Lo adolescente non si sviluppa

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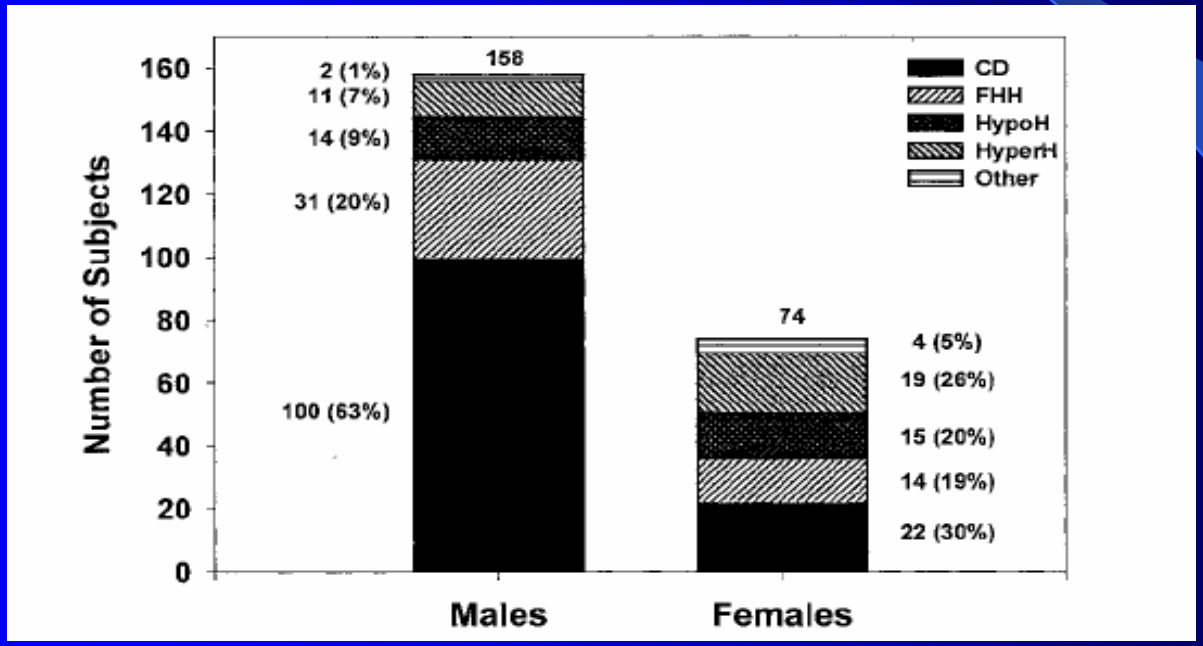
Delayed Puberty: Analysis of a Large Case Series from an Academic Center

I.L. SEDLMEYER AND M. R. PALMER

J Clin Endocrinol Metab 87: 1613–1620, 2002



CD= constitutional delay of growth and maturation; FHH= functional hypogonadotropic hypogonadism; Hyper H= hypergonadotropic hypogonadism; Hypo H = hypogonadotropic hypogonadism.

Reconsidering the Sex Differences in the Incidence of Pubertal Disorders

A. Papadimitriou, G. P. Chrousos

Horm Metab Res 2005; 37: 708±710

Table 1 Factors that have a role in the sex differences in the incidence of pubertal maturation

1. The onset of puberty is detected more easily in girls.
2. Pubertal growth spurt in girls starts soon after the onset of puberty, but is rather a late event in boys.
3. Boys experience more pressure on height than girls.
4. The secular trend for early puberty can only be substantiated for girls.

Avvicinarsi alla diagnosi con 5 domande

1° Domanda

1° Domanda

Quanti anni hai?

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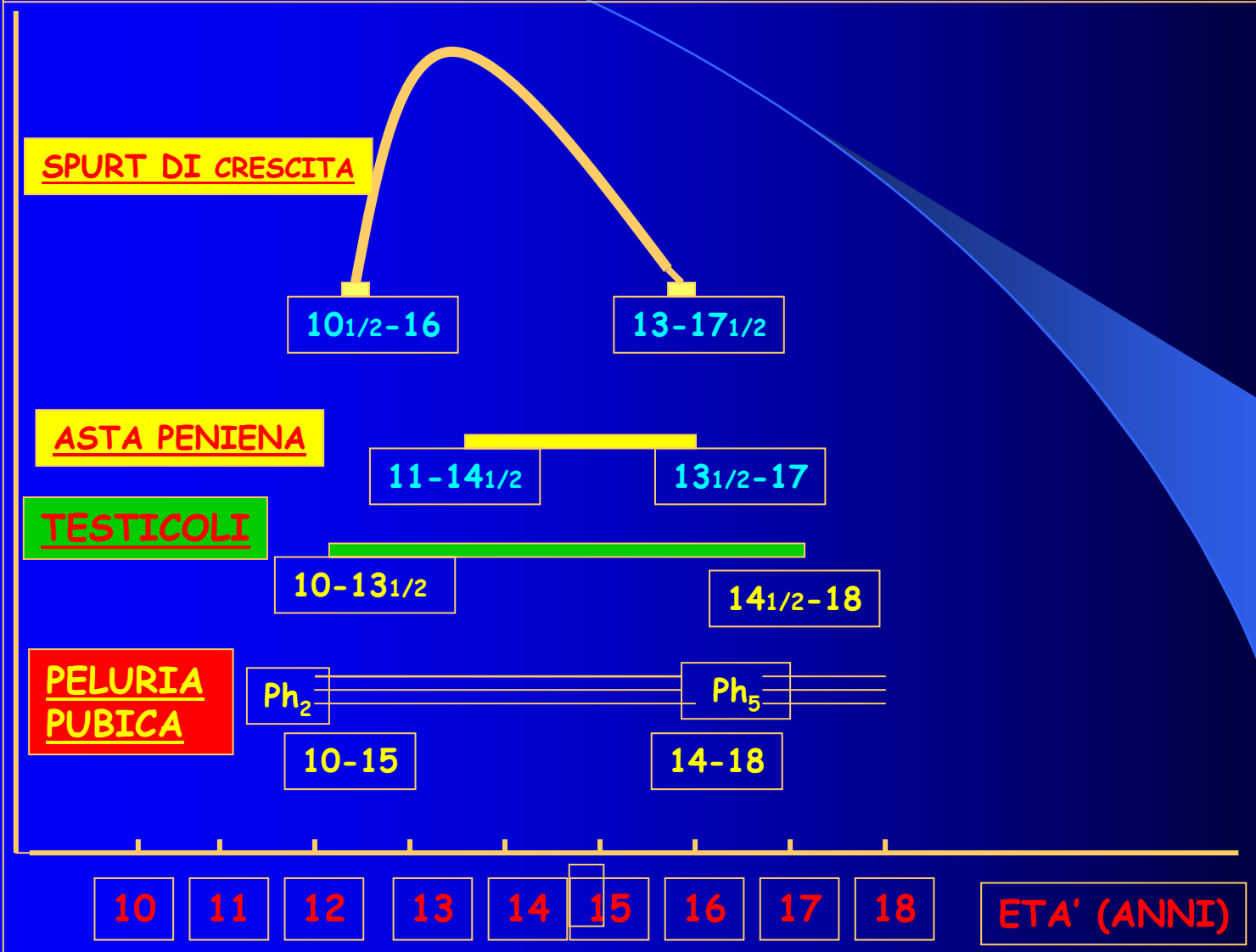
DELAYED PUBERTY is defined as lack of the initial signs of sexual maturation by an age that is more than 2–2.5 sd above the mean for the population (14 yr in boys)

Esperienza personale

Degli ultimi 30 ragazzi giunti alla mia osservazione per una valutazione del ritardo puberale l'87% aveva al massimo 13 anni.

Cronologia dello sviluppo puberale nei maschi



2° Domanda

2° Domanda

Quando sono comparsi i caratteri sessuali secondari e il menarca in genitori, avi e fratelli ?

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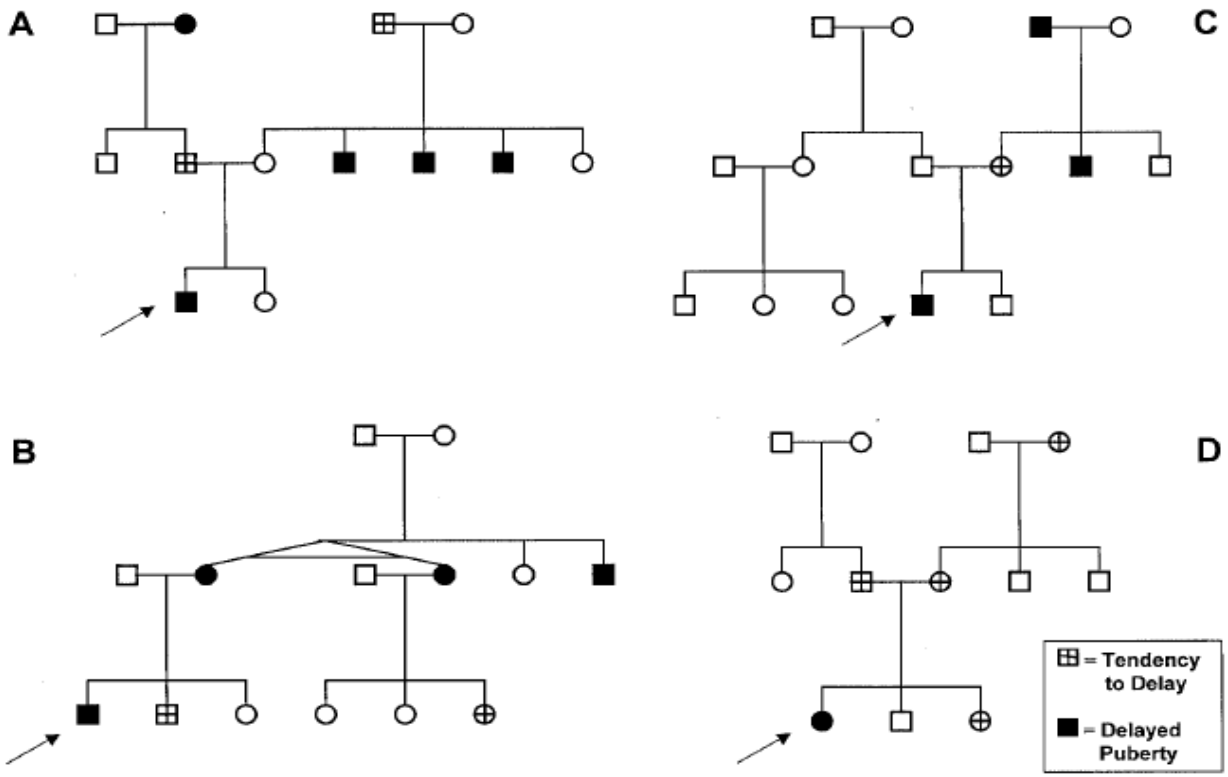

FIG. 3. Examples of pedigrees illustrating the extensive history of pubertal delay seen among some families within the constitutional delay group. Individuals with *blackened symbols* met criteria for the diagnosis of delayed puberty; those with *cross symbols* met criteria for tendency for pubertal delay. Pedigree D is included as an example of delay worsening through combined contribution from each parent or in subsequent generations. *Arrows* identify probands.

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Among CD subjects, data permitted classification of family history in 95 of 122 subjects. These histories were positive for at least a tendency to pubertal delay (development 1 sd beyond the mean) in 77% of the cases and for a diagnosis of delay (development 2 sd beyond the mean) in 38%.

(b)

Fig. 2 Father and son with constitutional delay in growth and puberty. The son is aged 12 years in (a) and the father (arrowed in b) is shown at age 14 years. No investigation was required in the son

3° Domanda

3° Domanda

Eventuali malattie remote e/o recenti
e terapia farmacologica connessa.

Delayed puberty in chronic illness

J.Pozo, J Argente

Best Practice& Research Clinical Endocrinology and Metabolism 2002

Table I. The main chronic diseases responsible for delayed puberty .

- Malnutrition
  - Caloric-protein
  - Micronutrients (Ca, Zn, etc)
- Recurrent infections/infestations
- Immunodeficiency
  - Congenital
  - AIDS
- Gastrointestinal diseases
  - Malabsorption
    - Coeliac disease
    - *Giardia lamblia* infestation
    - Pancreatic cystic fibrosis
  - Inflammatory bowel disease
  - Chronic hepatopathies
- Renal diseases
  - Glomerular nephropathies
  - Congenital tubular defects
  - Interstitial nephropathies
  - Nephrotic syndrome
  - Chronic renal failure
- Respiratory diseases
  - Chronic asthma
  - Pancreatic cystic fibrosis
- Haematological diseases
  - Leukaemia
  - Chronic anaemia
    - Thalassaemia major
    - Drepanocytic anaemia
  - Hystiocytosis
- Endocrinopathies
  - Hypogonadism, hypogonadotrophic
  - Hypogonadism, hypergonadotrophic
  - GH deficiency
  - Hypothyroidism/hyperthyroidism
  - Poorly controlled type I diabetes
  - Hypercortisolism
  - Hyperprolactinaemia
- Eating disorders
  - Anorexia and bulimia nervosa
- Strenuous exercise (athletic amenorrhea)
- Miscellaneous
  - Connective tissue inflammatory diseases
  - Psychological stress
  - Gaucher's disease
  - Cancer and tumour therapy
  - Chronic cardiopathies

Ca, calcium; Zn, zinc; AIDS, acquired immunodeficiency syndrome; GH, growth hormone.

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  - Connective tissue inflammatory diseases
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  - Chronic cardiopathies

Ca, calcium; Zn, zinc; AIDS, acquired immunodeficiency syndrome; GH, growth hormone.

v. Ital. Ped. (I.J.P.), 10, 229-232, 1984

Articoli originali

Original articles

La bassa statura come manifestazione principale di malattia celiaca
Valutazione auxologica prima e dopo dieta senza glutin

Short stature as the most relevant sign of coeliac disease.
Auxological evaluation before and after gluten free diet

G. Banchini, G. L. de Angelis, G. Gregori, C. Zanacca, C. Volta, S. Bernasconi, G. Giovannelli

4° Domanda

4° Domanda

Alimentazione e “stili di vita” (attività fisico-sportiva)

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Ca, calcium; Zn, zinc; AIDS, acquired immunodeficiency syndrome; GH, growth hormone.

Delayed puberty in chronic illness

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Best Practice& Research Clinical Endocrinology and Metabolism 2002

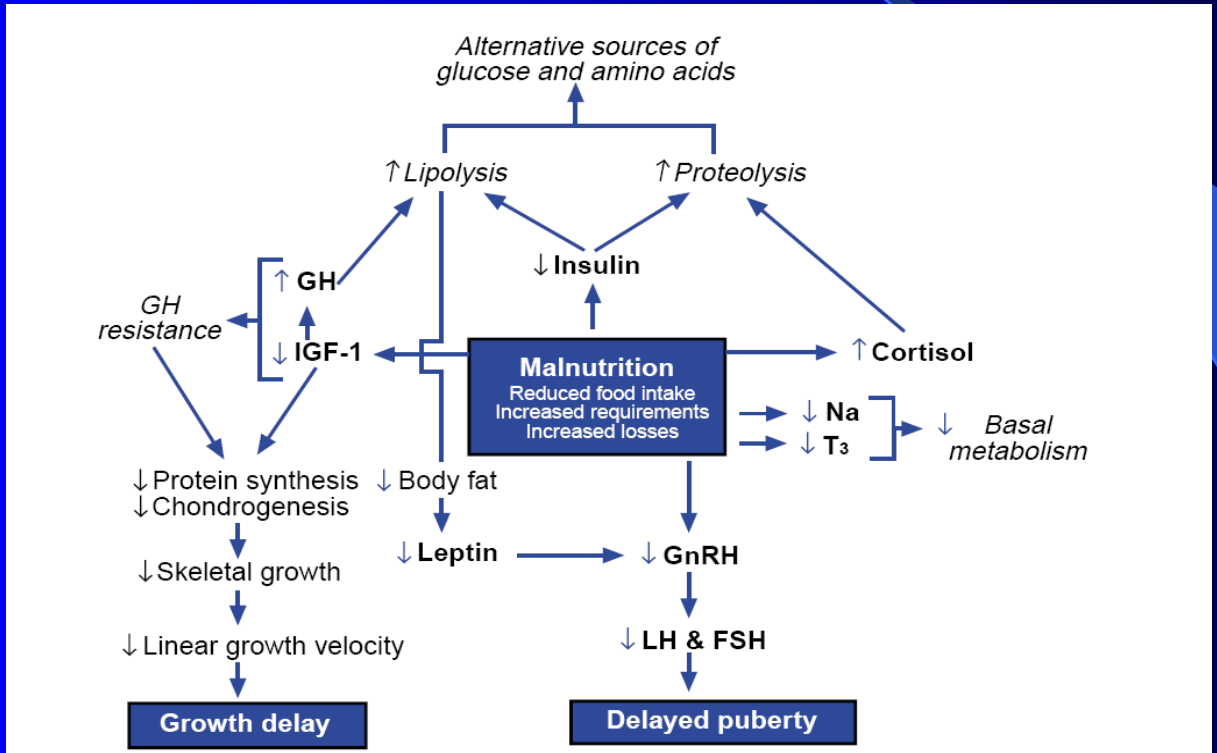
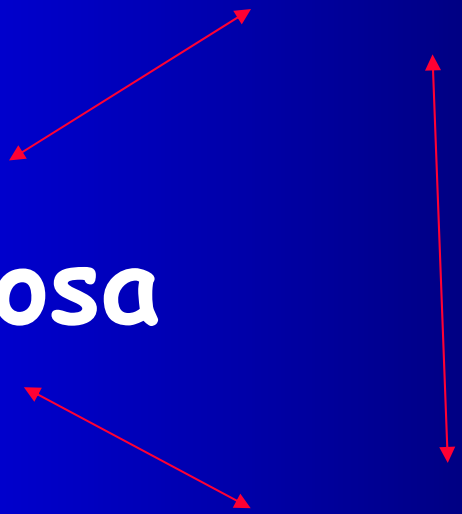


Figure 1. Schematic representation showing how malnutrition can produce growth delay and delayed puberty. GH, growth hormone; IGF-1, insulin-like growth factor-1; Na, Sodium; T_3, 3,5,3′-teilodothyronine, GnRH, gonadotrophin releasing hormone; LH, luteinizing hormone, FSH, follicle stimulating hormone.

Esercizio fisico (atleti)



Anoressia nervosa

Malnutrizione

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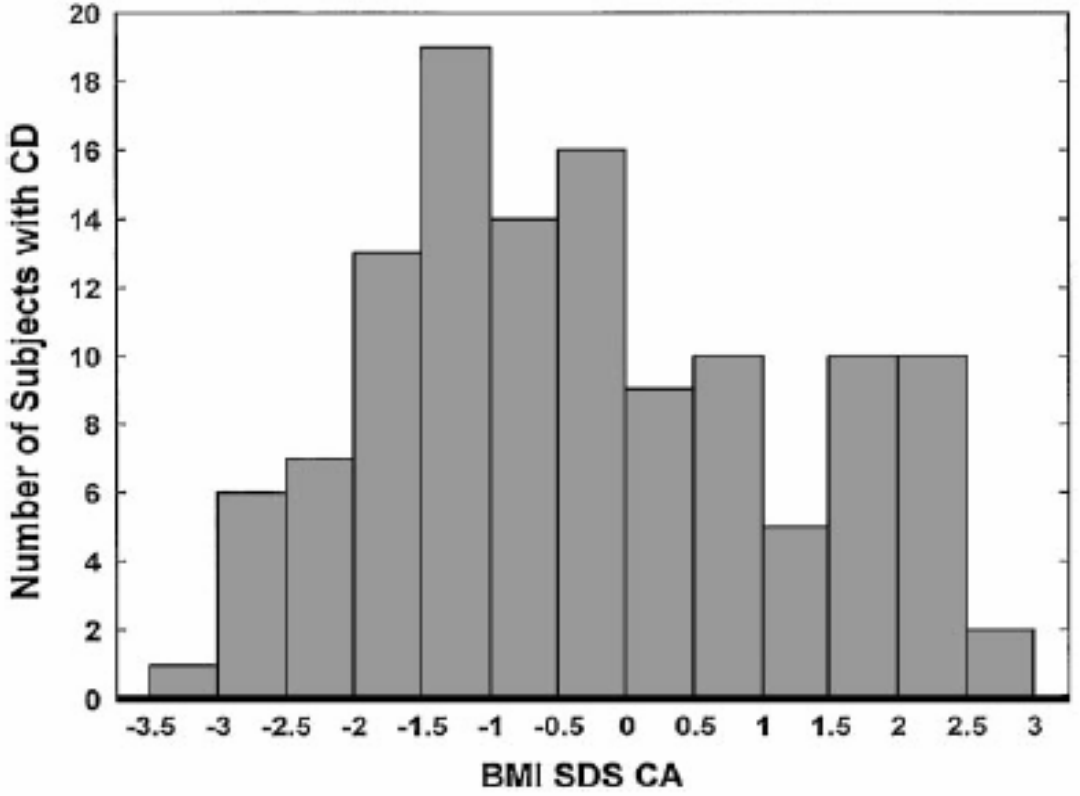

FIG. 4. BMI SD scores for CA (BMI SDS CA) among subjects with CD. Overweight is defined as a BMI SDS CA of 85% or more (SD score, ≥1.0375). The distribution is not normal ($P = 0.001$) and suggests a bimodal pattern.

Evidence for Hypermetabolism in Boys with Constitutional Delay of Growth and Maturation

J. C. Han, P. Balagopal, S. Sweeten, D. Darmaun, and N. Mauras

J Clin Endocrinol Metab 91: 2081–2086, 2006

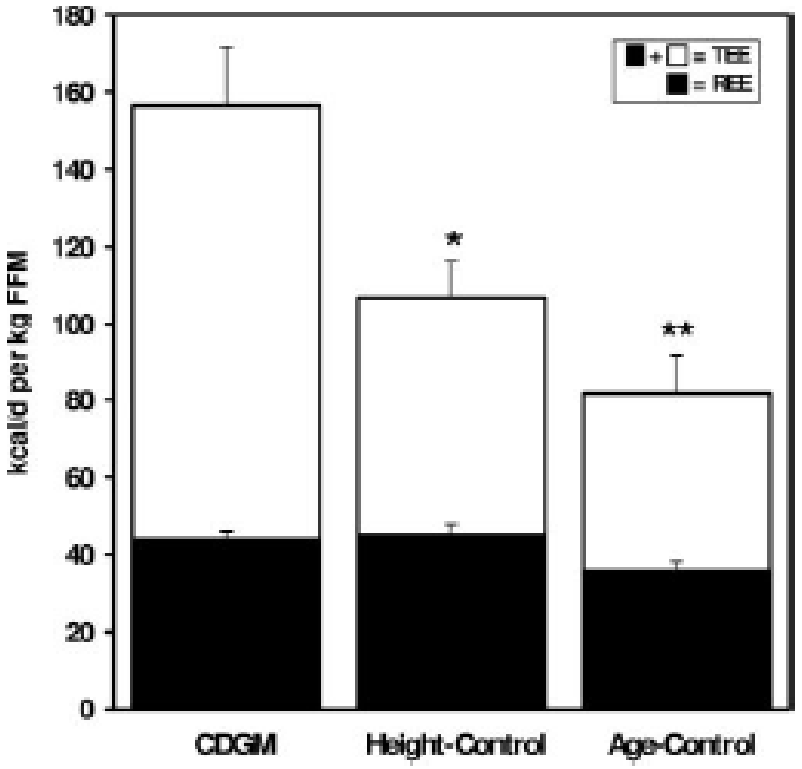

FIG. 1. Energy expenditure per kilogram FFM: comparison of TEE (kcal/d·kg FFM) in the boys with CDGM *vs.* height-matched (younger, prepubertal) and age-matched (taller, pubertal) controls (n = 12 per group). Data are expressed as mean ± SEM. *Solid bar* represents the REE contribution to TEE. *, $P < 0.05$ *vs.* CDGM; **, $P < 0.001$ *vs.* CDGM.

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J Clin Endocrinol Metab 91: 2081–2086, 2006

- Increased NEAT (nonexercise-activity thermogenesis) could contribute to the decreased total body weight, lower percent body fat,and lower FFM observed in CDGM
- Plymorphism in the gene for uncopling protein 1 (UCP1), a carrier protein located in the mithochondrial inner membrane of brown adipose tissue,have been associated with difference in weight changes in response to dietary restriction and exercise,mediated presumably through alterations in thermogenic proton leakage….

Vitamin A and iron supplementation is as efficient as hormonal therapy in constitutionally delayed children

Table 2 Height, BMI, height velocity, change in bone age/year (D-BA) and IGF-I and vitamin A during the study (mean ± SD)

	Oxandrolone + nutrition*	Oxandrolone	Nutrition	Testosterone 3 months	Testosterone 6 months	Observation
Number	15	15	17	15	20	20
Height (SDS)						
0 month	−2·7 (0·6)†	−2·6 (0·8)†	−2·7 (0·7)†	−2·6 (0·5)†	−2·6 (0·5)	−2·6 (0·6)
6 months	−2·2 (0·8)	−2·1 (0·7)	−2·2 (0·3)	−2·1 (0·3)	−2·1 (0·5)	−2·6 (0·5)**
12 months	−2·0 (1·0)†	−1·9 (0·6)†	−1·9 (0·5)†	−1·8 (0·5)†	−1·8 (0·5)	−2·9 (0·7)¶
BMI (kg/m^2)						
0 month	16·3 2·0	16·2 (1·9)	15·8 (1·8)	15·9 (1·9)	16·0 (1·9)	16·0 (2·0)
6 months	16·8 (2·1)	16·8 (2·0)	15·9 (1·9)	16·1 (2·0)	16·0 (1·9)	15·9 (2·0)
12 months	17·1 (2·1)	17·1 (2·1)	15·9 (1·9)	16·3 (2·0)	16·0 (2·0)	16·0 (2·0)
% Boys testicular volume ≥ 6						
6 month	0	0	100	0	0	0
12 months	100	100	100	100	100	0
Height velocity (cm/year)						
0 month	4·2 (1·4)‡§	3·9 (1·5)	4·4 (0·7)‡§	4·2 (0·8)‡§	4·3 (1·2)	4·4 (1·2)
6 months	11·4 (2·4)§	9·6 (2·3)§	7·8 (1·9)§	10·5 (1·6)§	10·5 (1·6)§	4·2 (0·6)¶
12 months	8·1 (1·2)‡	9·6 (1·2)‡	9·3 (2·9)‡	8·8 (1·0)‡	10·5 (1·0)‡	4·0 (0·9)¶
Change in bone age/year (years)						
6 months	0·5 (0·1)	0·5 (0·1)	0·5 (0·1)	0·5 (0·1)	0·5 (0·1)	0·4 (0·2)
12 months	0·8 (0·1)	0·8 (0·1)	0·9 (0·1)	1·0 (0·1)	1·5 (0·4)‡	0·6 (0·2)¶
IGF-I (nmol/l)						
0 month	13·7 (8·5)‡§	15·0 (8·3)‡§	11·4 (4·2)‡§	11·2 (4·8)‡§	11·4 (4·8)	11·5 (4·9)
6 months	24·7 (6·7)§	25·1 (7·7)§	18·7 (5·7)§	23·2 (6·0)§	24·1 (6·2)	15·3 (7·4)
12 months	29·5 (9·6)	26·8 (8·5)‡	23·2 (4·2)‡	21·5 (4·9)‡	22·2 (6·2)	17·1 (8·9)
Iron µg/dl						
0 month	62·5 (10·1)	62·8 (9·5)	58·3 (13·6)	65·7 (10·4)	59·7 (12·7)	61·7 (17·6)
6 months	64·9 (10·4)	78·4 (10·9)‡††	74·6 (11·8)‡††	62·8 (9·5)	62·0 (7·8)	61·6 (14·9)
12 months	66·8 (11·5)	93·9 (11·0)††	87·7 (19·3)††	64·6 (8·9)	61·2 (8·9)	59·6 (9·5)
Vitamin A µg/dl						
0 month	22·7 (5·3)	20·5 (5·8)	20·5 (5·2)	20·3 (5·8)	20·4 (5·2)	22·3 (8·2)
6 months	24·9 (5·1)	40·5 (9·9)‡††	40·5 (10·9)‡††	21·1 (5·5)	22·0 (5·8)	26·1 (7·2)
12 months	27·2 (5·3)	41·2 (11·0)††	41·2 (11·1)††	28·3 (5·7)	26·8 (6·1)	28·4 (8·1)

*The group of oxandrolone + nutrition was identical in all parameters to the oxandrolone group, except for the vitamin A levels that were not different than those of the nutrition group.
†Significant change over 12 months, $P < 0·05$ (ANOVA).
‡Significant change over 12 months, $P < 0·01$ (ANOVA).
§Significant change over 12 months, $P < 0·01$ (ANOVA).
¶Significantly lower than other groups, $P < 0·01$ (ANOVA).
**Significantly lower than other groups, $P < 0·05$ (ANOVA).

Z. Zadik et al.

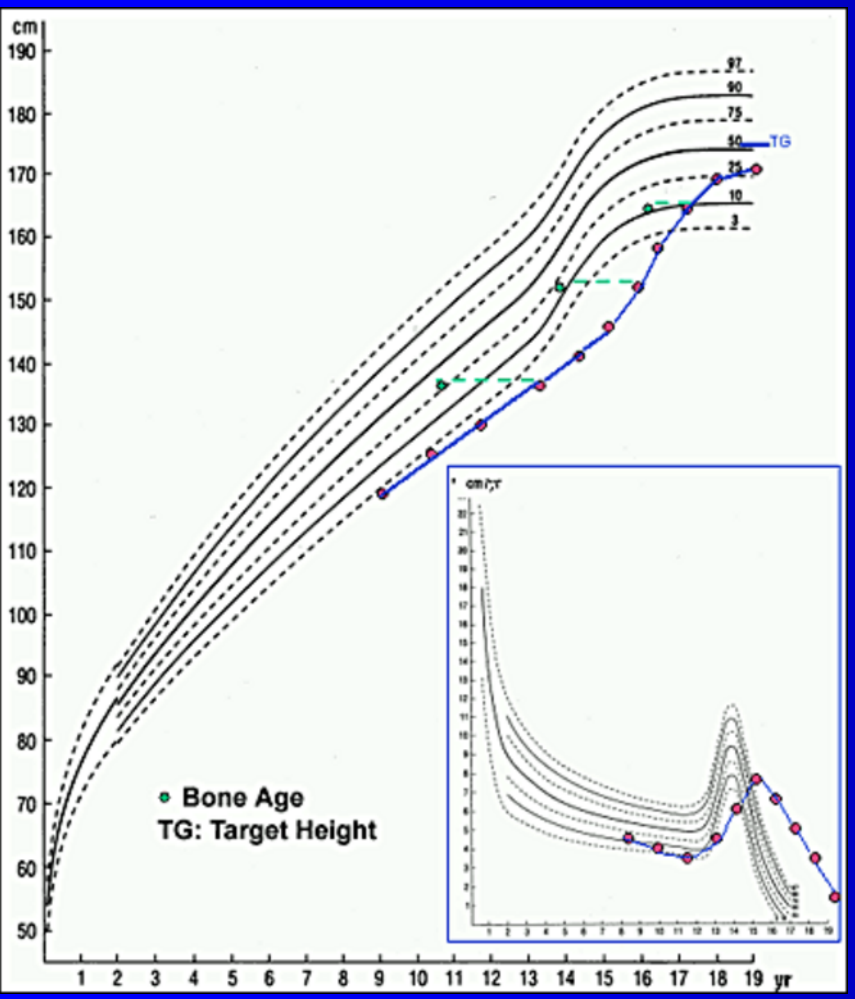
Clinical Endocrinology (2004)

5° Domanda

5° Domanda

Crescita staturo-ponderale e maturazione ossea negli anni precedenti la visita.

Growth curve of a boy with constitutional delay showing slower growth in the peripubertal time and then achievement of the normal range by the end of the growth process. The growth velocity curve is shown with a more attenuated and lower increase at puberty (Ghizzoni, Street 2007)



Età ossea ritardata

L'inizio della pubertà correla maggiormente con l'età ossea che con l'età cronologica.

Esame obiettivo

- Valutazione clinica e psicologica generale
- **Valutazione degli stadi puberali**: stadiazione secondo Tanner di A B P, volume testicolare e presenza o meno di sudorazione acre

Valutazione del volume testicolare

Delayed Puberty

C. Traggiai, R.Stanhope

Best Practice & Research Clinical Endocrinology and Metabolism 2002

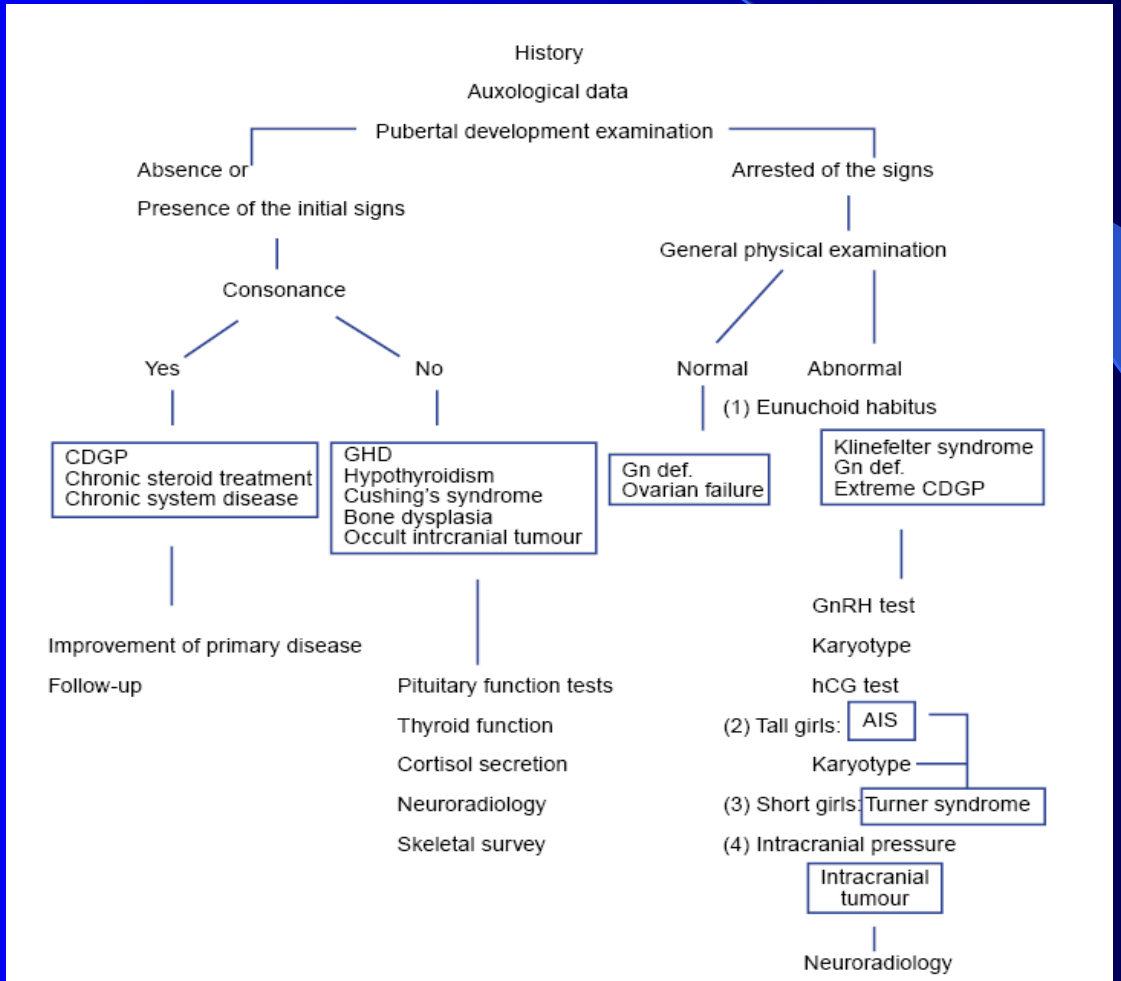
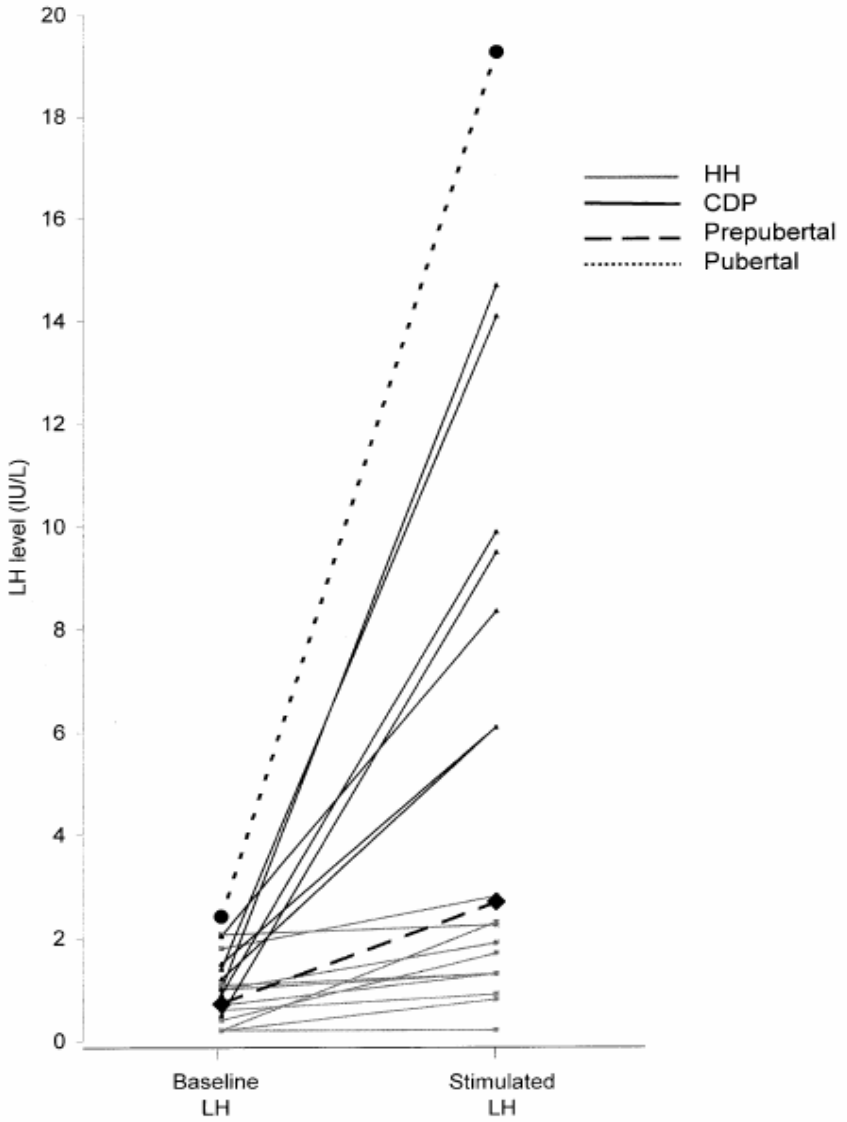


Figure 1. Flow chart for the investigation of delayed puberty. CDGP, constitutional delay of growth and puberty; GHD, growth hormone deficiency; Gn def, gonadotrophin deficiency; Gn RH, gonadotrophin



Street. Stimulated LH discriminates delayed puberty. Fertil Steril 2002.

EVALUATION OF THE BUSERELIN STIMULATION TEST IN DIAGNOSING GONADOTROPIN DEFICIENCY IN MALES WITH DELAYED PUBERTY

DYANNE A. WILSON, MBChB, DCH, P. L. HOFMAN, BHB, MBChB, DipObs, FRACP, H. L. MILES, BM, BS, MRCPCH, K. E. UNWIN, NZRCpN, C. E. McGRAIL, NZRGON, AND WAYNE S. CUTFIELD, BHB, MBChB, DCH, FRACP, MD

J Pediatr 2006;148:89-94

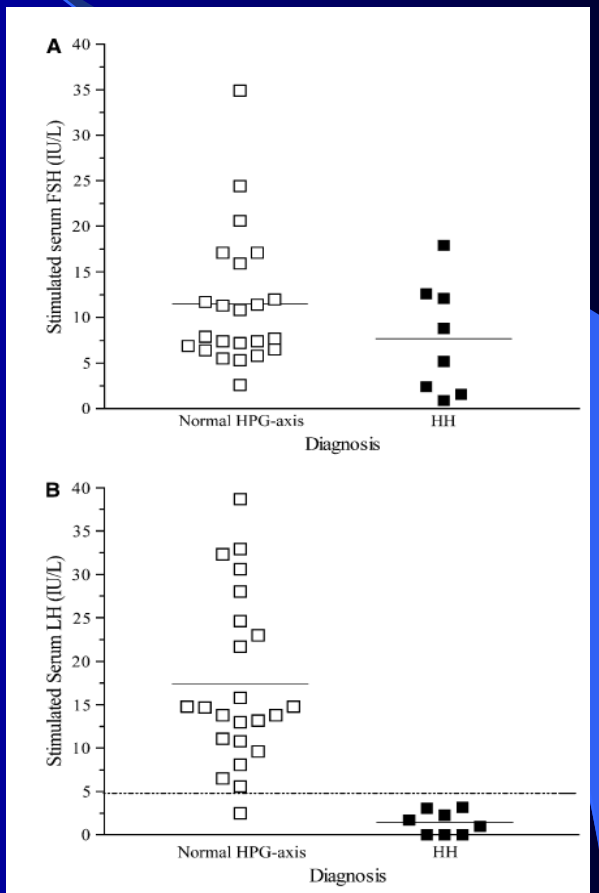


Figure. (**A**) Comparison of 4-hour stimulated serum FSH values in males diagnosed with normal HPG axis to those with HH ($P = .27$ between groups). (**B**) Comparison of 4-hour stimulated serum LH values in males diagnosed with normal HPG axis to those with HH ($P < .0001$ between groups).

Come tranquillizzare..

La diagnosi è una diagnosi di esclusione, quindi:

- il ritardo costituzionale è un processo fisiologico con buona prognosi;
- se si tratta di un problema psicologico di identificazione corporea, di accettazione della propria immagine, il pediatra deve essere in grado di affrontare il problema e di rassicurare il paziente e la famiglia, indirizzando eventualmente verso un intervento dello psicologo.
- dal momento della prima osservazione, è spesso sufficiente attendere sei mesi-un anno per avere comunque uno sviluppo spontaneo.

Ascertainment and Treatment of Delayed Puberty

J.Pozo, J. Argente.

Horm Res 2003;60(suppl 3):35–48

Table 1. Hormone treatment of CDGP

	Route	Dose	Duration	Start
Boys				
Testosterone	i.m.	Testosterone enantate or cipionate 50–100 mg/month	Cycles of 3–6 months with intervals of no treatment for 5–6 months	≥ 12 years bone age ≥ 14 years chronological age
	p.o.	Testosterone undecanoate 20–40 mg/day	Cycles of 3–6 months with intervals of no treatment for 5–6 months	≥ 12 years bone age ≥ 14 years chronological age
Oxandrolone	p.o.	0.1 mg/kg per day	Until testicular volume of 4–6 ml	≥ 9–10 years bone age
Girls				
Ethinyloestradiol	p.o.	0.05–0.1 μg/kg per day 2.5 μg/day for 6–12 months Increase after 6 months to 5 μg/day if necessary	Until breast development reaches B3	≥ 11–12 years bone age ≥ 13 years chronological age
Conjugated oestrogens	p.o.	0.3 mg on alternate days for 6–12 months Increase after 6 months to 0.3 mg/day if necessary	Until breast development reaches B3	≥ 11–12 years bone age ≥ 13 years chronological age
17β-Oestradiol	p.o.	5 μg/kg per day Increase after 6 months to 10 μg/day if necessary	Until breast development reaches B3	≥ 11–12 years bone age ≥ 13 years chronological age
	trans-dermal	0.08–0.12 μg/kg per day $^1/_8$–$^1/_6$ of a patch of 25 μg for 10 h/day over 6–12 months Increase to $^1/_4$–$^1/_3$ patch after 6 months if necessary	Until breast development reaches B3	≥ 11–12 years bone age ≥ 13 years chronological age

Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty

M. Hero, S. Wickman and L. Dunkel

Clinical Endocrinology (2006) **64**, 510–513

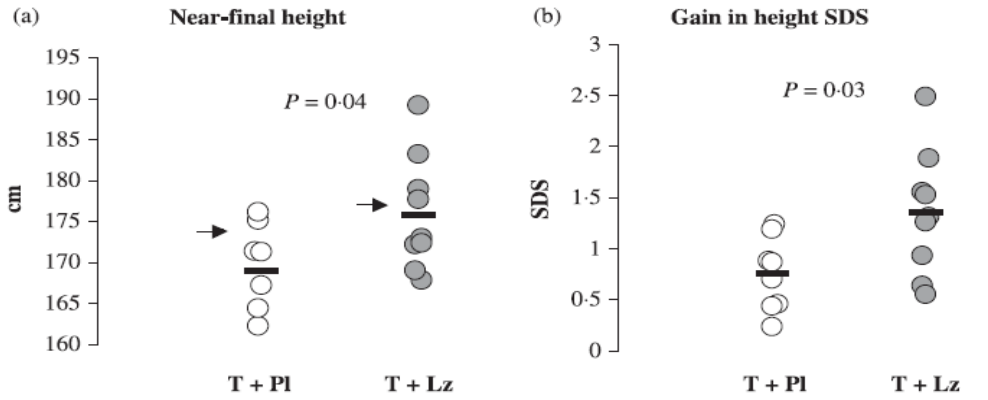


Fig. 1 Near-final height (a) and gain in height standard deviation score (SDS) (b) in boys with constitutional delay of puberty treated during adolescence either with a combination of testosterone and letrozole (T + Lz), or testosterone and placebo (T + Pl). Gain in height SDS was calculated as height SDS at near-final height minus pretreatment height SDS. Black arrow, mean mid-parental target height; black bar, mean.

terapia

- Qualsiasi trattamento non migliora la prognosi staturale (la statura è al momento della diagnosi penalizzata come lo sviluppo puberale, ma alla fine viene raggiunto il range del target familiare sia con che senza trattamento);

- la terapia in questi casi si sconsiglia perché può essere: invasiva, costosa e tossica (Androgeni somministrati oralmente possono avere effetti collaterali a livello epatico).

terapia

- la diagnosi di ritardo di sviluppo puberale costituzionale non è sempre così agevole e si corre il rischio di deludere il paziente alla fine della terapia, quando lo sviluppo non procede.

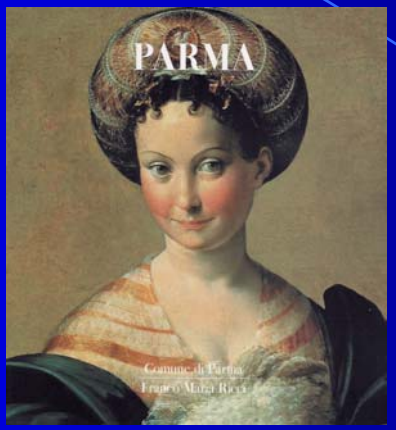
- usando dosi inadeguate (eccessive per lo scopo) di Androgeni per ottenere effetti migliori si rischia di penalizzare la statura definitiva agendo sulla maturazione scheletrica.

- è una MEDICALIZZAZIONE di un problema che è solo una variante della norma o che nasconde altre problematiche (malattie croniche, nutrizionali ecc. che devono essere prima risolte)

Caratteristiche fondamentali del ritardo costituzionale di crescita

- Frequente familiarità
- Adrenarca ritardato
- Età ossea ritardata
- Il ritardo puberale di solito non supera il 16° anno d'età
- L'inizio della pubertà correla con l'età ossea, ma non con l'età cronologica
- Lo sviluppo puberale, una volta iniziato, in genere progredisce normalmente

Grazie per l'attenzione



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