Percorsi AME Roma
9-11 Novembre 2012

Roma,
9-11 novembre 2012

PerCorso Endocrinologia Pediatrica 2

Sabato 10 novembre ore 10.30– 12.30

(Replica domenica 11 novembre ore 10.30– 12.30)

Roma,
9-11 novembre 2012

Quando sospettare e come indagare un ritardo di sviluppo puberale

Armando Grossi, U.O. Endocrinologia Ospedale “Bambino Gesù”, Roma

Bambino Gesù
OSPEDALE PEDIATRICO

mancata comparsa:

- dell'aumento del volume testicolare nel maschio
- dello sviluppo del seno nella femmina

ad un'età di oltre 2 DS in ritardo rispetto alla età media della popolazione generale

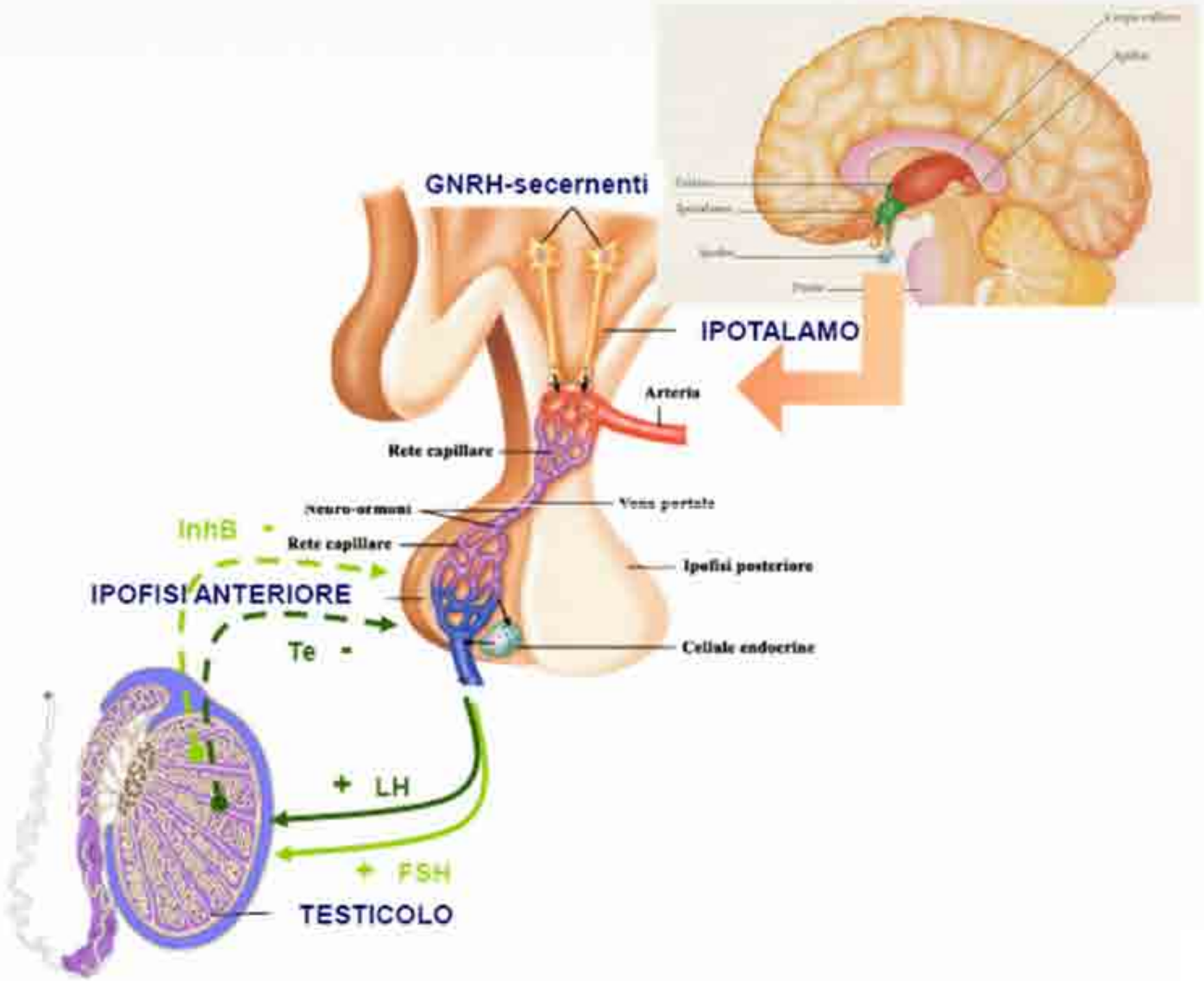
in pratica:

un maschio di età > 14 anni

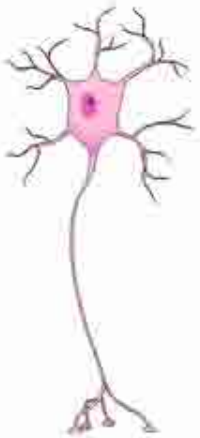
una femmina di età > 13 anni

- **Un po’ di fisiologia……**

Rappresentazione schematica asse ipotalamo-ipofisi-gonadi

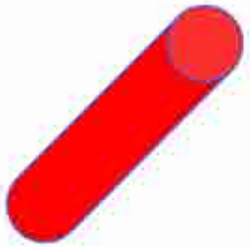


Secrezione di GnRH

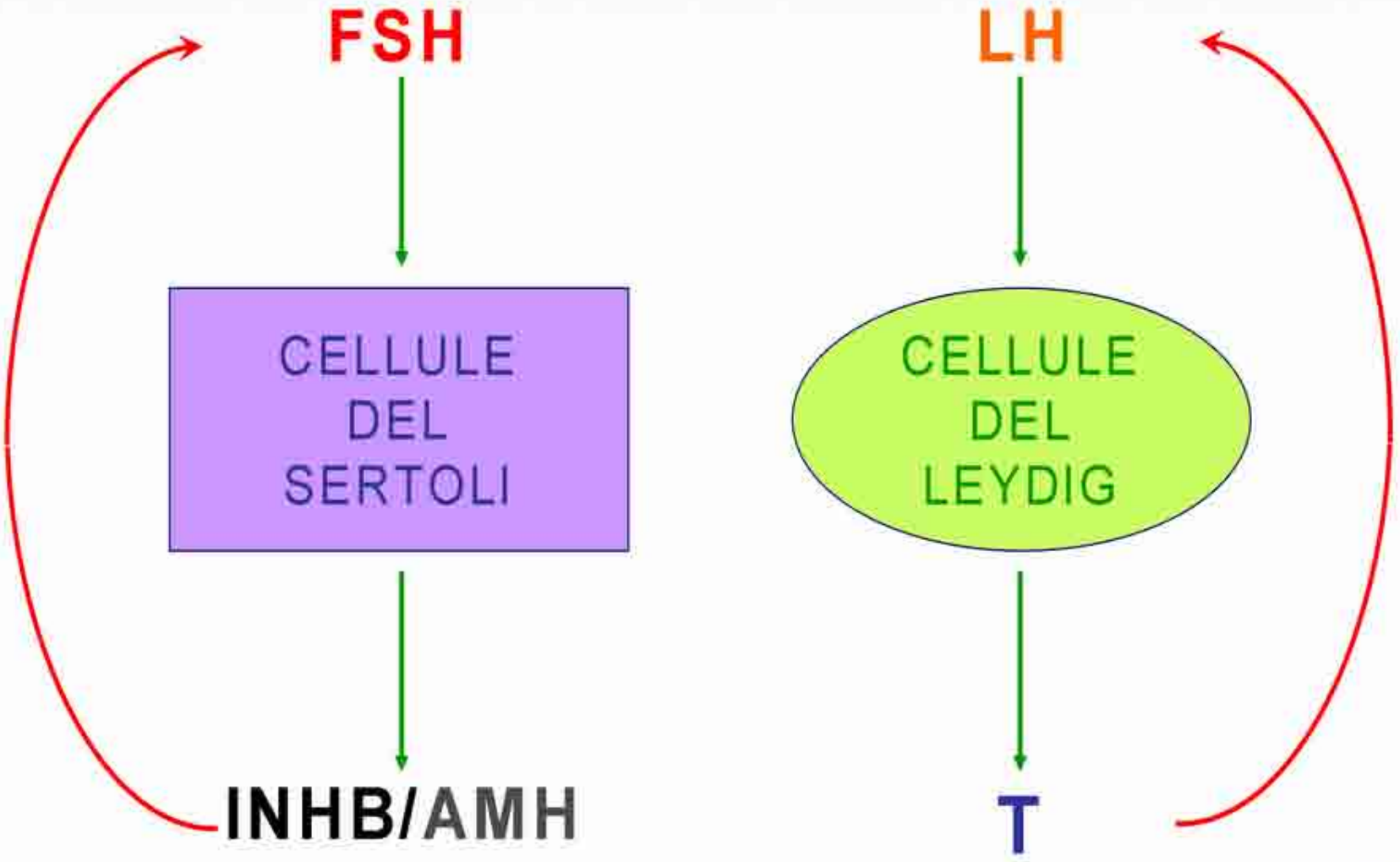
Migrazione  per **GnRH** dal PLACODE OLFATTORIO all'IPOTALAMO BASALE

Regolata dal gene **KAL** (cr **X**)

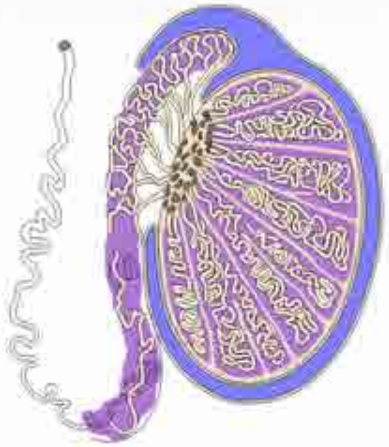
GnRH →
- Secrezione pulsatoria
- T1/2= 2-4min



Funzioni della gonade maschile....

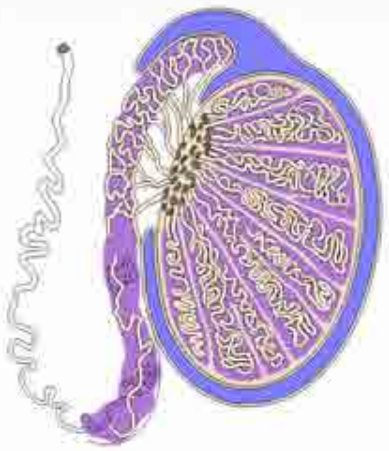


Stadi dello sviluppo testicolare



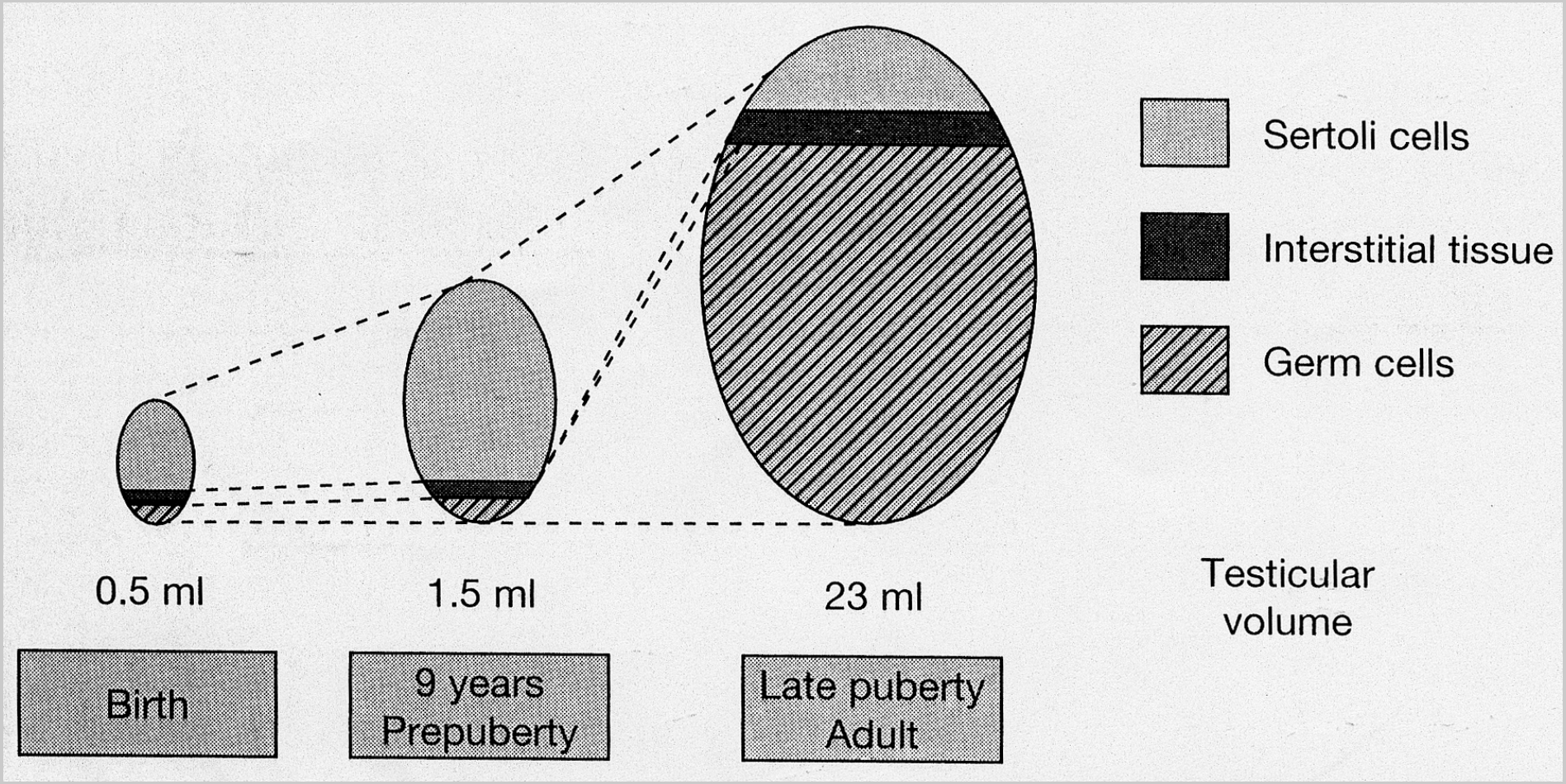
PREPUBERE

> Cellule del Sertoli



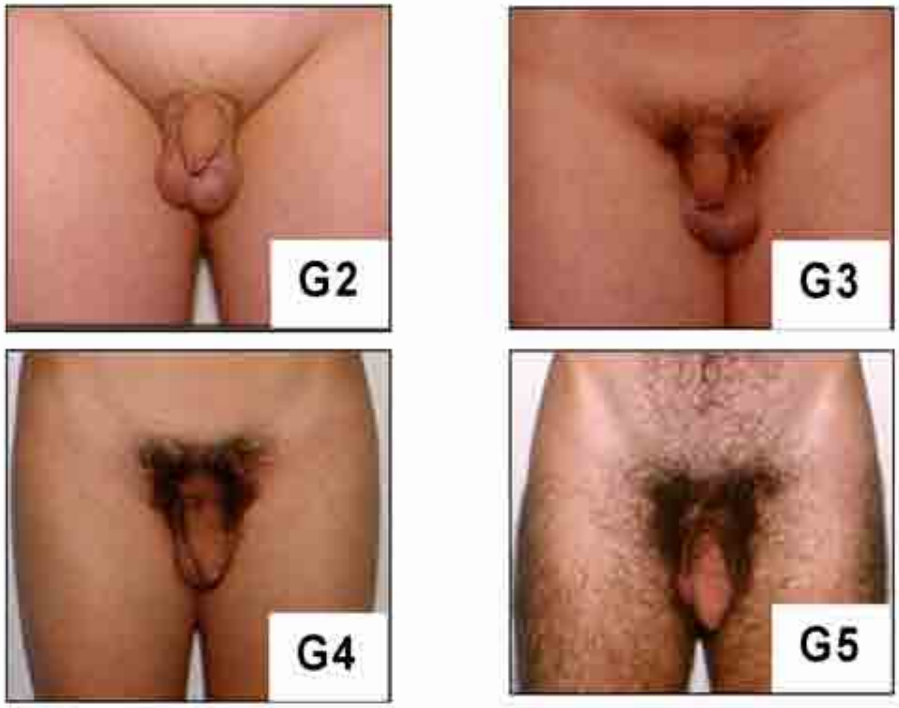
ADULTO

> Cellule germinali


Sertoli cells
Interstitial tissue
Germ cells
0.5 ml
1.5 ml
23 ml
Testicular volume
Birth
9 years
Prepuberty
Late puberty
Adult

- **E di obiettività clinica……..**

Stadi puberali

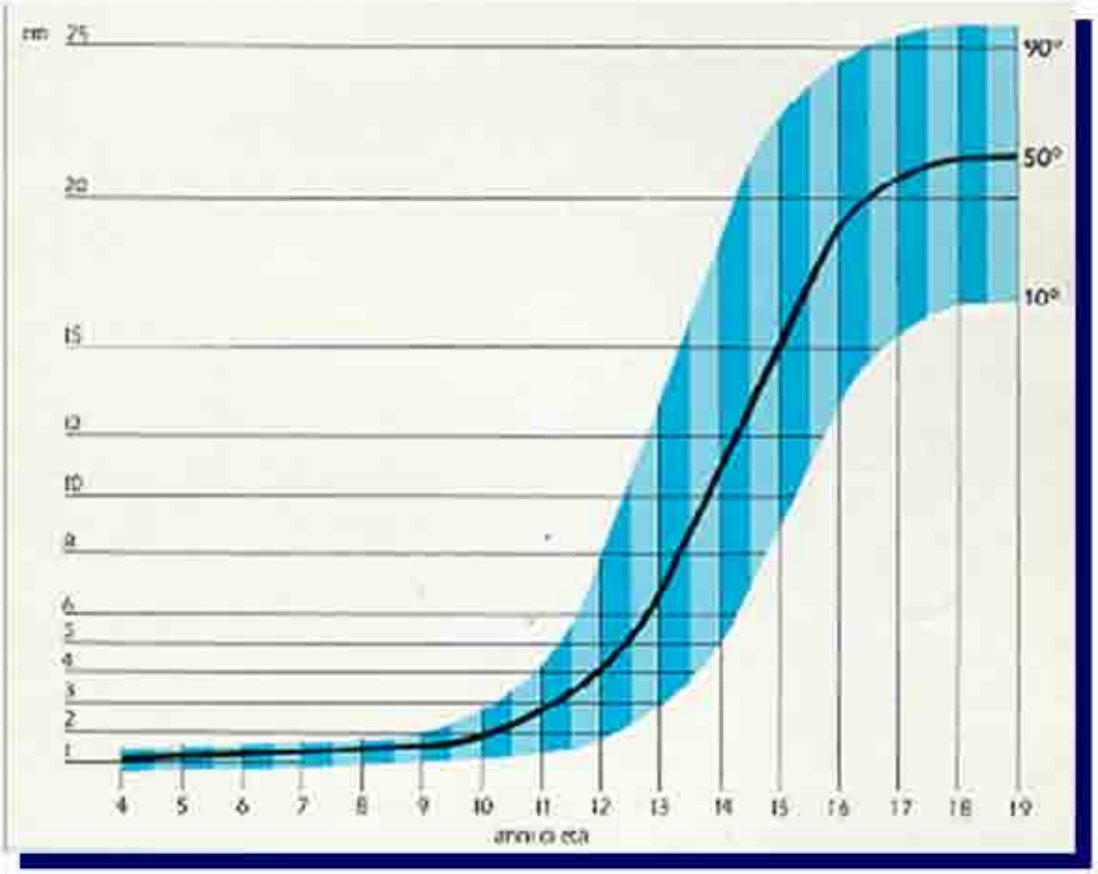


Marshall & Tanner, 1970

Curva di crescita del volume testicolare

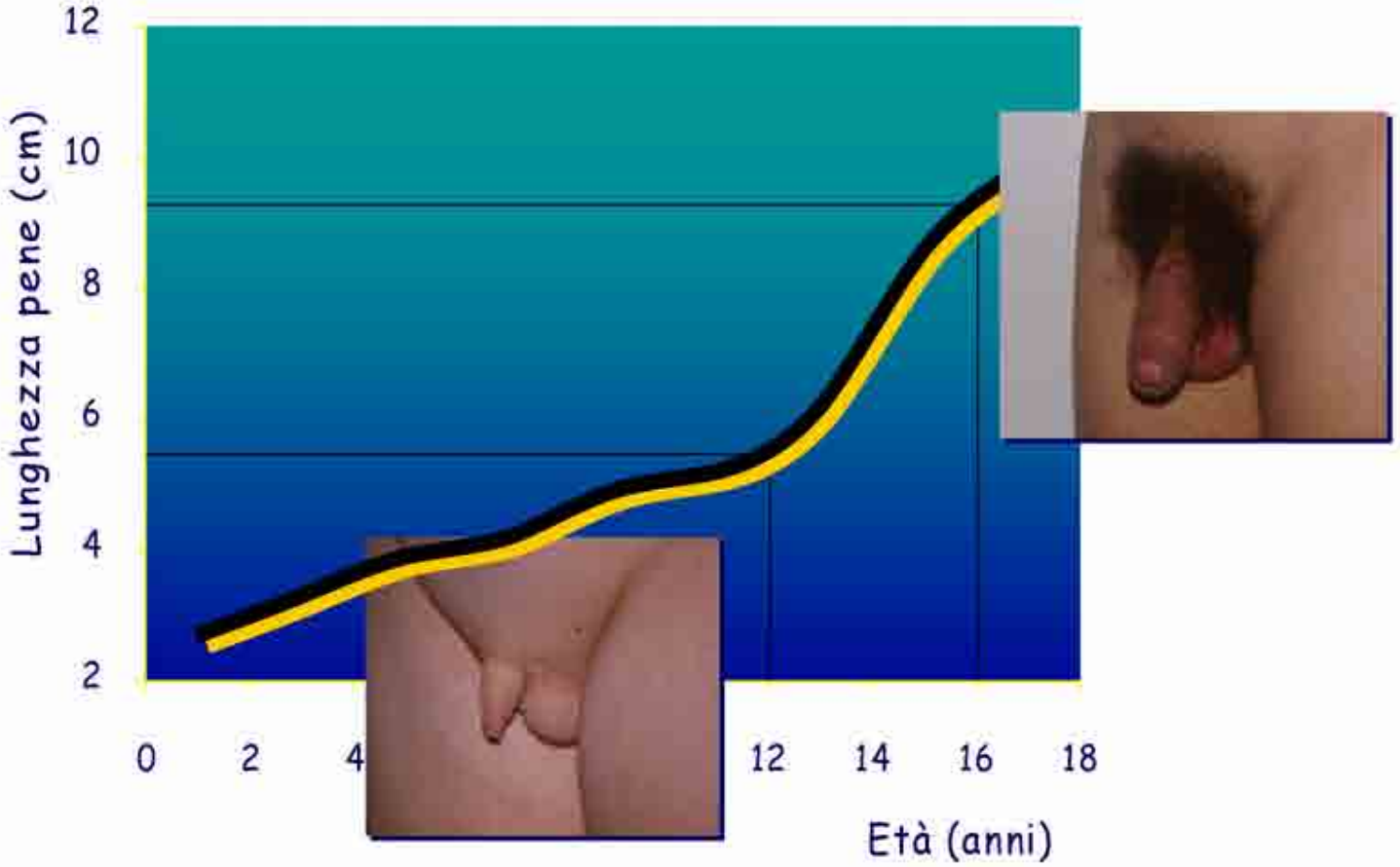
dati orchidometrici

Olanda (van Wieringen '71), Svizzera (Zachmann '74), Svezia (Taranger '76)



Foetus into Man (2nd ed. 1989) - J.M. Tanner

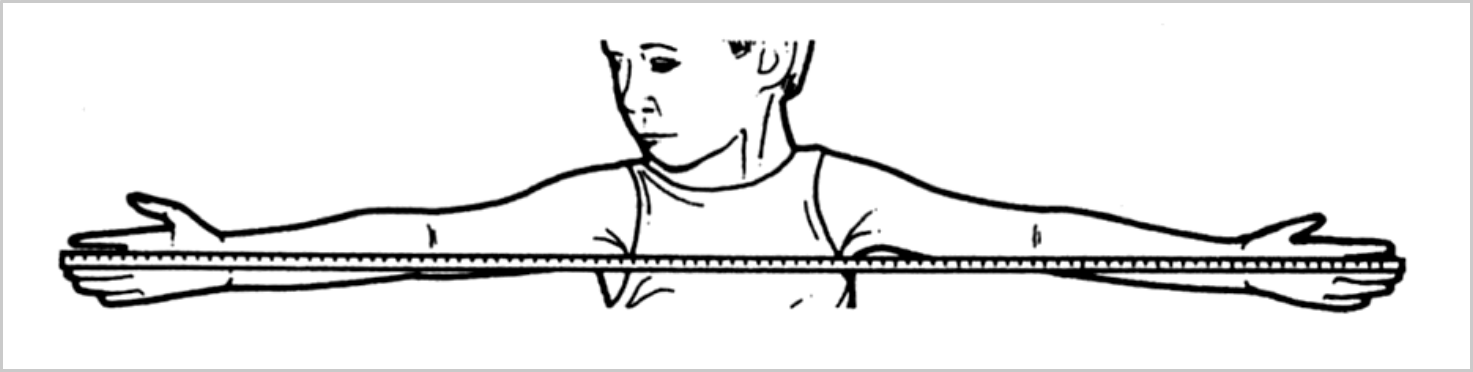
Curva di crescita della lunghezza del pene



volume testicolare

- nel prepubere: 1-3 ml
- in pubertà: eguale o > 4 ml

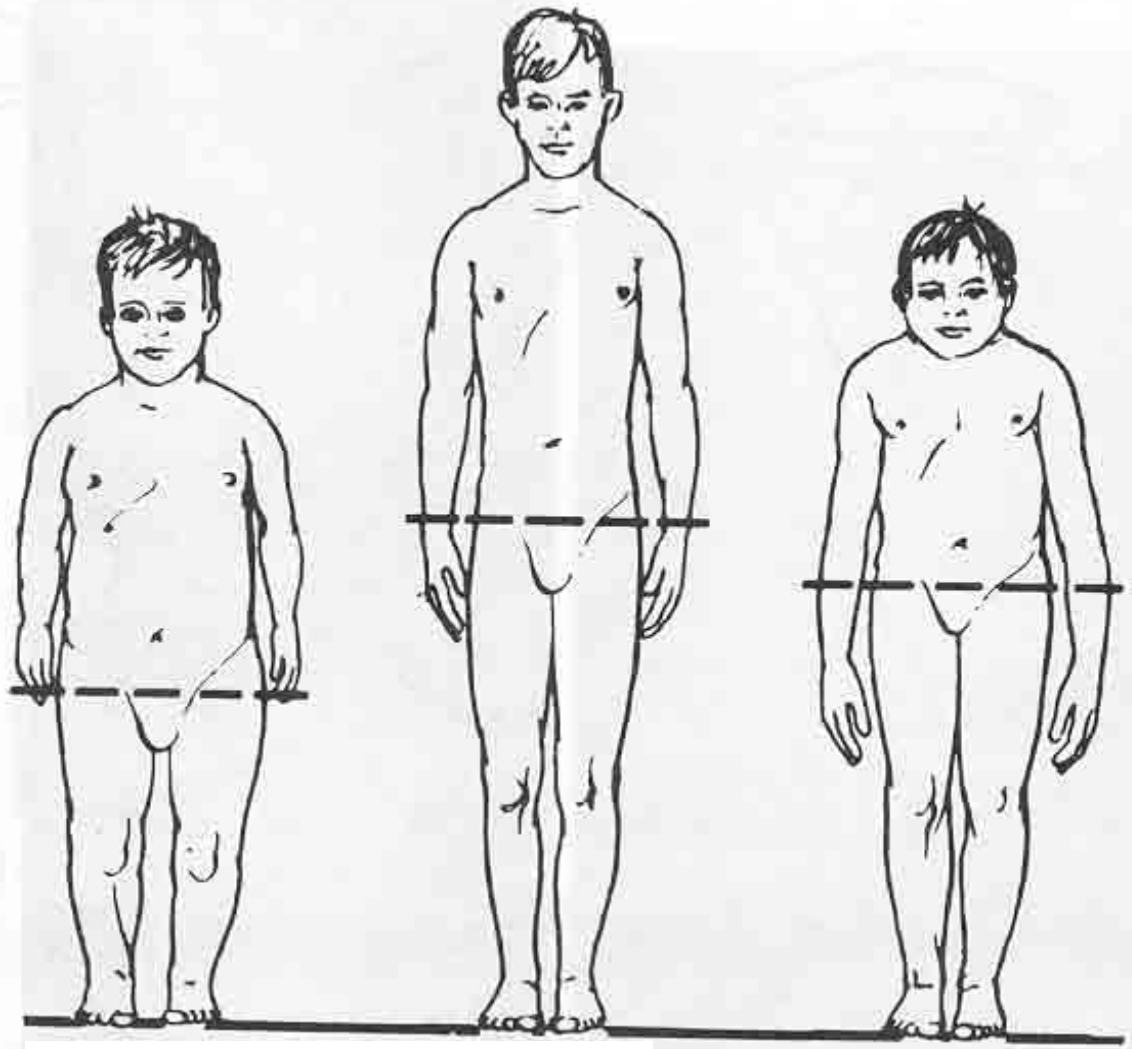
Lunghezza arto superiore totale



Arm span: distanza tra le due estremità del 3° dito, la misurazione và effettuata ponendosi anteriormente o posteriormente al soggetto.

Arm span vs Statura

- 1-2 cm < statura <10 aa maschio e <12 aa femmina
- = statura ≥ 10 aa maschio e ≥12 aa femmina
- (*arm span* superiore alla statura di almeno 5 cm e riduzione del rapporto segmento superiore / segmento inferiore)


U/L
1.25
1.00
0.80

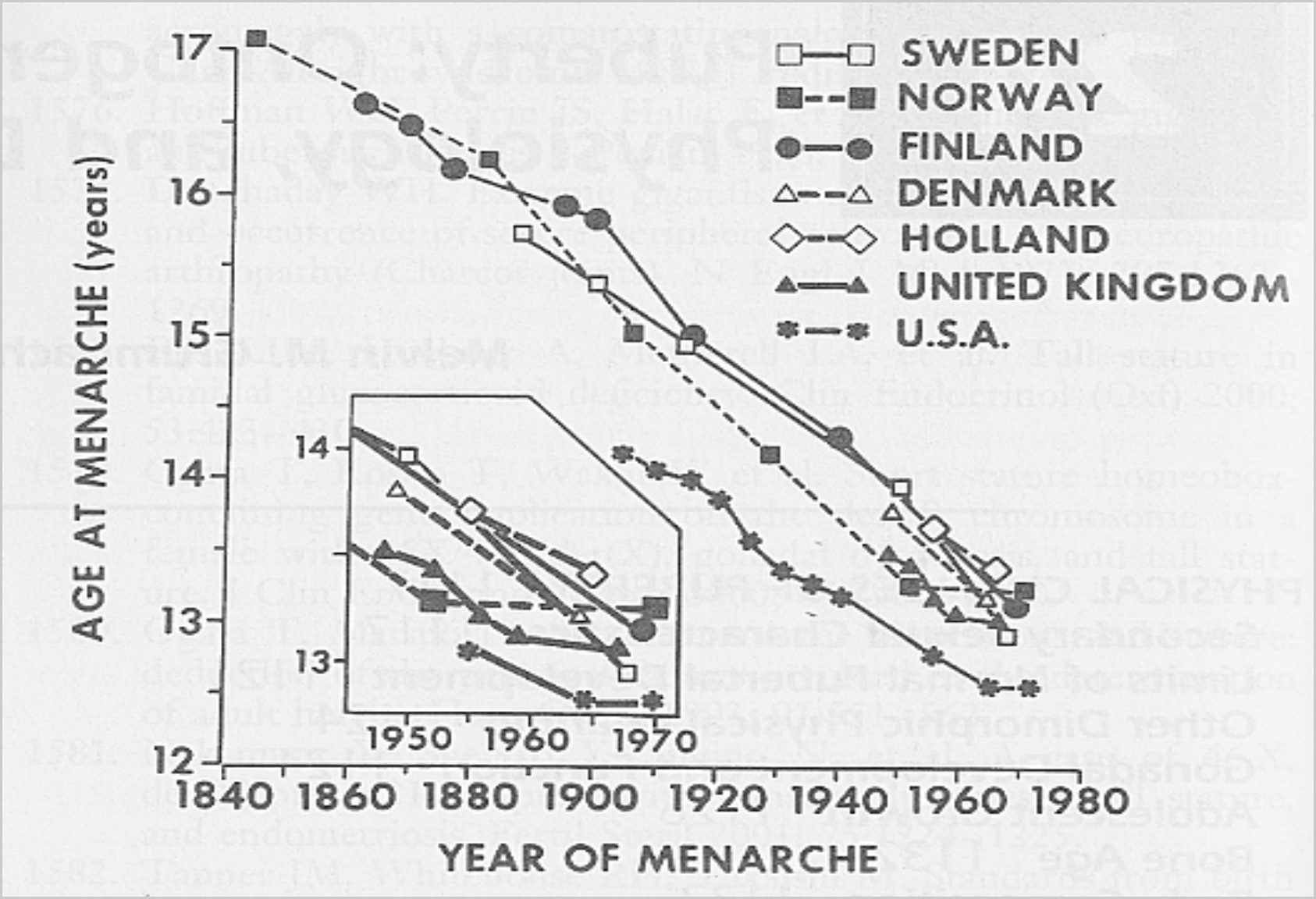
Cronologia dello sviluppo puberale

Femmine

Inizio tra 8 e 13 anni
Menarca mediamente dopo 2 anni dal telarca
Spurt puberale B2/B3
Durata complessiva media 4.2 anni

Maschi

- **Inizio tra 9,5 e 14 anni**
- **Spurt puberale G3/G4**
- **Durata complessiva media 4 anni**


SWEDEN
NORWAY
FINLAND
DENMARK
HOLLAND
UNITED KINGDOM
U.S.A.
AGE AT MENARCHE (years)
17
16
15
14
13
12
1840
1860
1880
1900
1920
1940
1960
1980
YEAR OF MENARCHE
14
13
1950
1960
1970

Cause di ritardo puberale

- **Ritardo costituzionale di crescita e di maturazione (RCCM)**

- **Ipogonadismo ipogonadotropo funzionale**
  Disfunzione ipotalamica transitoria

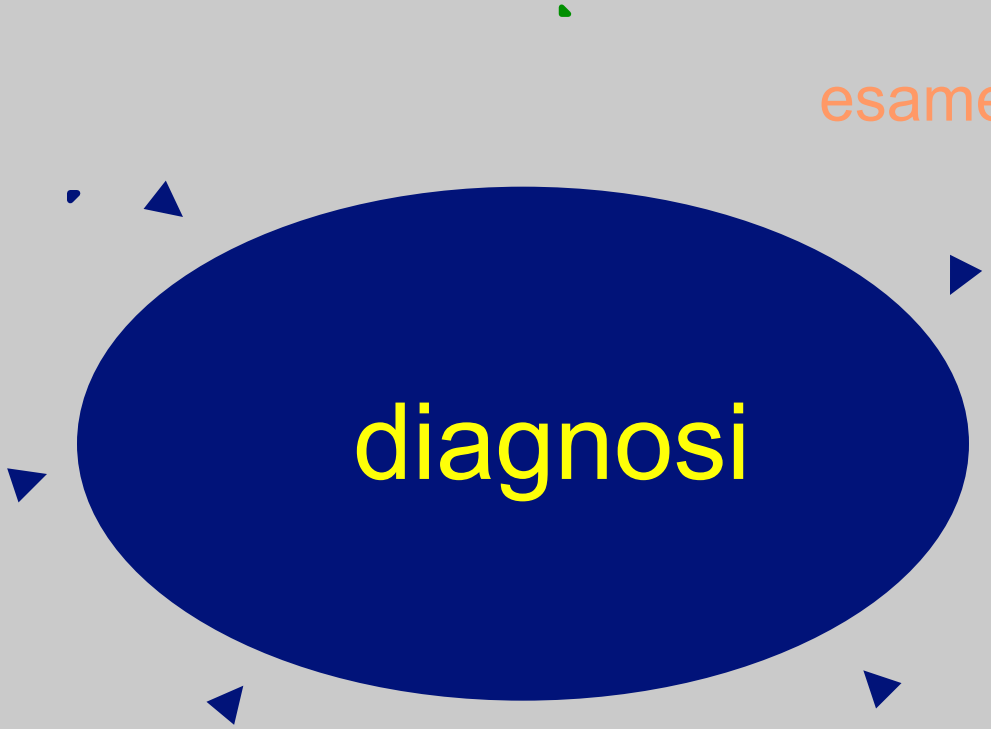
- **Ipogonadismo ipogonadotropo permanente**

- **Ipogonadismo ipergonadotropo**


esame obiettivo
anamnesi
diagnosi
laboratorio
esami strumentali
neuroradiologia

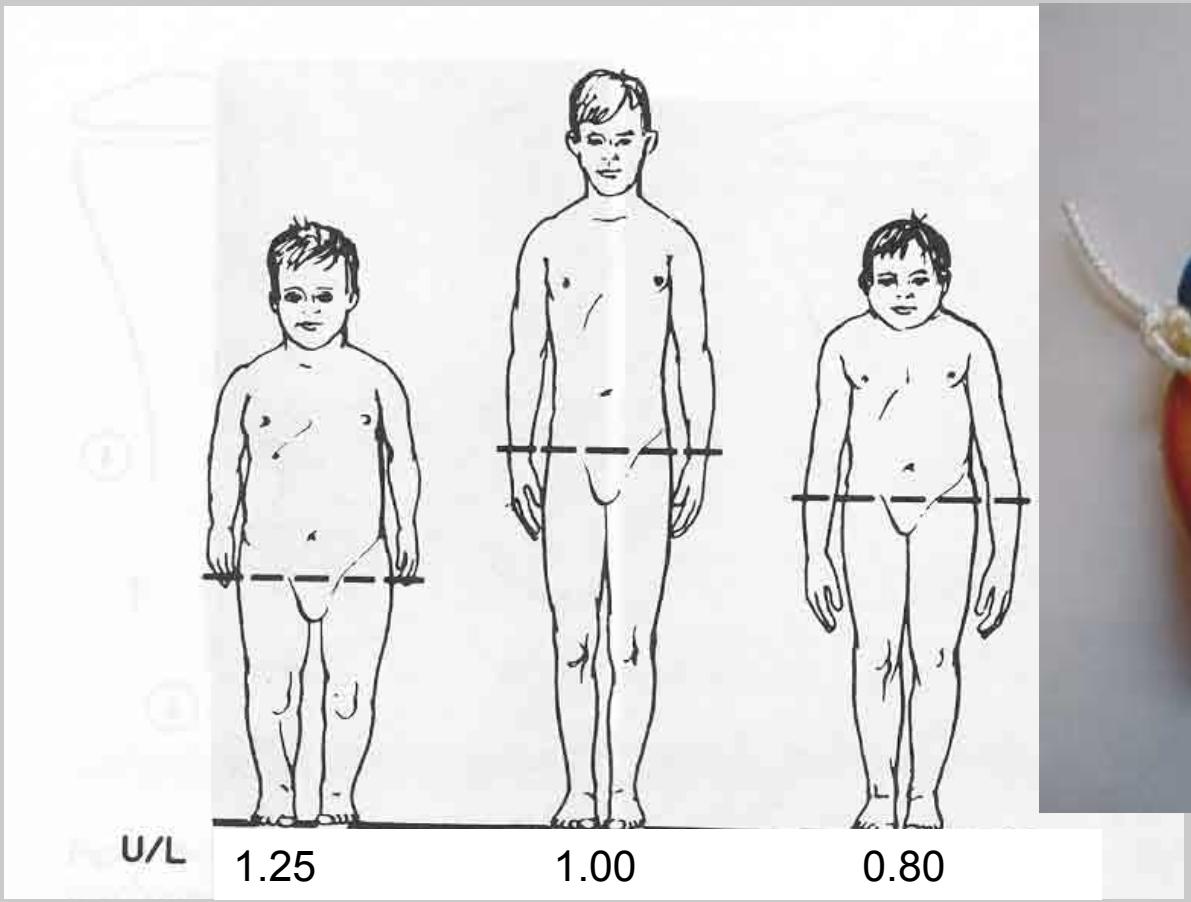
Anamnesi

- ✓età della madre, delle nonne e di eventuali sorelle al momento del menarca
- ✓epoca della pubertà del padre e di eventuali fratelli e sorelle
- ✓curva di crescita
- ✓malattie croniche (eventuale radioterapia e/o chemioterapia)
- ✓**stress**
- ✓atteggiamento del ragazzo di fronte al problema
- ✓ **olfatto**


anamnesi
esame obiettivo
diagnosi
laboratorio
esami strumentali
neuroradiologia

Esame obiettivo

- ✓statura e peso
- ✓aspetto armonico o meno (abitus eunucoide, segni sindromici)
- ✓caratteri sessuali secondari
- ✓volume testicolare


U/L
1.25
1.00
0.80


5
3
8
10
12
15
20
25

Ritardo costituzionale di crescita e di maturazione (RCCM)

- **È la causa più frequente di ritardo della pubertà nel maschio (63%), ma è meno comune nelle femmine (30%)**

  spesso la pubertà tarda costituzionale non è altro che la fase “puberale” del ritardo costituzionale di crescita e di maturazione

Ritardo costituzionale di crescita e di maturazione

Bassa statura con velocità di crescita normale con rallentamento prepuberale
(variante normale della crescita)

Anamnesi familiare positiva per pubertà tarda

Età ossea ritardata (< - 2 DS)

Previsione statura definitiva normale

Pubertà tarda

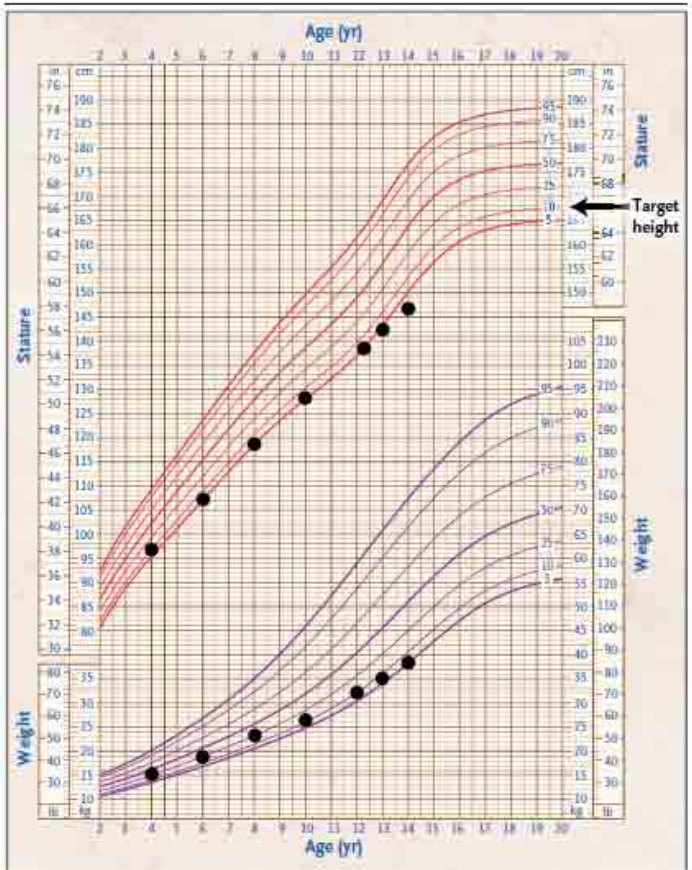


Figure 2. Linear Growth in Delayed Puberty.

In children with delayed puberty (data points), linear growth progresses with a normal preadolescent height velocity (>3 cm per year). Height relative to that of peers (height percentile) may decrease slightly before the usual adolescent age range, but this effect is accentuated when the child with delayed puberty does not undergo a growth spurt in concert with his or her peers. Consequently, the height percentile decreases in the early teenage years. In children with constitutional delay of growth and puberty, a late growth spurt will facilitate subsequent catch-up growth, but adult heights are often slightly shorter than expected on the basis of parental heights.

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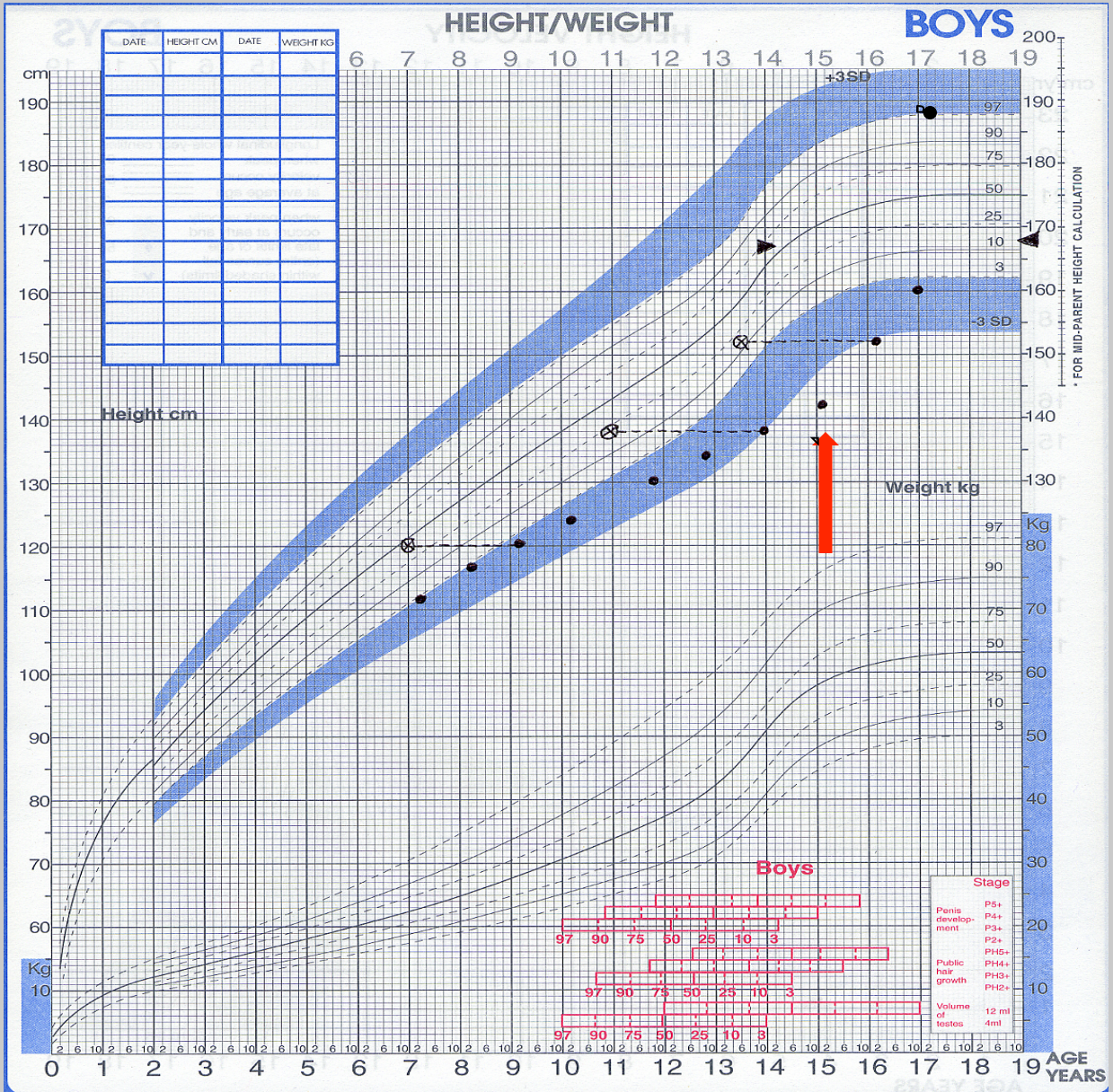
CLINICAL PRACTICE

Delayed Puberty

Mark R. Palmert, M.D., Ph.D., and Leo Dunkel, M.D., Ph.D.


HEIGHT/WEIGHT
BOYS
DATE
HEIGHT CM
DATE
WEIGHT KG
cm
Height cm
+3SD
-3 SD
97
90
75
50
25
10
3
* FOR MID-PARENT HEIGHT CALCULATION
Weight kg
Kg
Boys
Stage
Penis development
Public hair growth
Volume of testes
P5+
P4+
P3+
P2+
PH5+
PH4+
PH3+
PH2+
12 ml
4ml
AGE YEARS

Ipogonadismo ipogonadotropo funzionale

Disfunzione ipotalamica transitoria:

alterazione funzionale della secrezione ipotalamica di GnRH (alterata ciclicità e pulsatilità) dovuta a:

- malattie croniche (es. m. infiammatorie croniche dell'intestino, celiachia)
- anoressia nervosa, bulimia
- ipotiroidismo
- **attività agonistica**
- **stress psicologici ed emotivi**

anamnesi

esame obiettivo

laboratorio

esami strumentali

neuroradiologia

FSH- LH

test LHRH
test analogo

testosterone

17 beta estradiolo

FT4, TSH

cariotipo

Inibina

Prolattinemia

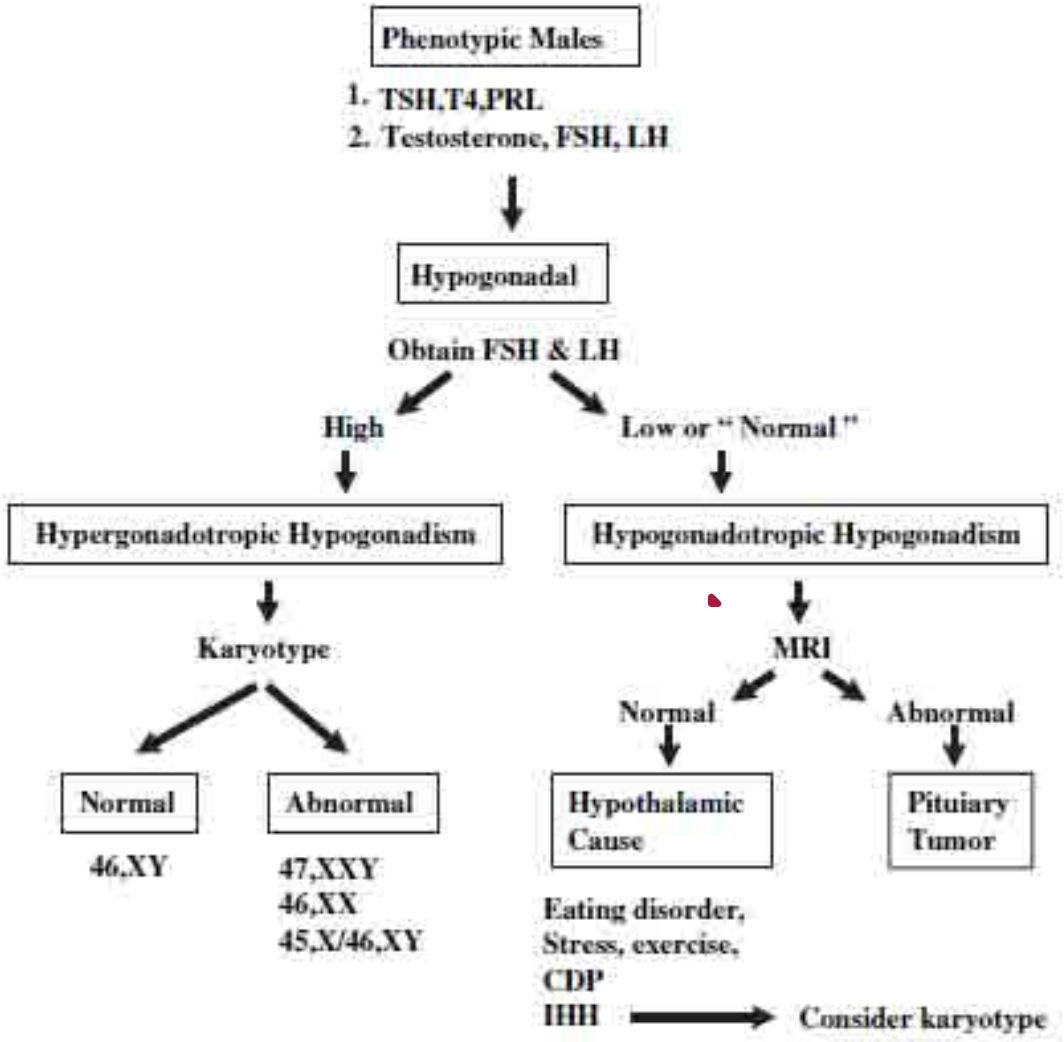


Fig. 1. An algorithm for the evaluation of delayed puberty in a phenotypic male patient is shown.

ELSEVIER SAUNDERS

Endocrinol Metab Clin N Am
36 (2007) 283–296

ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA

Hypogonadotropic Hypogonadism

Lawrence C. Layman, MD[a,b,*]

[a]Section of Reproductive Endocrinology, Infertility, and Genetics, Department of Obstetrics and Gynecology, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912, USA
[b]Program in Reproductive Medicine, Developmental Neurobiology Program, Institute of Molecular Medicine and Genetics, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912, USA

Ma quale livello di Gonadotropine deve essere considerato come cut-off nei vari stadi puberali ?

0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Diagnostic Value of Fluorometric Assays in the Evaluation of Precocious Puberty*

V. N. BRITO, M. C. BATISTA, M. F. BORGES, A. C. LATRONICO, M. B. F. KOHEK, A. C. P. THIRONE, B. H. JORGE, I. J. P. ARNHOLD, AND B. B. MENDONCA

Pubertal stage	Males			
	n	Chronological age (yr)	Basal LH (IU/L)	Basal FSH (IU/L)
Tanner 1	60	7.3 ± 2.9[a] (2–11.9)[b]	0.6 ± 0.1 (<0.6 to 0.7)	1.1 ± 0.3 (<1 to 3)
Tanner 2	26	12.5 ± 1.2 (10.5–14.8)	0.9 ± 0.5 (<0.6 to 2.7)	1.7 ± 1 (<1 to 4.4)
Tanner 3	16	14 ± 0.9 (12.3–15)	1.5 ± 0.7 (<0.6 to 3.1)	2.3 ± 1.3 (<1 to 6.3)
Tanner 4–5[c]	25	15.4 ± 1.5 (13–17.9)	2.2 ± 1.4 (<0.6 to 5.1)	2.8 ± 2 (<1 to 7.9)
Adults	35	27.3 ± 4.7 (23–37)	3.9 ± 1.8 (1.4–9.2)	2.7 ± 2 (<1 to 10.5)

Pubertal stage	Males	
	n	Testosterone (ng/dL)
Tanner 1	56	14.1 ± 0.8[a] (<14 to 19)[b]
Tanner 2	25	36.8 ± 41.2 (<14 to 154)
Tanner 3	16	274.3 ± 172.4 (22–542)
Tanner 4–5[c]	25	402.5 ± 182.4 (109–669)
Adults	9	624 ± 146.6 (444–845)

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(4):1424–1429

doi: 10.1210/jc.2006-1569

Assessment of Basal and Gonadotropin-Releasing Hormone-Stimulated Gonadotropins by Immunochemiluminometric and Immunofluorometric Assays in Normal Children

E. A. M. R. Resende, B. H. J. Lara, J. D. Reis, B. P. Ferreira, G. A. Pereira, and M. F. Borges

Discipline of Endocrinology and Statistics, Faculdade de Medicina da Universidade Federal do Triângulo Mineiro, 38025-180 Uberaba, Minas Gerais, Brazil

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(4):1424–1429

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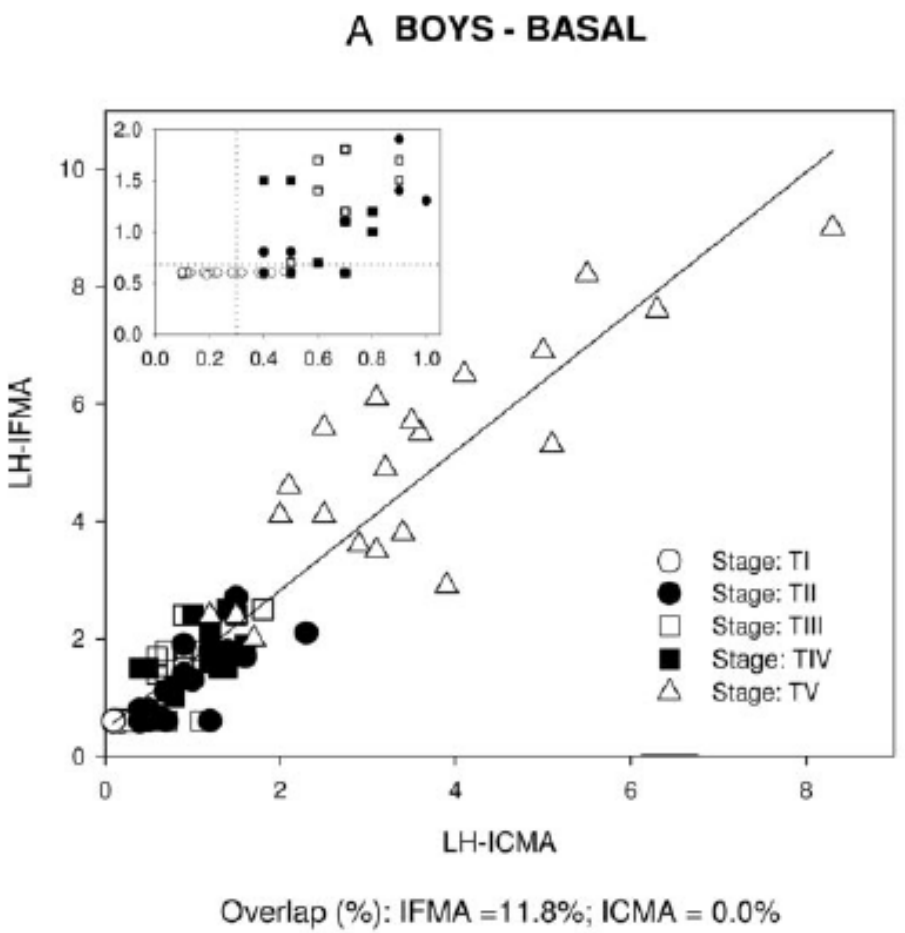
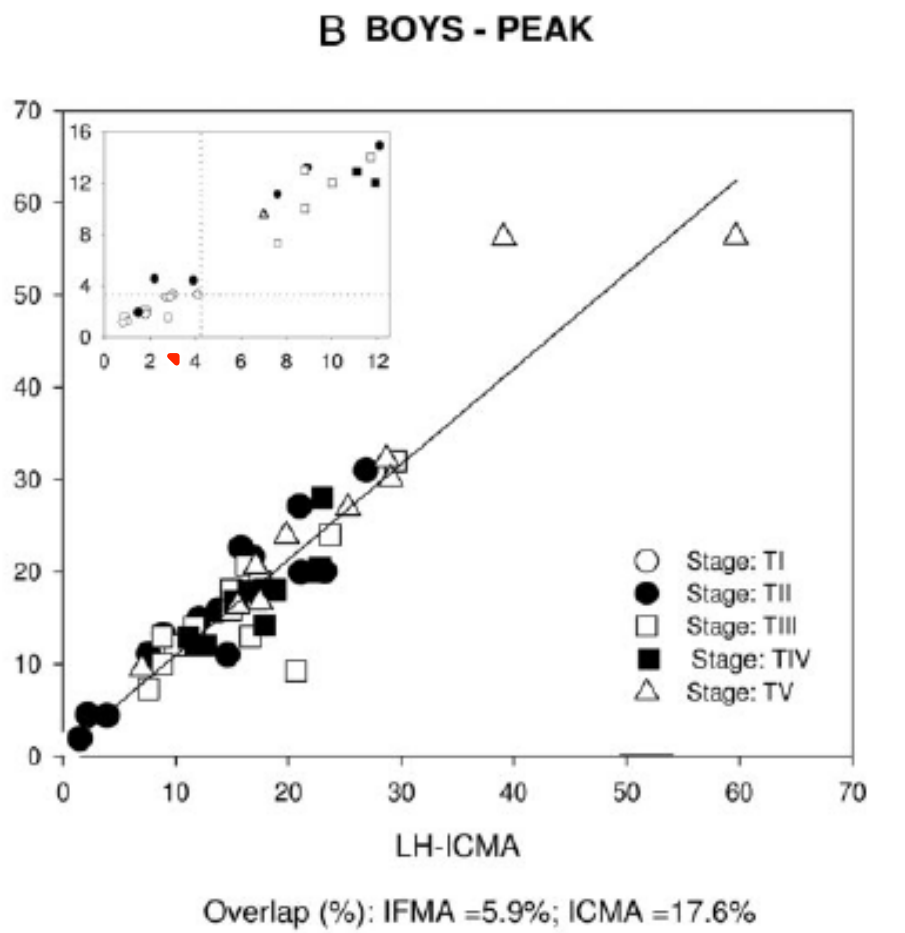
Discipline of Endocrinology and Statistics, Faculdade de Medicina da Universidade Federal do Triângulo Mineiro, 38025-180 Uberaba, Minas Gerais, Brazil

Pubertal stage	Males						
	n	Age (yr)	LH (IU/liter)		FSH (IU/liter)		n
			ICMA	IFMA	ICMA	IFMA	
TI-$_1$	20	1.6 ± 0.7 (0.6–2.5)	0.1 ± 0.02 (0.1–0.2)	0.6 ± 0.0[a] (0.6–0.6)	0.2 ± 0.3 (0.1–0.9)	1.0 ± 0.2[a] (1.0–1.4)	25
TI-$_2$	82	7.1 ± 2.4 (2.7–12.0)	0.1 ± 0.1 (0.1–0.3)	0.6 ± 0.0[a] (0.6–0.6)	0.3 ± 0.2 (0.1–0.9)	1.1 ± 0.2[a] (1.1–1.6)	56
TII	17	12.5 ± 1.5 (10.1–14.8)	1.0 ± 0.5 (0.4–2.3)	1.3 ± 0.6 (0.6–2.7)	1.1 ± 0.8 (0.1–2.8)	1.8 ± 1.0[a] (1.0–4.3)	13
TIII	14	13.6 ± 1.1 (11.3–15.0)	0.8 ± 0.3 (0.5–1.8)	1.4 ± 0.5[a] (0.6–2.5)	1.1 ± 0.8 (0.3–3.0)	2.1 ± 1.2[a] (1.0–5.5)	12
TIV	16	14.7 ± 8.3 (12.9–16.1)	1.0 ± 0.4 (0.3–1.6)	1.6 ± 0.6[a] (0.7–2.5)	1.4 ± 1.2 (0.4–5.0)	2.1 ± 1.3[a] (1.0–5.2)	11
TV	21	22.1 ± 2.8 (18.3–27.0)	3.5 ± 1.7 (1.5–6.3)	4.7 ± 1.9[a] (2.4–8.2)	2.3 ± 1.5 (0.6–5.0)	3.2 ± 1.7[a] (1.2–5.7)	28

Pubertal stage	Males					
	n	LH (IU/liter)		FSH (IU/liter)		n
		ICMA	IFMA	ICMA	IFMA	
TI-$_2$	10	2.2 ± 1.09 (0.8–4.1)	2.2 ± 0.9 (1.1–3.3)	3.0 ± 4.9 (1.4–10.4)	5.7 ± 2.6 (2.4–10.6)	10
TII	14	13.5 ± 8.0 (1.5–26.9)	15.6 ± 8.7 (1.9–31.0)	2.5 ± 2.8 (0.8–9.2)	3.6 ± 2.4 (1.4–10.2)	10
TIII	14	15.6 ± 6.2 (7.6–29.5)	16.1 ± 6.5 (7.3–32.0)	3.1 ± 3.3 (0.7–11.8)	4.2 ± 3.3 (1.1–13.0)	9
TIV	11	17.3 ± 4.3 (11.1–23.0)	17.3 ± 4.7 (12.0–28.0)	3.4 ± 4.1 (1.2–13.2)	4.8 ± 3.1 (1.7–12.0)	9
TV	10	25.9 ± 14.8 (7.0–59.7)	28.9 ± 15.9 (9.5–56.3)	4.9 ± 5.6 (1.0–16.7)	5.3 ± 3.9 (1.8–12.0)	9


A BOYS - BASAL
LH-IFMA
LH-ICMA
Stage: TI
Stage: TII
Stage: TIII
Stage: TIV
Stage: TV
Overlap (%): IFMA =11.8%; ICMA = 0.0%


B BOYS - PEAK
LH-ICMA
Stage: TI
Stage: TII
Stage: TIII
Stage: TIV
Stage: TV
Overlap (%): IFMA =5.9%; ICMA =17.6%

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Delayed Puberty

Mark R. Palmert, M.D., Ph.D., and Leo Dunkel, M.D., Ph.D.

Serum luteinizing hormone	At low levels, values obtained on immunochemiluminometric (ICMA) assays are at least 50% lower than those obtained on immunofluorometric (IFMA) assays.[24] Values of <0.1 IU per liter are not specific for hypogonadotropic hypogonadism. Values of >0.2 IU per liter on ICMA or >0.6 IU per liter on IFMA are specific but not sensitive for the initiation of central puberty; some adolescents in early puberty have lower values.[24] In delayed puberty, elevated values suggest primary hypogonadism. In general, luteinizing hormone is a better marker of pubertal initiation than follicle-stimulating hormone.

Valori normali test GnRH e testosterone

Valori normali test GnRH

- prepubertà: picco LH <3-4 mU/ml;
- pubertà: picco LH 5-8 mU/ml

Valori normali del testosterone (nel maschio)

- prepubertà <20 ng/dl
- predittivi di un incipiente inizio della pubertà (12-15 mesi) >20 ng/dl
- adulto: 250-1000 ng/dl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Delayed Puberty

Mark R. Palmert, M.D., Ph.D., and Leo Dunkel, M.D., Ph.D.

Distinguishing Constitutional Delay of Growth and Puberty from Isolated Hypogonadotropic Hypogonadism: Critical Appraisal of Available Diagnostic Tests

Jennifer Harrington and Mark R. Palmert

Division of Endocrinology, The Hospital for Sick Children and Department of Pediatrics, The University of Toronto, Toronto, Canada M5G1X8

Thus, the evidence-based literature regarding the available tests is insufficient to recommend any of them for routine clinical use. Further validation of previously published diagnostic thresholds as well as prospective studies focusing on prepubertal 14- to 15-yr-old adolescents are still needed

J Clin Endocrinol Metab, September 2012, 97(9):3056–3067

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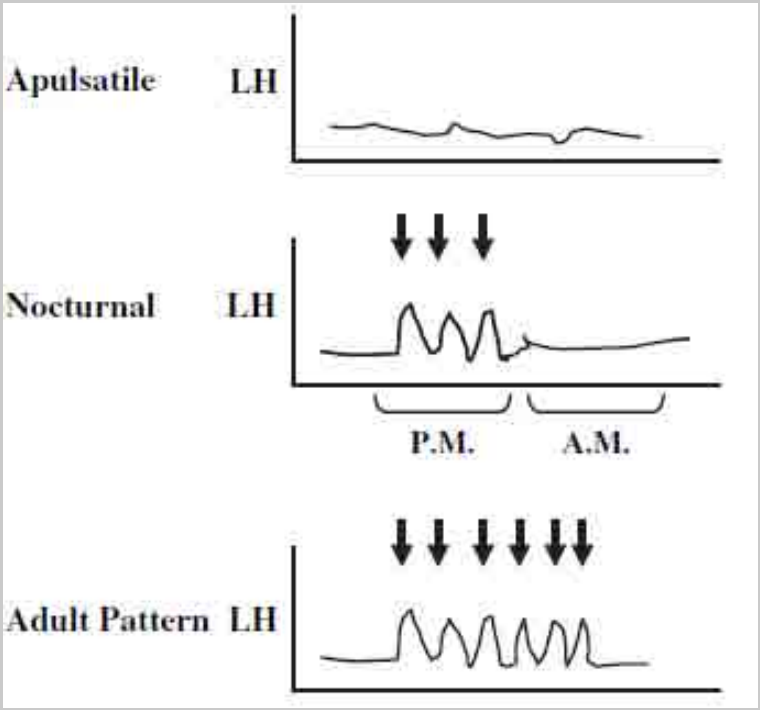
Endocrinol Metab Clin N Am
36 (2007) 283–296

ENDOCRINOLOGY
AND METABOLISM
CLINICS
OF NORTH AMERICA

Hypogonadotropic Hypogonadism

Lawrence C. Layman, MD[a,b,*]

[a]*Section of Reproductive Endocrinology, Infertility, and Genetics, Department of Obstetrics and Gynecology, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912, USA*
[b]*Program in Reproductive Medicine, Developmental Neurobiology Program, Institute of Molecular Medicine and Genetics, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912, USA*



Box 1. Medical conditions associated with hypogonadotropic hypogonadism

Disorders

Central nervous system (CNS) developmental abnormalities
Parasitic diseases
Head trauma
Crohn's disease
β-thalassemia/hemoglobinopathies
Metabolic disorders, such as amino acidopathies and carbohydrate, lipid metabolism, or lysosomal storage disease
Hemochromatosis
Malignancy
Pituitary tumors
Autoimmune diseases
Granulomatous disease
HIV
Lymphocytic hypophysitis

esame obiettivo

anamnesi

laboratorio

esami strumentali

neuroradiologia

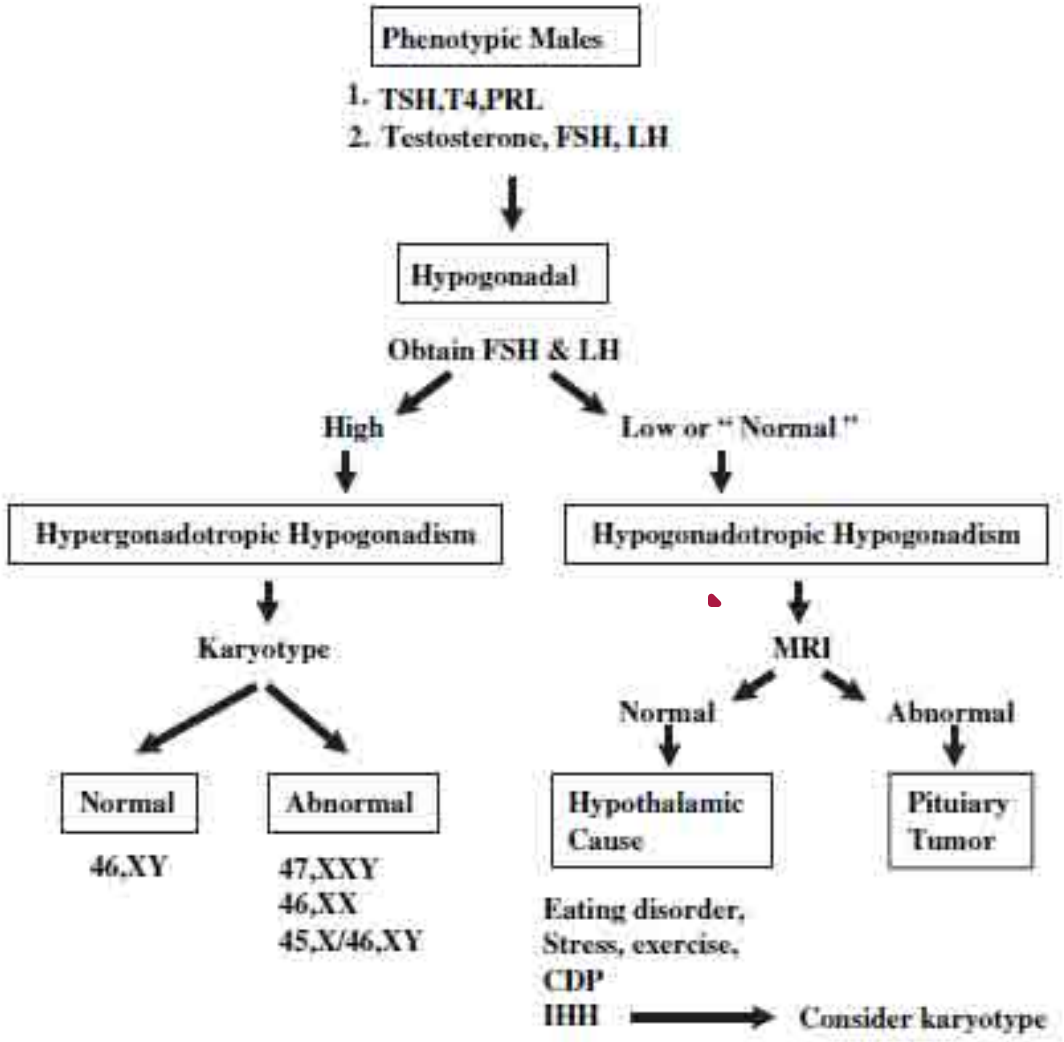


Fig. 1. An algorithm for the evaluation of delayed puberty in a phenotypic male patient is shown.

ELSEVIER SAUNDERS

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ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA

Hypogonadotropic Hypogonadism

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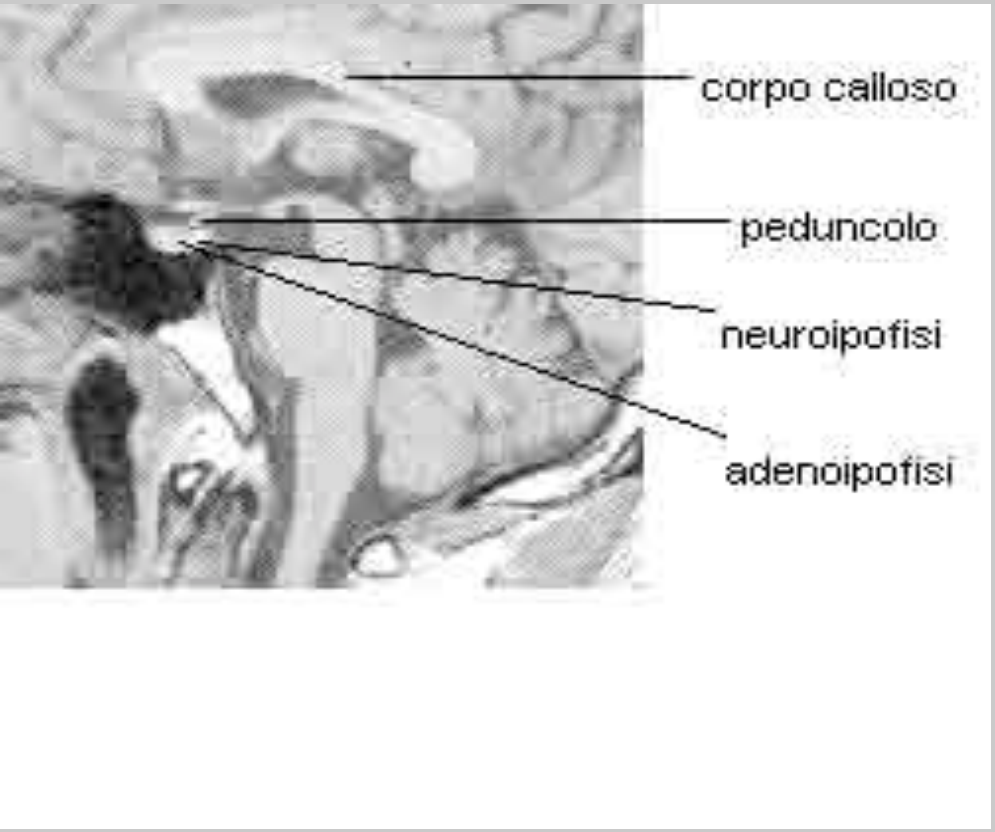
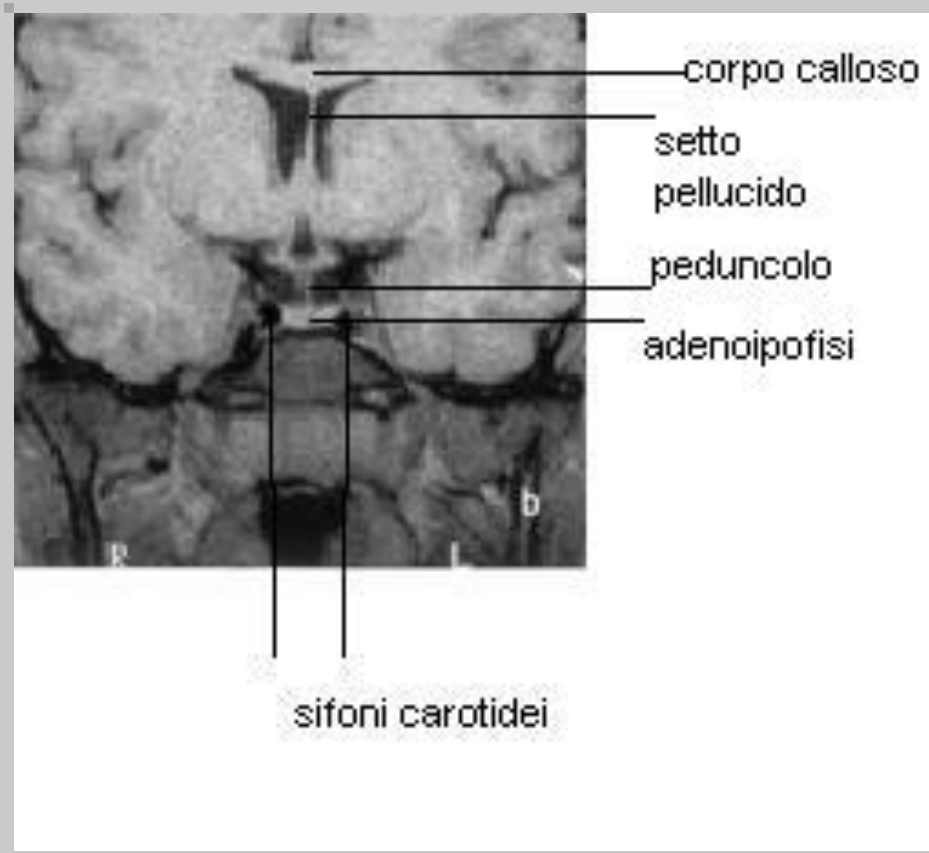
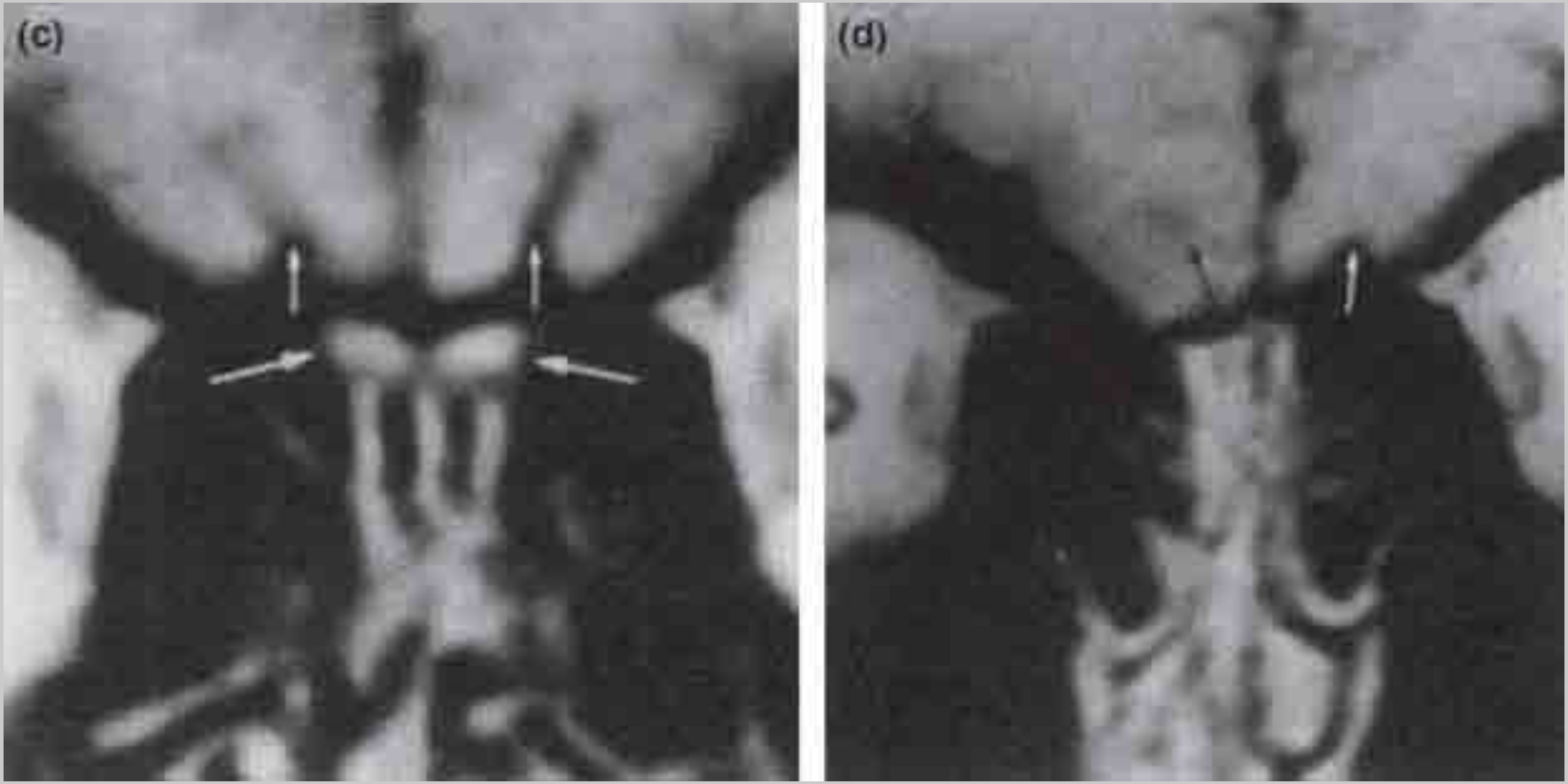
Neuroradiologia

- ✓ RM encefalo






(c)
(d)

Grazie …