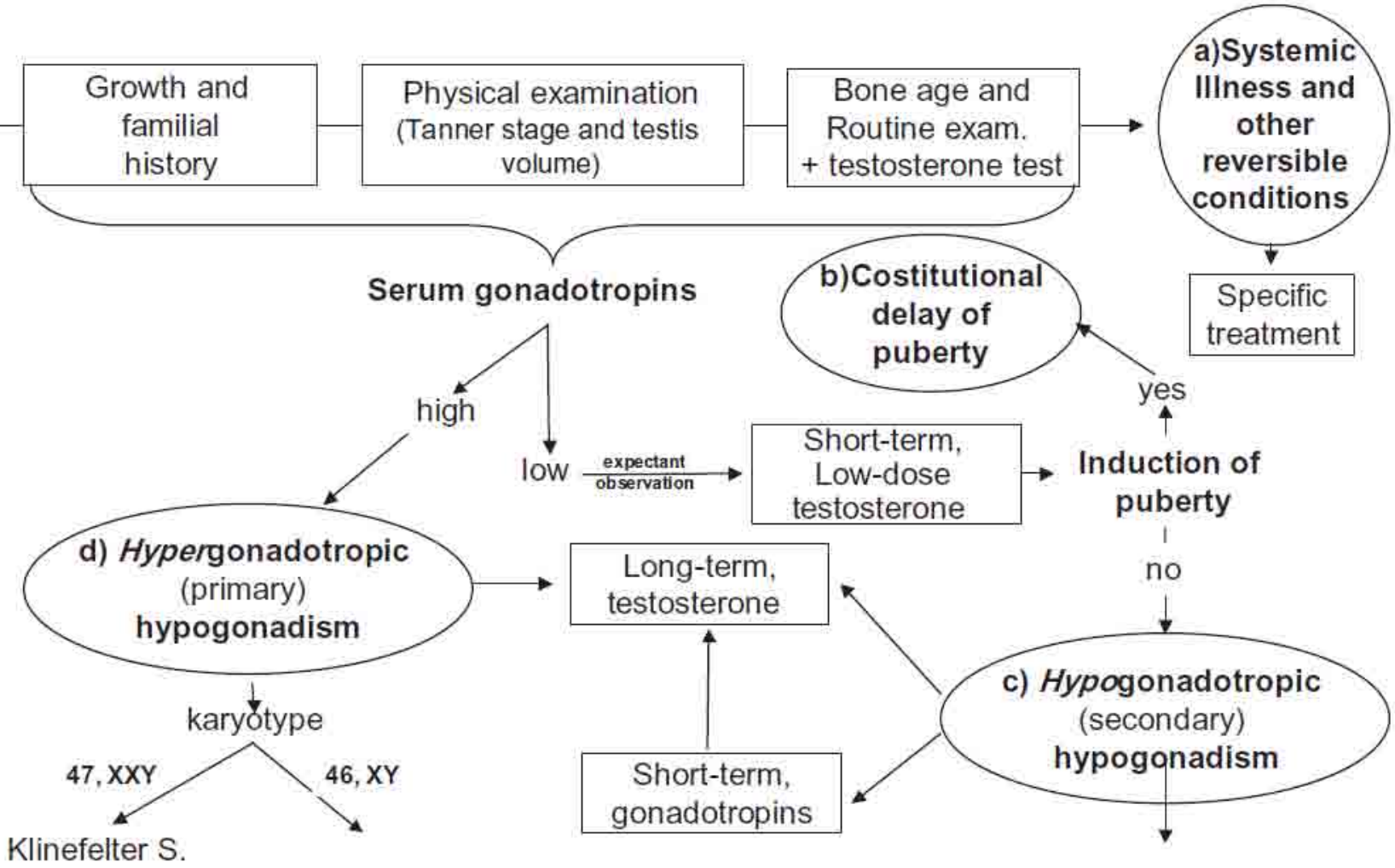


Figure 2 Flow chart of male delayed puberty: delay in onset of secondary sexual development after 14 years. Letters in bubbles correspond to those used in Table 2.

Standard Operating Procedures: Pubertas Tarda/Delayed Puberty—Male

Mario Maggi, MD* and Jaques Buvat, MD†

Roma,
9-11 novembre 2012

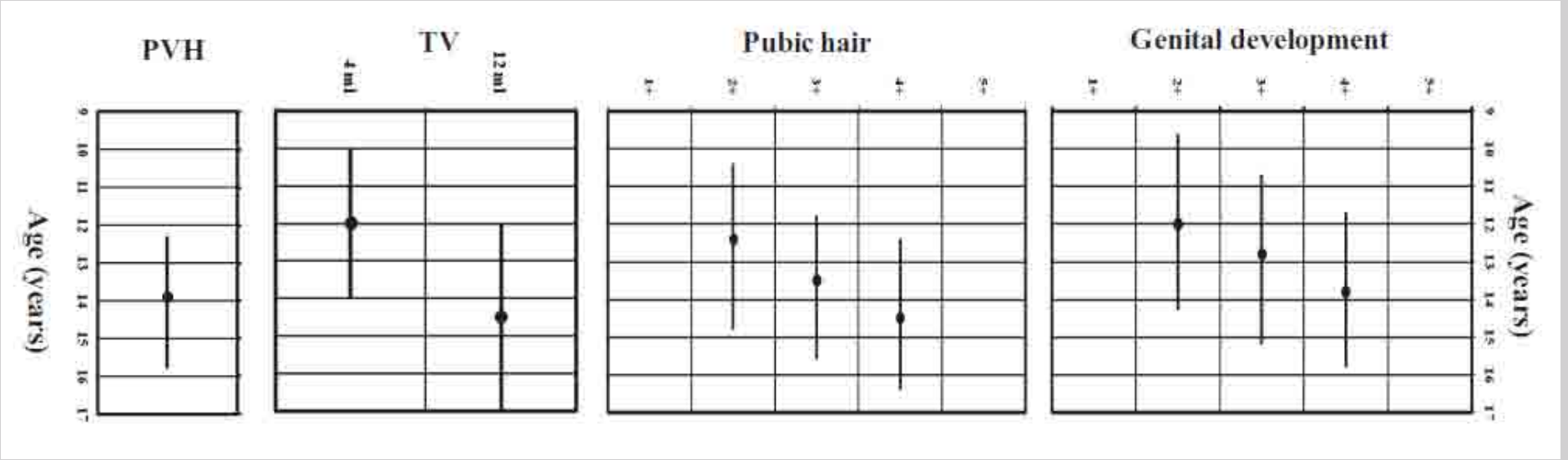


Figure 1 Major physical changes in pubertal boys, according to age. Bars shows standard deviation of the mean (closed circles). TV = testicular volume, PVH = peak height velocity, G = Tunner's stages.

J Sex Med

Cambiamenti puberali

Table 1 Main normal physical and mood changes in pubertal males

Physical changes
Gonadarche: testicle enlargement greater than 4 mL (11.5 years [9.5–13.5])
Pubarche: hair growth in the pubic area (12 years [10–14])
Growth spurts (14 years)
Growth of the penis (measured stretched) from 6.2 to 12.4 ± 2.7 cm
Erections or wet dreams
Deepening of the voice (later stages of puberty)
Appearance of facial hair
Broadening of shoulder muscles, development of chest muscles
Body odor
Pimples or facial breakouts
Mood changes
Development of personal and sexual identity
Interest more often in the opposite sex
Anxiety or excitement about the changes he is going through
Shy, nervousness around girls, or flirtatious with girls
Abstract thinking
Emergence of skills and coping strategies to overcome problems and crises
Growing ability to absorb the perspectives or viewpoints of others
Increased ability of introspection
Establishment of a system of values
Less talkative and open with parents
Increasing autonomy and personal independence
Greater importance of peer relationships

Scopi della Terapia

- Riprodurre gli steps dello sviluppo puberale
- Determinare incremento del Testosterone verso i livelli normali per l'età
- Indurre la fertilità se e quando il paziente la desideri

Le età dell'uomo (Giorgione 1510)

Androgen therapy for delayed male puberty

Geoffrey R. Ambler

Roma,
9-11 novembre 2012

Constitutional Delay of Growth and Puberty (CDGP)

- **Opzioni**
  - Attesa
  - Terapia Androgenica

- **Considerare** :
  - Severità del problema e condizioni associate
  - Aspettative familiari e del paziente
  - **Impatto psicologico**

- **The Oakland Growth Study (1980)** :
  - 16 ragazzi normopuberi e 16 CDGP
  - Follow up fino all'età adulta
  - Adolescenza : inadeguatezza e scarsa accettazione sociale
  - In alcuni casi persistenza sino all'età adulta
- **Crowne (1990)** :
  - CDGP non trattata causa di insuccessi scolastici e lavorativi

Current Opinion in Endocrinology, Diabetes & Obesity 2009, 16:232–239

- Statura finale :
  - Crowne 1990 :
    - 2 cm in meno della statura attesa
    - 6.5 cm in meno della statura media dei genitori
  - Albanese (1993) :
    - Deficit di 0.5 DS da statura attesa
    - Deficit di 1.4 DS rispetto statura media dei genitori
  - Wehkalampi (2007) :
    - Progressivo peggioramento della curva di crescita 3-9 anni predittivo di ridotta statura finale

Terapia sostitutiva con androgeni

- Atleti (doping)
- Pazienti con disturbi della coagulazione
- Cefalea o epilessia sensibile agli steroidi sessuali
- Cardiopatia, insufficienza renale o grave ipertensione per ritenzione idrica e sodio
- Apnee notturne

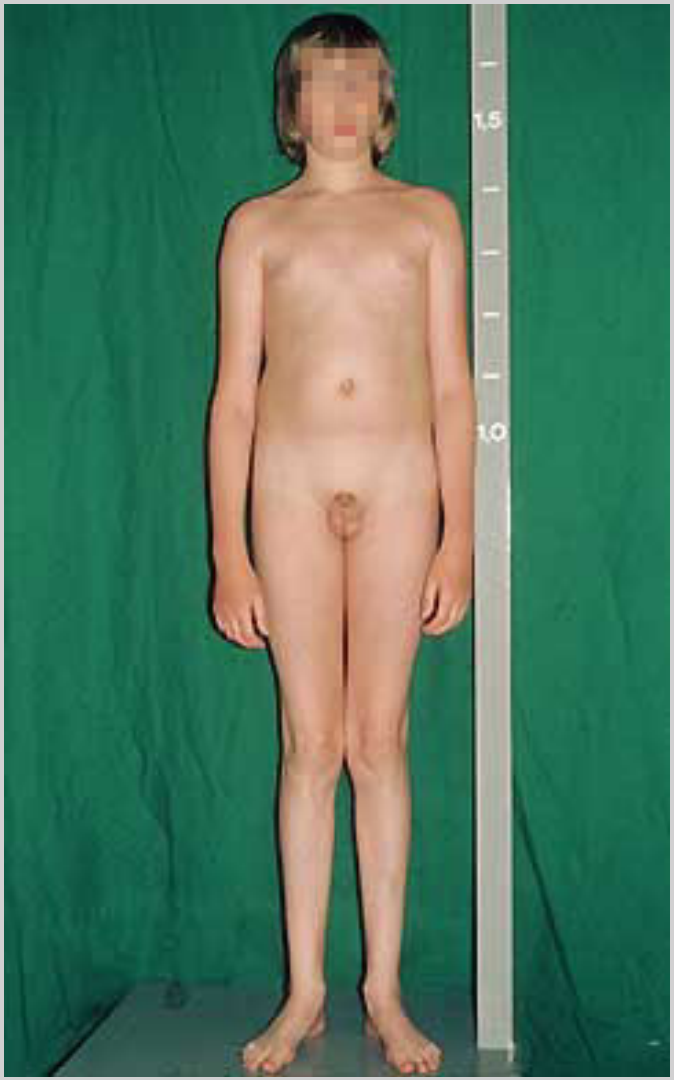
CDGP : Trattamento e follow up

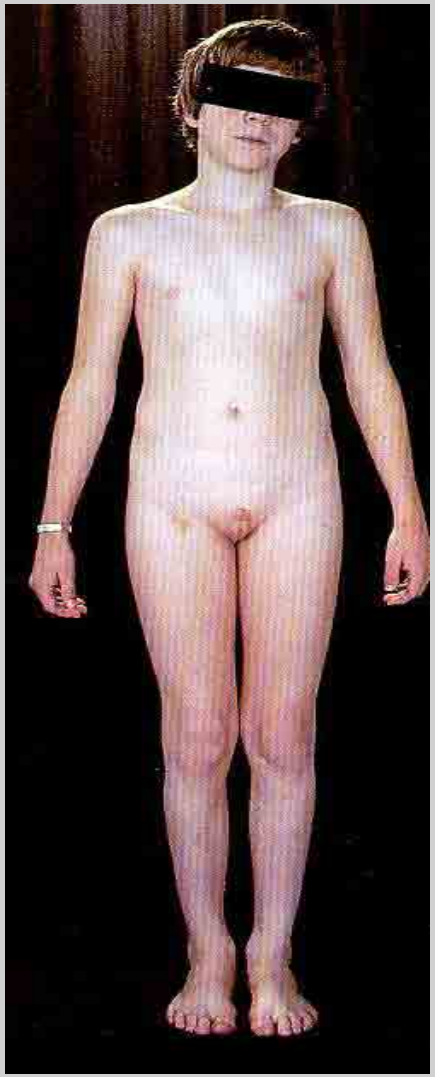
- Periodo di osservazione dipende dal “distress” del paziente (e famiglia!)
- TRT “short-term” no effetti su statura finale **(EMB level 1a)**
- TRT non determina saldatura epifisi **(EBM level 1b)**
- Durata : da 3 a 6 mesi
- Sospensione ed attesa per 3-6 mesi
- Ripresa se non effetti (2° ciclo) **(EBM level 1b)**

- Rivalutazione a 1 anno

H.H.

Roma,
9-11 novembre 2012





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*

Roma,
9-11 novembre 2012

9 HH

15 controlli

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

Groups	Diagnosis	Case no.	Age (years)	BMI (kg/m^2)	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 ± 3.8	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 = luteinizing hormone; SHBG = sex hormone binding globulin; T = total testosterone.

J Sex Med 2011;8:3471–3478

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

Testosterone Undecanoato (TU) orale 120 mg/die per 3 mesi seguito da TU i.m. per tot. 27 mesi
Dosaggio di T dopo 3 mesi per TU orale
Dopo 3, 12, 18 e 24 mesi per TU i.m.

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.

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

Table 3 Serum T, free T, BioT, and SHBG after oral TU (third month) and parenteral TU (8th, 12th, 18th, and 24th months) therapy

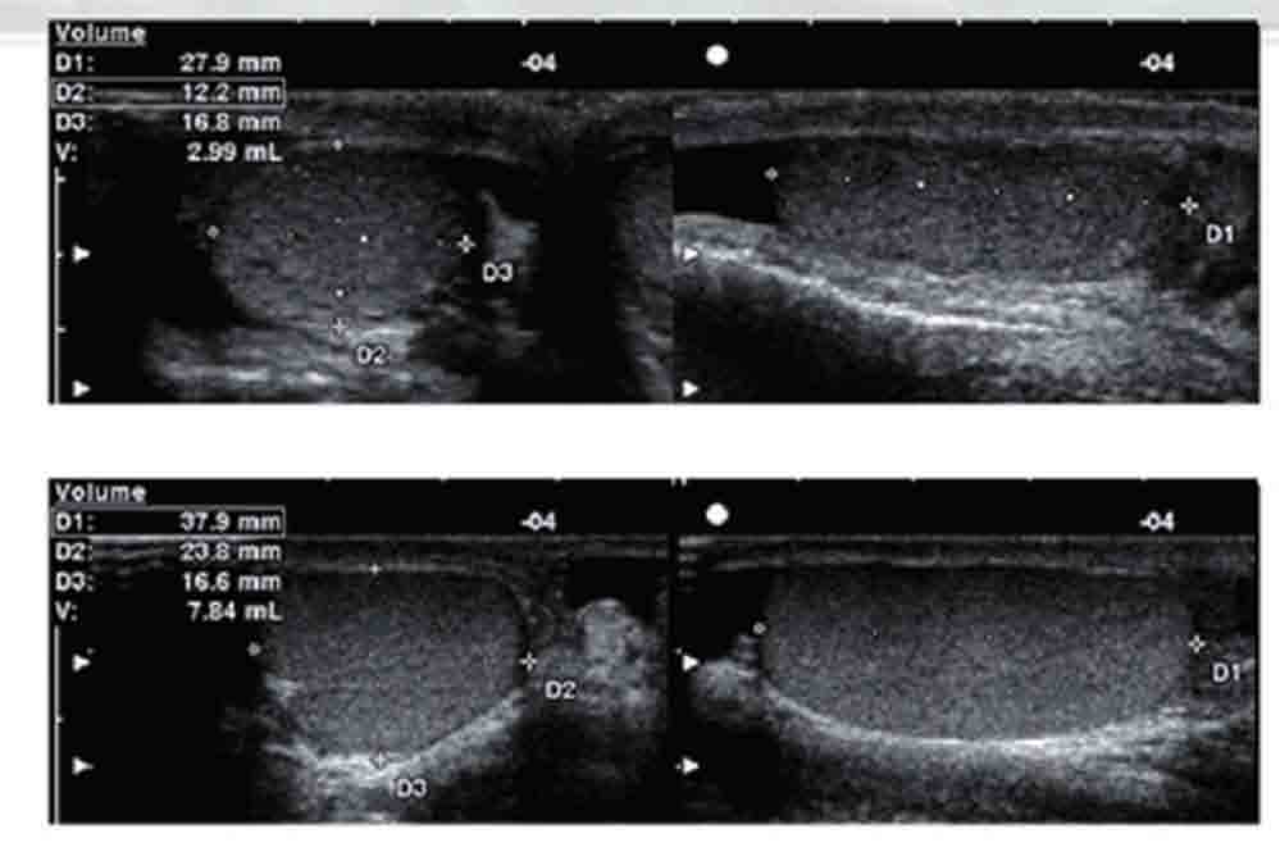
	Basal	3rd month	8th month	12th month	18th month	24th month
T (ng/dL)	127.2 ± 29.2	175.8 ± 75.7	241.9 ± 81.1*	350.7 ± 69.9**	380.7 ± 76.3***	460.6 ± 79.7***
SHBG (nmoL/L)	53.7 ± 3.8	49.5 ± 3.9	47.5 ± 2.5*	45.4 ± 2.9**	43.9 ± 2.9***	40.2 ± 2.8***
Free T (ng/dL)	1.7 ± 0.39	2.58 ± 0.28*	3.67 ± 0.12**	5.76 ± 2.1***	6.43 ± 2.9***	8.02 ± 2.8***
BioT (ng/dL)	40.01 ± 9.27	60.5 ± 16.5*	86 ± 23*	135 ± 28.9**	151.1 ± 36.1***	167.2 ± 37.4***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (paired *t*-test).
BioT = biologically active testosterone; SHBG = sex hormone binding globulin; T = total testosterone; TU = testosterone undecanoate.

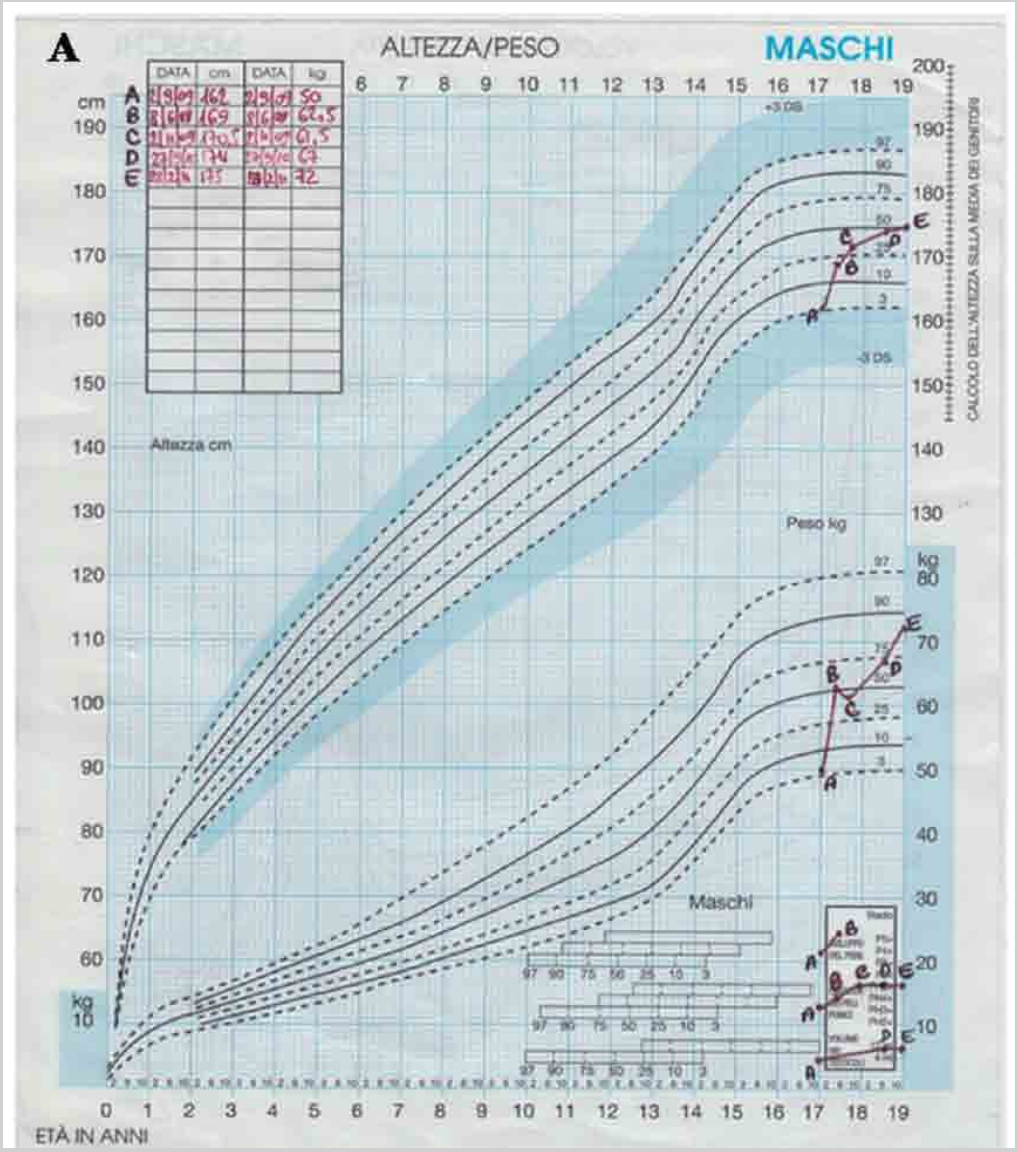
Table 4 Pubertal characteristics and penis length in hypogonadal subjects subdivided in two groups according to number of CAG repeats

	Group no. 1 (no. 6 subjects with CAG N ≤ 24)				Group no. 2 (no. 3 subjects with CAG N > 24)			
	Basal	8th month	12th month	24th month	Basal	8th month	12th month	24th month
T (ng/dL)	115.2 ± 29.7	159.2 ± 35.3	359.8 ± 64.5	455.1 ± 67.1	131 ± 22.4	161.1 ± 19.5	344.8 ± 59.7	488.1 ± 57.9
SHBG (nmol/L)	51.5 ± 4.1	49.0 ± 2.9	42.5 ± 3.3	39.8 ± 3.1	52.9 ± 4.4	52.10 ± 3.0	43.4 ± 4.0	41.0 ± 4.4
FT (ng/dL)	1.60 ± 0.22	2.33 ± 0.30	6.23 ± 2.1	8.40 ± 1.9	2.09 ± 0.4	2.35 ± 0.3	5.9 ± 0.5	9.0 ± 0.4
BioT (ng/dL)	38.2 ± 6.2	54.6 ± 4.8	146.1 ± 33.1	197.1 ± 38.3	49.4 ± 18.9	53.1 ± 16.8	142.8 ± 36.1	215.2 ± 39.2
Pubic hair stages	PH1	PH2	PH3	PH4	PH1	PH2	PH2	PH3
Penis length (cm)	5.50 ± 2.5	7.50 ± 2.8	8.80 ± 2.0	10.80 ± 2.5	5.20 ± 2.8	7.0 ± 2.5	8.20 ± 2.1	9.80 ± 2.9

BioT = biologically active testosterone; CAG = polymorphism Cytosine, Adenine, and Guanine trinucleotide repeats of androgen receptor; FT = testosterone-free fraction; PH = pubic hair; SHBG = sex hormone binding globulin; T = total testosterone.



- Co
  - e,
  - zioni,
  - aggio
- Quando
  - prima, dopo tre e sei mesi dall'inizio della terapia poi ogni 6 mesi
  - Valuta l'adeguatezza della terapia, eventuali effetti indesiderati o dannosi


A
ALTEZZA/PESO
MASCHI
DATA
cm
DATA
kg
A
B
C
D
E
Altezza cm
Peso kg
Maschi
CALCOLO DELL'ALTEZZA SULLA MEDIA DEI GENITORI
+3 DS
-3 DS
97
90
75
50
25
10
3
cm
kg
ETÀ IN ANNI

FOLLOW UP

- Dosaggio del T plasmatico
  - E' il miglior indice dell'appropriatezza delle dosi e modalità di somministrazione
    - Aggiustare la dose e l'intervallo di somministrazione se i livelli non sono soddisfacenti

- Quando
  - prima, dopo tre e sei mesi dall'inizio della terapia poi ogni 6 mesi
    - Alle 0800 e prima della successiva somministrazione iniettiva

FOLLOW UP

- Emocromo
  - Se l'ematocrito > 52 % rivalutare il dosaggio e studiare il paziente per l'ipossia e l'apnea notturna
- Quando ?
  - da effettuare prima, dopo tre e sei mesi dall'inizio della terapia poi ogni 6 mesi
  - E' un buon parametro per gli effetti sull'eritropoiesi e aiuta a ridurre i rischi tromboembolici

FOLLOW UP

- Transaminasi
  - Se aumentate rivalutare le dosi o il farmaco e studiare il paziente per eventuale epatopatia
- Quando ?
  - da effettuare prima, dopo tre e sei mesi dall'inizio della terapia poi annualmente

Enea e Ascanio (Tiepolo 1757)

Roma,
9-11 novembre 2012

Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis

Margaret Zacharin, M.B.B.S.,[a] Matthew A. Sabin, Ph.D.,[a] Veena V. Nair, M.D.,[b] and Preeti Dagabdhao, M.D.[b]

2 gruppi :
hCG
hCG +rFSH

Follow up trimestrale

TABLE 1

Clinical, biochemical, and semen analysis parameters for nine adolescent males with hypogonadotropic hypogonadism (HH) treated with human chorionic gonadotropin (hCG) alone, and nine treated with hCG and recombinant follicle-stimulating hormone (rFSH).

Patient study no.	Treatment type (group)	Decimal age at treatment (y)	Diagnosis	Testicular maldescent +/– associated features	Previous testosterone therapy (duration in mo)	Combined testicular volumes (CTVs) at 0 and 9 mo (mL)	Inhibin B concentration at 6–9 mo (pg/mL)	Testosterone concentration at 9 mo (nmol/L)	Sperm concentration at 6 mo ($\times 10^6$/mL)	Sperm concentration at 9 (and 12 where available) mo ($\times 10^6$/mL)	Percentage motility and abnormal morphology (reported only for counts $> 2 \times 10^6$/mL)
1	hCG (1)	14.6	Craniopharyngioma	No	No	6 and 20	107	17.0	Urine = 0	<1	
2	hCG (1)	14.5	Congenital hypopituitarism	No	No	4 and 11	<10	3.7	Urine = 0	0	
3[a]	hCG (1)	18.0	HH	No	No	4 and 30	35	4.1	0	<1	
4[a]	hCG (1)	15.9	Congenital hypopituitarism	No	No	2 and 14	NA	NA	0	0	
5	hCG (1)	18.1	Congenital hypopituitarism	No	No	4 and 7	114	18.9	0	0	
6	hCG (1)	18.9	Anosmia, Kallmann, HH	No	No	2 and 3	53	27.5	0	0	
7[a]	hCG (1)	19.5	Anosmia, Kallmann, HH	Inguinal hernia	Yes (6)	4 and 6	73.7	10.9	NA	0	
8[a]	hCG (1)	20.0	Congenital hypopituitarism	No	Yes (36)	8 and NA	58.5	26.4	NA	0	
9[a]	hCG (1)	31.0	HH	No	Yes (6)	NA	NA	NA	NA	<0.01	
10	hCG/rFSH (2)	16.0	Craniopharyngioma	No	No	3 and 30	42	30.6	0	1.2	
11	hCG/rFSH (2)	17.9	HH	No	No	4 and 11	31	33.0	2.8	9.5	Motility 12.3% Abnormal 87%
12	hCG/rFSH (2)	18.1	Congenital hypopituitarism	No	No	3 and 16	42	41.0	0.01	5	Motility 20% Abnormal 92%
13	hCG/rFSH (2)	22.4	Anosmia, Kallmann, HH	Yes	No	4 and 16	30	23.0	<2	15 (31)	Motility 15% Abnormal >99%
14	hCG/rFSH (2)	20.9	HH	No	Yes (12)	4 and 18	<10	11.0	0.3	0.7	
15	hCG/rFSH (2)	23.5	Anosmia, Kallmann, HH	No	Yes (24)	4 and 20	79	11.7	4	6	Motility 23% Abnormal 86%
16	hCG/rFSH (2)	19.5	Anosmia, Kallmann, HH	No	Yes (12)	2 and 8	<10	5.4	0	0.2	
17	hCG/rFSH (2)	24.6	Congenital hypopituitarism	Megaureter	Yes (24)	4 and 20	87	33.0	2	1.7 (5)	
18	hCG/rFSH (2)	25.0	HH	No	Yes (6)	2 and 20	87	30.7	<1	7 (23)	Motility 20% Abnormal 98%
19	hCG/rFSH (2)	16.0	HH	Micropenis	No	4 and 50	57	30.1	0.1	0.7	

Note: NA = not available.
[a] Indicates an Indian patient.

Zacharin. Recombinant FSH in hypogonadotropic hypogonadism. Fertil Steril 2012.

RISULTATI

- Gruppo 1, 9 pazienti (solo hCG) :
  - TV mediano da 4 a 11 ml a 9 mesi
  - No spermatozoi a 6 mesi in 6 soggetti
  - < 1 mil/ml in 3 pazienti a 9 mesi

- Gruppo 2, 10 pazienti (hCG+rFSH) :
  - TV mediano da 4 a 19 ml a 9 mesi
  - A 6 mesi spermatogenesi in 8/10
  - A 9 mesi spermatogenesi in tutti

- Nessuna differenza in n. tra HH congenito e acquisito

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

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

hCG
hCG+FSH

TABLE 2. Baseline participant and treatment emergent characteristics

Follow up trimestrale

	Sydney and Melbourne (n = 75 men)
Diagnosis	
IHH	34
Kallmann	17
Pituitary	24
Postpubertal onset	
No	58
Yes	16
Prior androgen exposure	
No	15
Yes	59
Adverse fertility factor	
No	34 (total)
Yes (All)	40 (total)
Yes (cryptorchid)	12
Yes (female factor)	20
Yes (other)	8
Age (yr)	34 ± 1
Partner's age (yr)	29 ± 1
Initial sum testis volume (ml)	13 ± 1
Treatment duration (month)	23 ± 2
Treatment duration with hCG alone (month)	5 ± 1

Values are expressed as total number or mean ± SEM. Individual sums may not total 75 due to incomplete data.

J Clin Endocrinol Metab, March 2009, 94(3):801–808

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

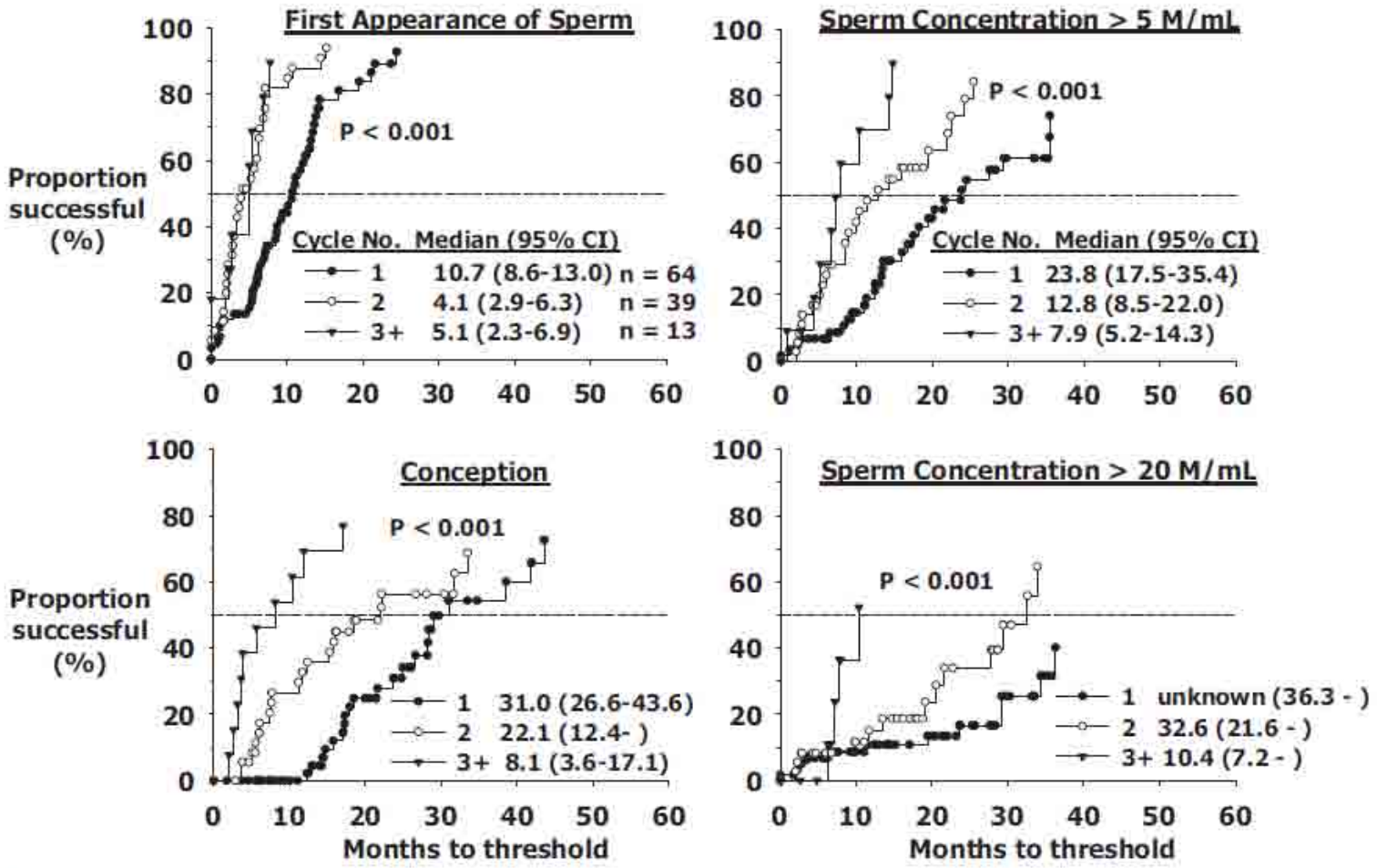


FIG. 4. Kaplan-Meier plots of the proportion of the time evolution by which sperm concentrations of more than 0 (*top left*), 5 (*top right*), and 20 M/ml (*bottom right*) and conception (*bottom left*) are achieved, stratified by cycle number. The median is plotted as a *dashed-horizontal line*. Data from 116 (64 first cycle, 39 second cycle, and 13 third or more cycle) courses of gonadotropin therapy are shown. Median and 95% CIs are tabulated. In some instances, any one or all of median, lower, and upper 95% CIs cannot be estimated and are unknown.

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

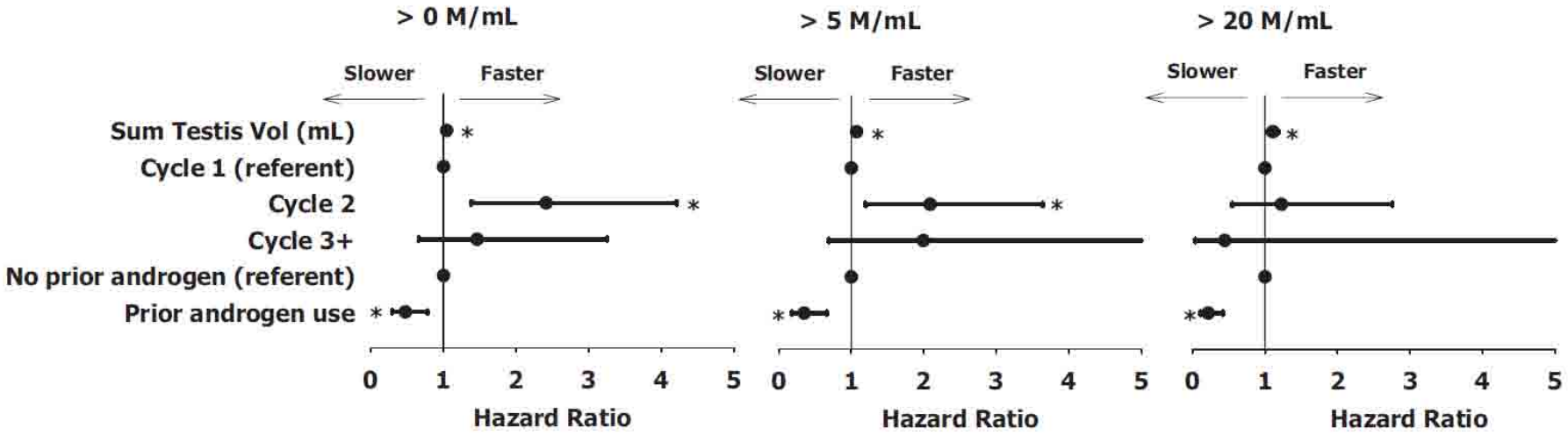


FIG. 2. Final multivariate variables selected after parsimonious stepwise correlated Cox regression. Hazard ratios and 95% CIs, with multivariate adjustment to exclude effects of other variables, are shown. Hazard ratios exceeding one indicate faster, whereas those less than one signify slower, rates of attainment of thresholds for each unit increase in the corresponding variable. The *asterisk* indicates hazard ratios that significantly differ from unity (*vertical line*).

- **38 paternità**
  - Mediana di comparsa spermatozoi : 7.1 mesi
  - Mediana al concepimento : 8 mil/ml

- **Fattori facilitanti** :
  - Volume testicolare
  - Terapia precedente con Gn
  - No androgeni

Stimulation of spermatogenesis with recombinant human follicle-stimulating hormone (follitropin alfa; GONAL-f®): long-term treatment in azoospermic men with hypogonadotropic hypogonadism

Alvin M. Matsumoto, M.D.

TABLE 1

Disease characteristics and basal hormone levels.

	Completed treatment (n = 25)	MITT (n = 29)	Safety (n = 36)
Disease characteristics			
Anosmia	9 (36.0%)	10 (34.5%)	13 (36.1%)
Previous therapy for HH	24 (96.0%)	28 (96.6%)	35 (97.2%)
Cryptorchidism[a]	1 (4.0%)	1 (3.4%)	1 (2.8%)
Basal hormone levels			
Testosterone (ng/dL)	22.0 ± 15.7	20.9 ± 14.8	21.3 ± 14.7
LH (IU/L)	0.7 ± 0.8	0.7 ± 0.7	0.7 ± 0.7
FSH (IU/L)	0.9 ± 0.6	1.0 ± 0.6	1.1 ± 0.7
Prolactin (ng/mL)	4.0 ± 1.9	4.1 ± 1.8	4.3 ± 2.2
TSH (μU/L)	1.9 ± 1.0	1.9 ± 1.0	1.8 ± 1.0
Cortisol (μg/dL)	14.5 ± 6.7	15.1 ± 6.5	15.1 ± 6.4

Note: Mean ± SD.

FSH = follicle-stimulating hormone; HH = hypogonadotropic hypogonadism; LH = luteinizing hormone; TSH = thyroid-stimulating hormone; MITT = modified intention-to-treat.

[a] Patient enrolled with a questionable history of cryptorchidism, which was not evident at screening.

Matsumoto. Follitropin alfa in hypogonadotropic men. Fertil Steril 2009.

36 giovani adulti con HH

hCG per 3-6 mesi

hCG + Follitropin alfa per 18 mesi (se T normale in 2 controlli)

Follow up trimestrale

Stimulation of spermatogenesis with recombinant human follicle-stimulating hormone (follitropin alfa; GONAL-f®): long-term treatment in azoospermic men with hypogonadotropic hypogonadism

TABLE 2

Individual patient listing of final efficacy and hormone levels for completed treatment patients (n = 25).

Patient number	Final hCG dose (U) during treatment phase (months receiving final dose)	Final FSH dose (IU) during treatment phase (months receiving final dose)	Final sperm concentration ($\times 10^6$/mL)	Final ejaculate volume (mL)	Final testis volume (mL)	Final testosterone (ng/dL)	Final inhibin[a] (pg/mL)	Final estradiol (pg/mL)	Final FSH (mIU/mL)
10001[b]	1000 (17.0)	150 (17.0)	22.8	1.4	13	670	69	61	1.4
10002	1000 (17.2)	225 (11.6)	0.06	2.3	13	575	93	38	5.2
10003	1000 (17.3)	225 (5.5)	5.6	2.2	14	580	42	79	6.1
10004	1000 (17.4)	225 (11.6)	6.3	5.8	14	170	62	27	0.6
20001	1000 (18.5)	150 (18.5)	5.1	1.2	20	1287	178	71	2.9
20004[b]	1000 (18.0)	225 (5.6)	0.1	1	7	676	—[c]	39	7.5
30001	1000 (19.5)	225 (11.0)	2	4.1	28	1331	237	66	5.4
30003	500 (7.8)	150 (18.2)	25	0.6	22	594	163	63	5.8
30005[b]	500 (5.3)	150 (18.3)	24.2	1.8	14	1249	74	115	2.1
30006	1500 (4.1)	225 (12.1)	0	0.5	11	478	8	65	4.1
30007	1500 (18.3)	300 (5.7)	2	2	14	683	25	60	5.8
30008	1500 (17.9)	150 (3.8)	21.9	1	13	768	70	37	1.7
30009	2500 (5.8)	225 (11.9)	5.2	2	18	660	—[c]	40	2.7
30010	2000 (18.1)	300 (300)	1.6	4.8	12	759	—[c]	49	4
30011[b]	1500 (17.9)	300 (4.9)	1.1	2	18	767	—[c]	52	3.4
30013	3000 (18.3)	150 (18.3)	7	3.2	14	629	—[c]	61	2.3
40003	1000 (17.3)	150 (17.3)	70	4.2	12	1375	155	141	4.3
40004	1000 (18.5)	225 (12.3)	1.4	1.1	7	884	—[c]	53	4.2
40006	1000 (17.6)	150 (17.6)	10.8	2	12	811	—[c]	40	2.8
60001	750 (16.1)	150 (22.0)	6	8	24	1104	179	74	2.6
70001[b]	1500 (19.6)	150 (19.6)	5.1	3.1	10	620	100	77	6.2
70003	1000 (19.2)	150 (19.2)	20	6	10	660	57	47	3.2
70004	2000 (18.4)	150 (18.4)	4.2	2.2	10	634	—[c]	61	2.3
90001	1000 (20.3)	150 (20.3)	1.8	1.6	25	1052	—[c]	62	2.8
90002	3333 (18.2)	225 (11.6)	5.2	1	14	834	—[c]	55	7.2

Note: FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

[a] For the inhibin assay, the limit of detection changed from 8 to 50 pg/mL during the study.

[b] Partner achieved pregnancy.

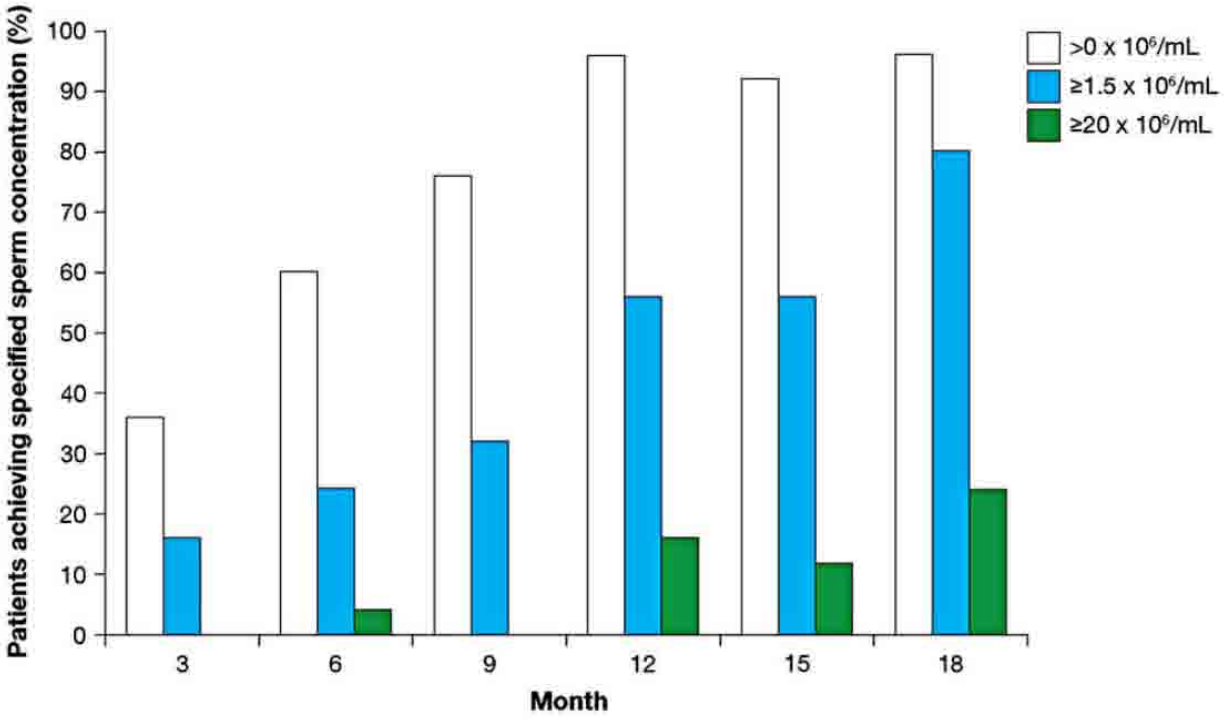
[c] Missing value.

Matsumoto. Follitropin alfa in hypogonadotropic men. Fertil Steril 2009.

Stimulation of spermatogenesis with recombinant human follicle-stimulating hormone (follitropin alfa; GONAL-f®): long-term treatment in azoospermic men with hypogonadotropic hypogonadism

FIGURE 1

Percentages of patients achieving any sperm concentration ($>0 \times 10^6$/mL), a sperm concentration $\geq 1.5 \times 10^6$/mL (the primary endpoint), and a sperm concentration $\geq 20 \times 10^6$/mL at 3-month intervals for patients who completed treatment (n = 25).

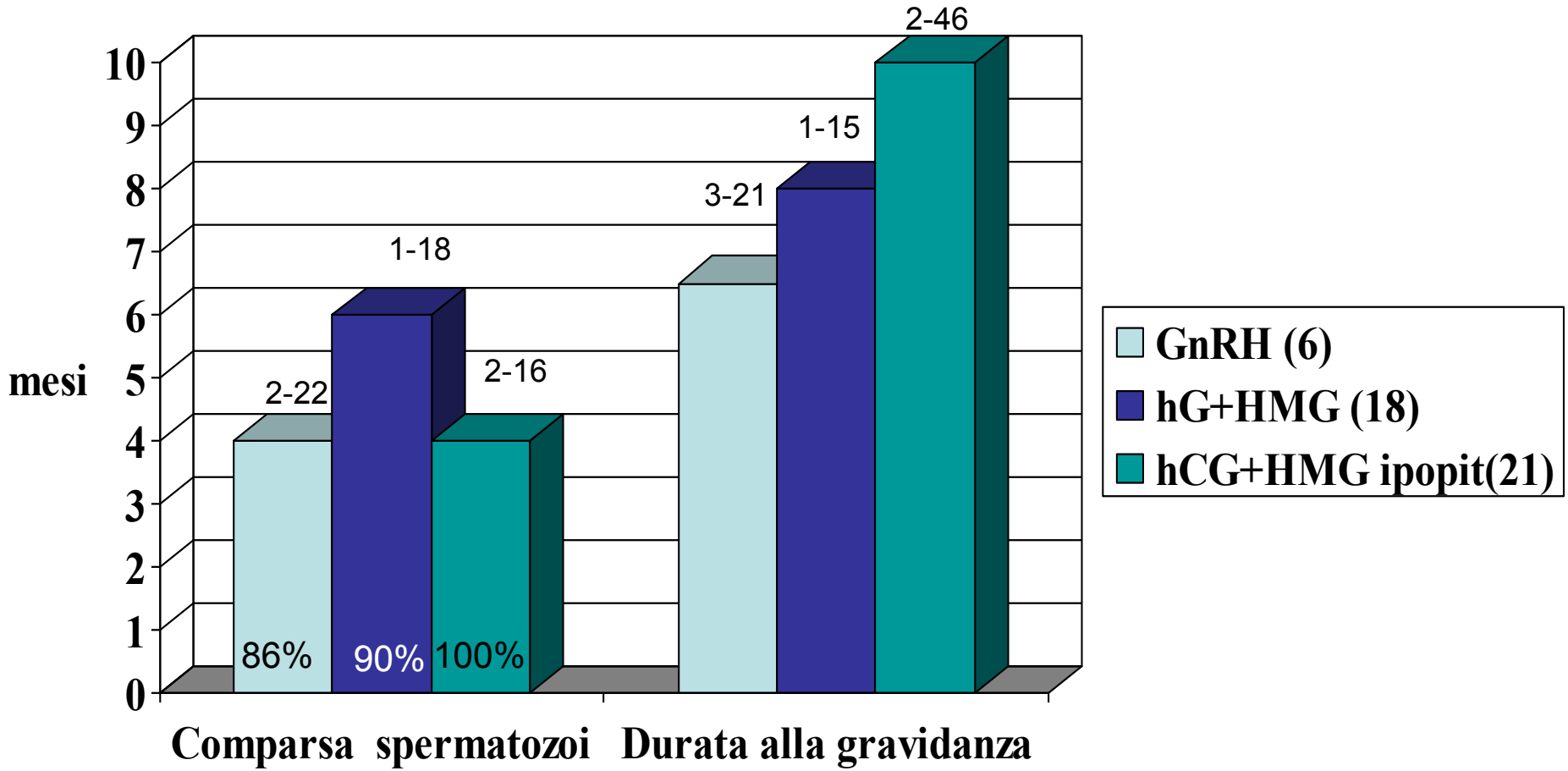


Matsumoto. Follitropin alfa in hypogonadotropic men. Fertil Steril 2009.

Terapia con GnRH o hMG/hCG

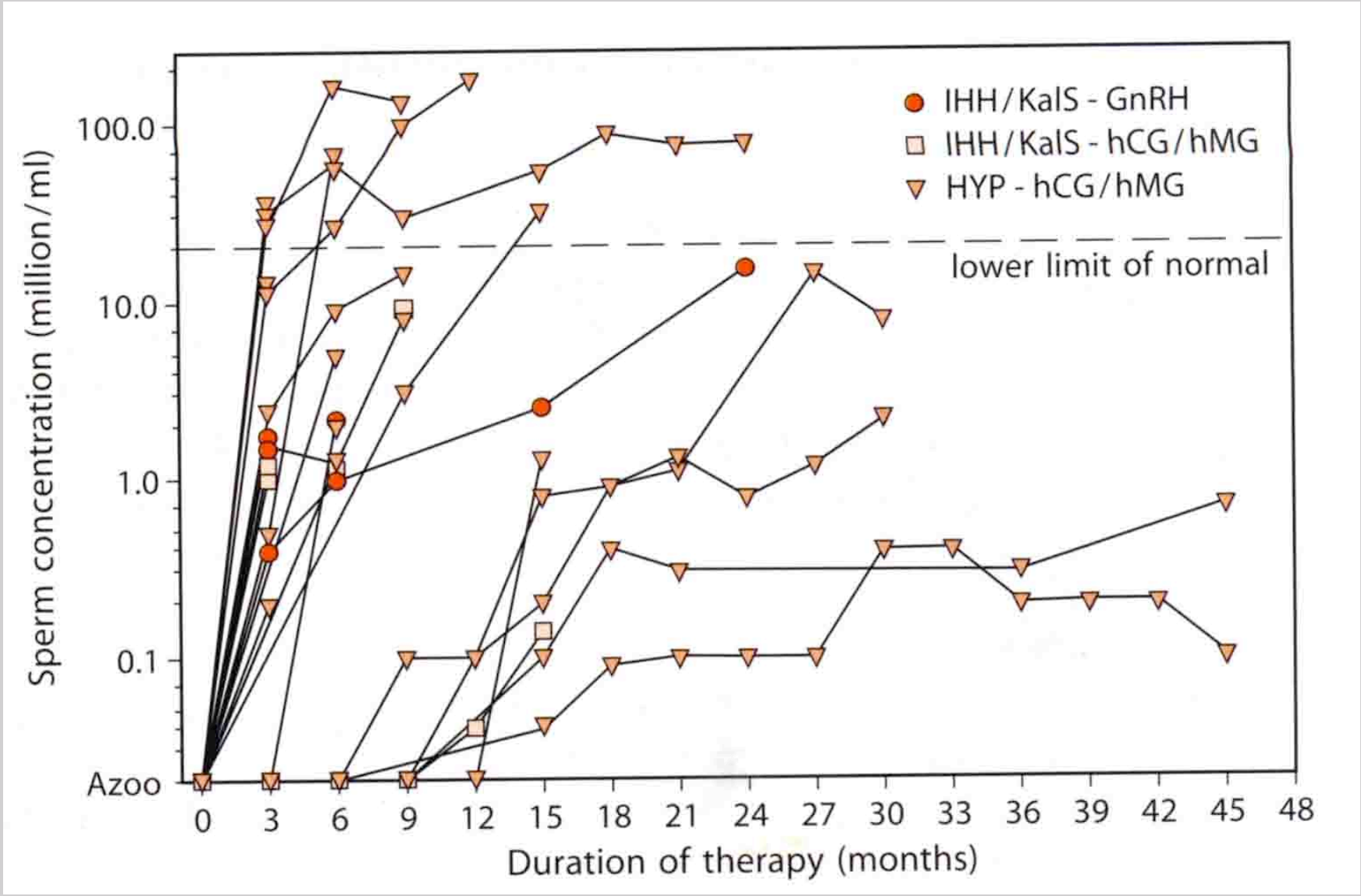
IHH - Kal - Ipopituitarismo

Roma,
9-11 novembre 2012



Buchter, EJE 1998

SPERMATOZOI AL CONCEPIMENTO



(Nieschlag and Behre, 2000)

RISULTATI DELLA TERAPIA

- Forme post puberali : si ottiene comparsa degli spermatozoi in un tempo abbastanza breve e al massimo entro 12 mesi ed è più frequente il riscontro di normozoospermia.
- Forme idiopatiche : la terapia richiede tempi molto più lunghi (24 – 36 mesi) e la percentuale di normospermici è significativamente inferiore.
- Risultati peggiori in presenza di criptorchidismo.

(Nieschlag and Behre, 2000)

QUALITY OF SPERM MOTILITY IN HYPOGONADOTROPIC HYPOGONADISM TREATED BY LHRH OR GONADOTROPINS

R.G. Motta, S. Botteon, A. Vazzoler, M. Schiesaro, G. Bonanni, I. Mastrogiacomo
Institute of Semeiotica Medica, University of Padua

8 HH vs 39 controlli fertili

CASA

VCL = Velocità curvilinea
VSL = Velocità lineare
LIN = Linearità
ALH = Spostamento laterale della testa

	Num.	Mot. %	VCL	VSL	LIN	ALH
H.H.(n. 8)						
mean	9.85	16.56	72.60	28.57	42.75	3.20
stand. dev.	5.46	8.18	15.60	8.32	10.60	0.68
Controls(n.39)						
mean	82.41	35.92	87.23	37.88	46.74	3.53
stand. dev.	51.63	18.33	19.89	9.28	10.67	0.88
p	< 0.0001	< 0.006	n.s.	< 0.01	n.s.	n.s.

JEI, 1995

Spermatozoi : 1 N Condensati
Spermatidi : 1 N (non condensati)
Cellule somatiche : 2N
Spermatociti : 4N

	1 N condensed	1 N	2 N	4N
CONTROLS (n=20)	87.6 ± 3.80	9.90 ± 2.7	1.8 ± 2.7	n.d.
HYPOG. (n = 7)	66.47 ± 14.27*	13.07 ± 6.64	19.73 ± 14.79*	0.55 ± 0.94
CRIPTOSP. (n = 13)	54.31 ± 18.87*	17.76 ± 5.21*	22.11 ± 21.35*	1.78 ± 1.96

* = p< 0.0001 vs. Controls

International Journal of Andrology, February 1996

Carlo II Re di Spagna (1661-1700)

Maria Luisa D' Orleans (1° moglie)

Anna Maria del Palatinato-Neuburg (2° moglie)

Spermatogenesi e KS

- Presenza di cellule germinali nella maggior parte dei KS (Wikstrom, 2004-2007)
- Rari foci di normale spermatogenesi (Sciurano, 2009)
- Calo progressivo degli spermatogoni nel primo anno di vita (Mikamo, 1968)
- Netta riduzione degli spermatogoni “dark”
- Alla pubertà progressiva deplezione di tali cells che precede
  ↑ Gonadotropine
- Arresto maturativo a livello di spermatociti o spermatidi (Foresta, 1999; Lanfranco, 2004)

Spermatogenesi e KS

- Persistente immaturità delle Cellule del Sertoli
- Riduzione dell'espressione di AR in Sertoli cells di KS
- Anomala localizzazione intracitoplasmatica di AR piuttosto che sulla superficie

Spermatogenesi e KS

- Aumento espressione genica in X soprannumerario
- Disequilibrio ormonale endotesticolare
- Esagerata apoptosi nelle Cellule del Leydig e del Sertoli
- Difetti degli spermatogoni

- Il processo inizia durante la vita fetale o neonatale

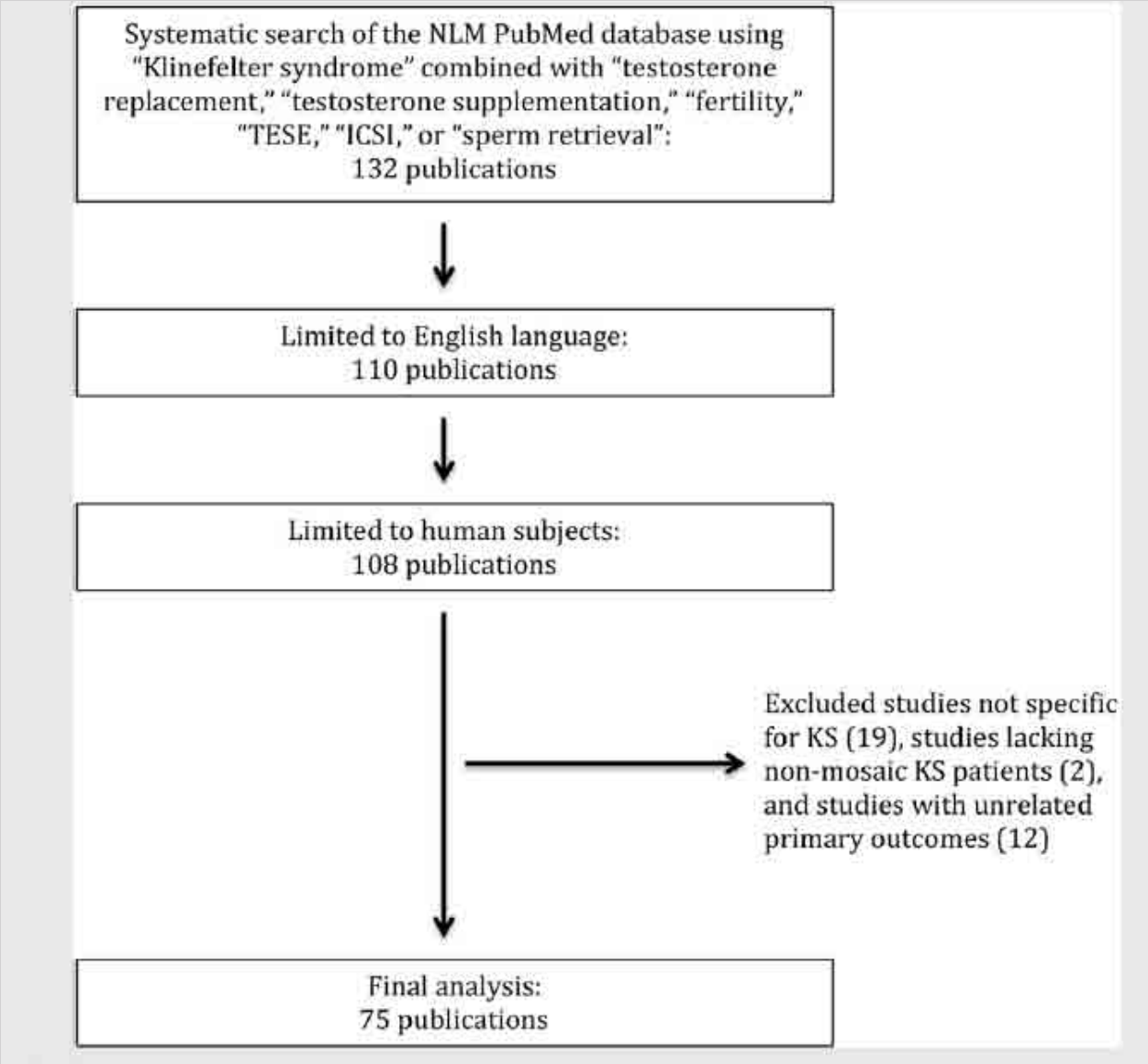
La sfida

CENNI STORICI

- 1° esperienza TESE (1996, Tournaye)
- ICSI con spermatozoi da prelievo testicolare (1998 : Palermo)
- Segnalazione di 101 nati da KS
- Con TESE risultati simili tra KS ed azoospermia non ostruttiva

Klinefelter syndrome: an argument for early aggressive hormonal and fertility management

Akanksha Mehta, M.D., and Darius A. Paduch, M.D., Ph.D.



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Klinefelter syndrome: an argument for early aggressive hormonal and fertility management

Akanksha Mehta, M.D., and Darius A. Paduch, M.D., Ph.D.

Roma,
9-11 novembre 2012

TABLE 1

Success rates and predictors of sperm retrieval in men with Klinefelter syndrome.

Reference	No. of patients[a]	Drug therapy	Procedure	Sperm retrieval rate (SRR %)	Predictors of sperm retrieval	Fertility outcome
Tournaye (1997)	15	None	TESE	8/15 (47)		Not reported
Friedler et al. (2001)	12	None	TESE	5/12 (42)		1 set of twins[c] and 2 singletons born using fresh sperm; 1 set of twins born and 1 spontaneous early abortion using frozen-thawed sperm
Levron et al. (2000)	20	None	TESE	8/20 (40)		1 set of triplets, 1 set of twins, and 2 singletons born
Yamamoto et al. (2002)	24	None	TTB[b]	12/24 (50)	Decreased levels of androgen-binding protein were a negative predictive factor	1 set of twins and 3 singletons born
Madgar et al. (2002)	20	None	TESE	9/20 (45)	No significant difference in SRR with respect to FSH or LH; higher serum T, testicular volume, and response to hCG stimulation test were positive predictive factors	Not reported
Westlander et al. (2003)	19	None	TESE	4/19 (21)	No significant difference in SRR with respect to inhibin B	2 pregnancies
Seo et al. (2004)	25	None	TESE	4/25 (16)	No significant difference in SRR with respect to age, FSH, T, or testicular volume	50% ICSI fertilization rate using fresh sperm
Vernaeve et al. (2004)	50	None	TESE	24/50 (48)	No significant difference with respect to age, testicular volume, FSH, T, FSH:LH ratio, or androgen sensitivity index	Not reported
Okada et al. (2005)	51	None	TESE	26/51 (51)	No significant difference in SRR with respect to T, LH, FSH, or testicular volume; age <35 y was a positive predictive factor	Not reported
Okada et al. (2005)	10	None	mTESE	6/10 (60)		3 singletons born and 1 spontaneous early abortion using frozen-thawed sperm

Mehta. Aggressive management of KS. Fertil Steril 2012.

Klinefelter syndrome: an argument for early aggressive hormonal and fertility management

Akanksha Mehta, M.D., and Darius A. Paduch, M.D., Ph.D.

Roma,
9-11 novembre 2012

TABLE 1

Continued.

Reference	No. of patients[a]	Drug therapy	Procedure	Sperm retrieval rate (SRR %)	Predictors of sperm retrieval	Fertility outcome
Schiff et al. (2005)	42[d]	5/42 had received TRT (stopped at least 6 mo before mTESE); 36/42 with serum T < 300 ng/dL were treated with hCG, CC, aromatase inhibitors, or combined therapy before mTESE	mTESE	29/42 (69)	No significant difference in age with respect to SRR; prior TRT was associated with lower SRR (20%)	18 pregnancies, 21 live births
Emre Bakiricioglu et al. (2006)	74	14/74 had received TRT (stopped at least 6 mo before mTESE)	mTESE	42/74 (57)	No significant difference in SRR with respect to T, FSH, LH, or testicular volume; younger age was a positive predictive factor	Not reported
Kyono et al. (2007)	17	None	TESE	6/17 (35)	No significant difference in SRR with respect to T, FSH, LH, or testicular volume; younger age was a positive predictive factor	5 singletons born using fresh sperm; 1 set of twins and 1 singleton born using frozen sperm
Koga et al. (2007)	26	None	mTESE	13/26 (50)	No significant difference with respect to age, testicular volume, T, FSH, LH, PRL, E_2, inhibin B	Not reported
Ramasamy et al. (2009)	68	8/68 had received TRT (stopped at least 6 mo before mTESE); 56/58 with serum T < 300 ng/dL were treated with hCG, CC, or aromatase inhibitors before mTESE	mTESE	45/68 (66)	No significant difference with respect to FSH, LH, or testicular volume; age <35 y, and normal preop T and T:E ratio[e] were positive predictive factors; prior TRT was associated with lower SRR (25%)	28/68 (41%) men achieved paternity
Selice et al. (2010)	24		TESE	9/24 (38)	No significant difference with respect to age, testicular volume, FSH, LH, T, free T, E_2, SHBG, inhibin B; signs of hypoandrogenism were a negative predictive factor	Not reported

Note: CC = clomiphene citrate; ICSI = intracytoplasmic sperm injection; mTESE = microdissection testicular sperm extraction; preop = preoperative; SHBG = sex hormone-binding globulin; SRR = sperm retrieval rate; TESE = testicular sperm extraction; TTB = therapeutic testicular biopsy; TRT = testosterone replacement therapy.

[a] Reflects the number of patients with nonmosaic Klinefelter syndrome included in each study.

[b] Therapeutic testis biopsy.

[c] Triplet pregnancy reduced to twin pregnancy.

[d] 39 (93%) had nonmosaic Klinefelter syndrome, 3 (7%) were mosaic 46,XY/47,XXY. Unable to distinguish mosaic patients for exclusion. Overall outcomes reported.

Spermatogenesis in Klinefelter syndrome

R. Selice[1], A. Di Mambro[1], A. Garolla[1], V. Ficarra[2], M. Iafrate[2], A. Ferlin[1], and C. Foresta[1]

Roma,
9-11 novembre 2012

Studio retrospettivo
84 KS
Es. seminale : 7 KS con spermatozoi (8.3%); 77 azoo.
24/77 : TESE con 9 recuperi (37.5%)

Table 2 - *Clinical and hormonal parameters in subjects with or without spermatozoa in semen analysis or by testicular sperm extraction (TESE). All data not significant.*

	Sperm positive in semen analysis or TESE (no.=16)	Sperm negative in semen analysis and TESE (no.=15)
Age (yr)	30.0±7.2	29.5±7.8
FSH (IU/l)	33.1±13.4	38.6±14.9
LH (IU/l)	18.4±5.7	21.6±7.0
Total testosterone (nmol/l)	11.6±3.0	10.3±3.9
SHBG (nmol/l)	24.3±10.2	27.6±13.0
Free testosterone (nmol/l) (calculated)	0.26±0.08	0.21±0.08
Estradiol (pmol/l)	107.6±32.9	105.3±30.5
Inhibin B (pg/ml)	28.9±28.9	37.4±59.7
Testicular volume (ml)	2.0±0.5	1.7±0.8

Table 4 - *Sex chromosome aneuploidies in ejaculated spermatozoa from men with 47,XXY non-mosaic.*

	Normal spermatozoa		Disomy			Other
	X-bearing	Y-bearing	XX	YY	XY	
Klinefelter subjects (no.=7)	51.6±1.7*	26.9±1.5*	6.2±0.9*	0.4±0.6	13.3±2.5*	1.8±1.9*
Controls (no.=103)	49.4±1.6	49.0±1.7	0.1±0.5	0.1±0.9	0.2±0.5	0.1±0.4
Non-genetic severe oligozoospermia (no.=387)	48.3±1.5	48.0±1.6	0.6±0.8	0.6±0.8	1.4±1.8	0.1±0.3

*$p<0.01$ *vs* controls and *vs* non-genetic severe oligozoospermia.

J. Endocrinol. Invest. 33: 789-793, 2010

Preservazione fertilità in KS

- Il declino della funzione testicolare in KS è progressivo dalla pubertà alla vita adulta

- ***Raccomandazioni :***
  - recupero di spermatozoi e crioconservazione prima possibile
  - Sempre prima di ART

- ***Diagnosi genetica pre-impianto***
  - Anche se maggioranza embrioni normali geneticamente

Il battesimo dell'eunuco

Salvator Rosa
Napoli 1615-Roma 1673