5th Joint Meeting on Adolescence Medicine

10th - 12th November 2011

Aula Consiliare e Sala dei Concerti, Palazzo de Nobili, Catanzaro (Italy)

Non conventional uses of GH

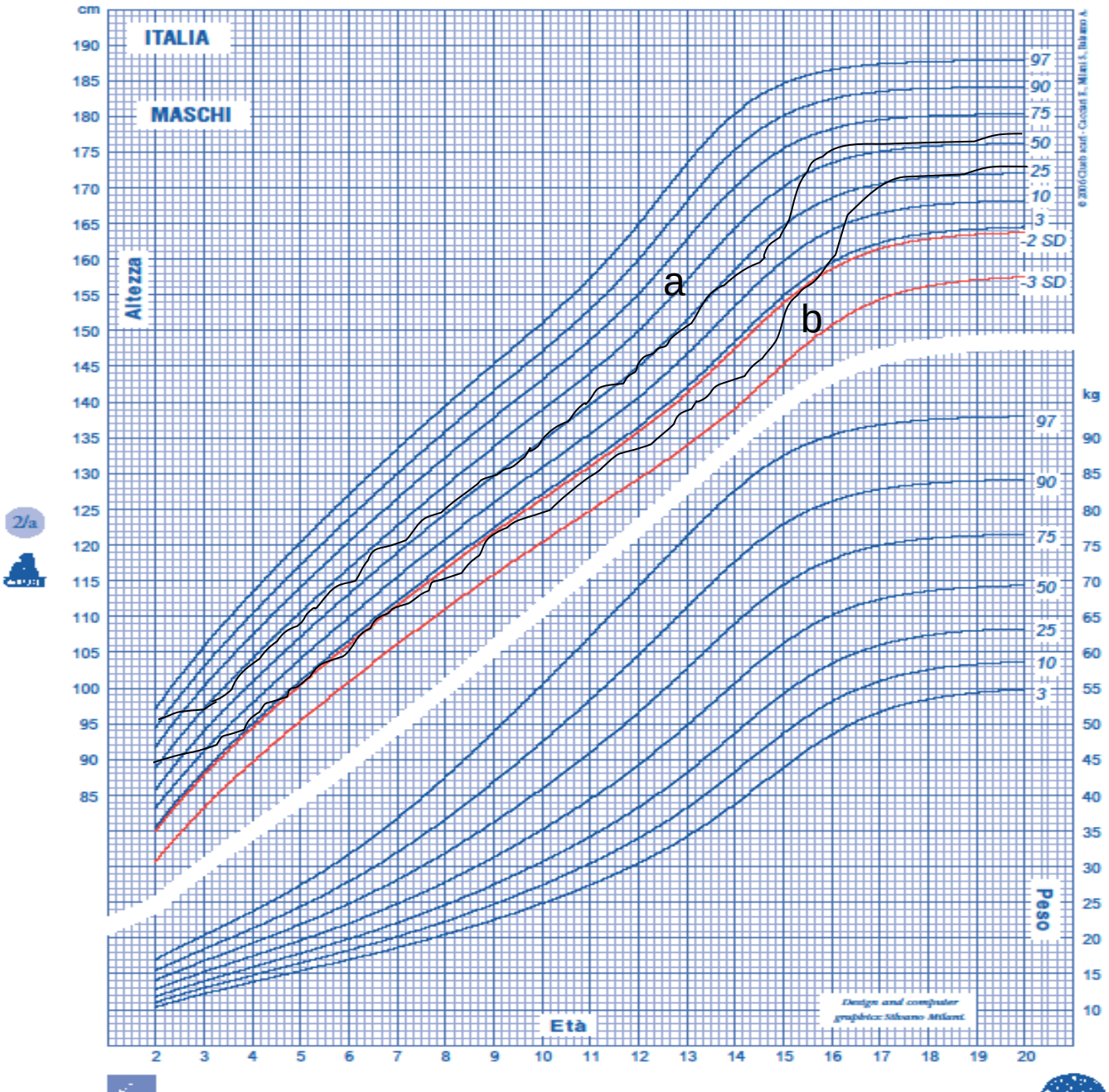
Salvatore Di Maio, Napoli

CDGP

- ***Classic***, clear familiarity
- ***Sporadic***, without demonstrable familiarity
- ***[****Acquired "CDGP like" pattern*, (prior self-limited but growth-suppressing illnesses)**]**

Centili Italiani di riferimento [2-20 anni] per altezza, peso e BMI

Cognome | Nome | Data di nascita



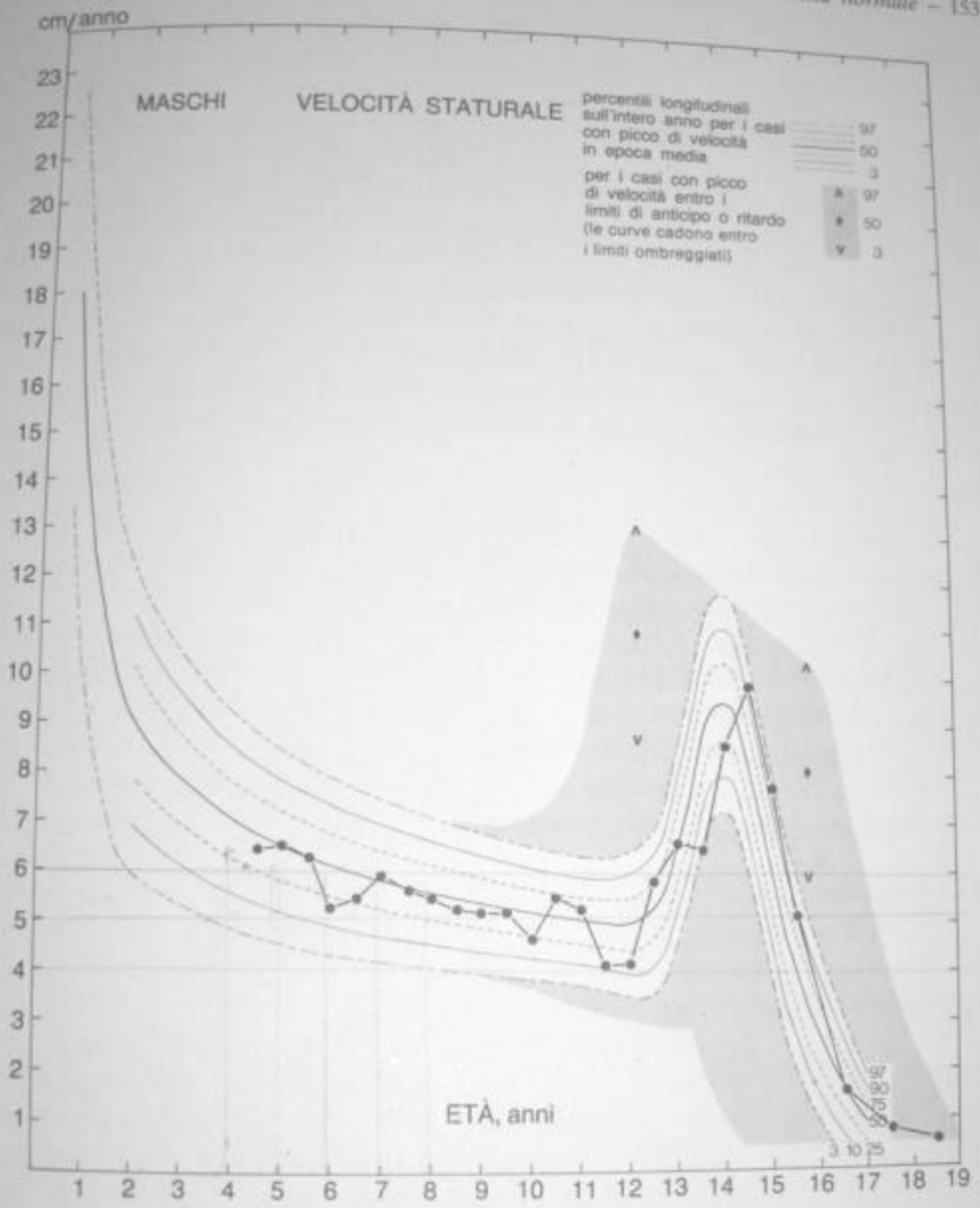


Fig. 59. Standard della velocità staturale nei maschi. Vi è riportato il maschio normale della fig. 55, considerato per periodi di un anno intero; ogni nuovo periodo comincia ogni 6 mesi. (Da Tanner e Whitehouse, 1976).

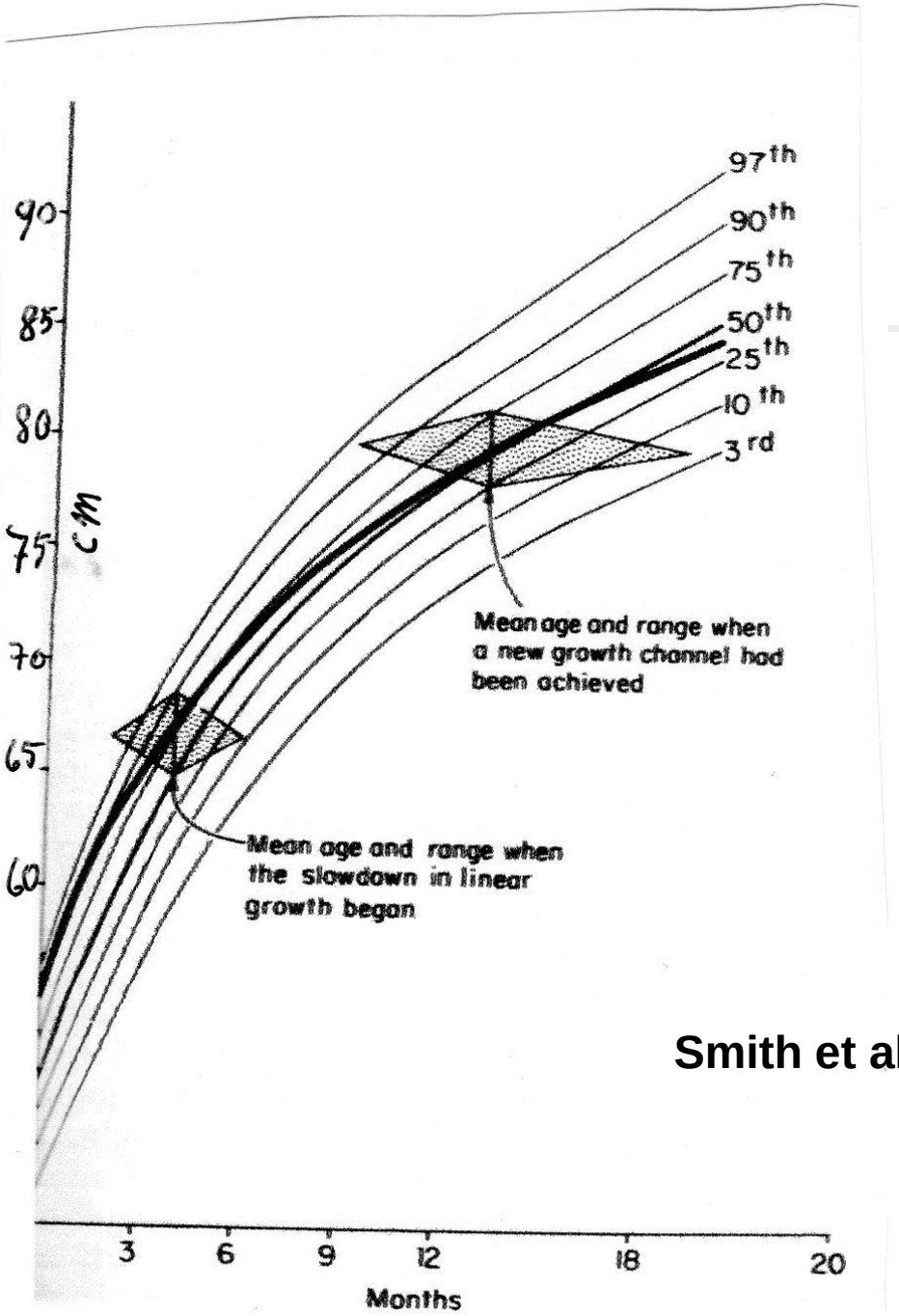
Pathological Growth Velocity in paediatric ages

In ***childhood*** if is below 25° percentile for at least one year

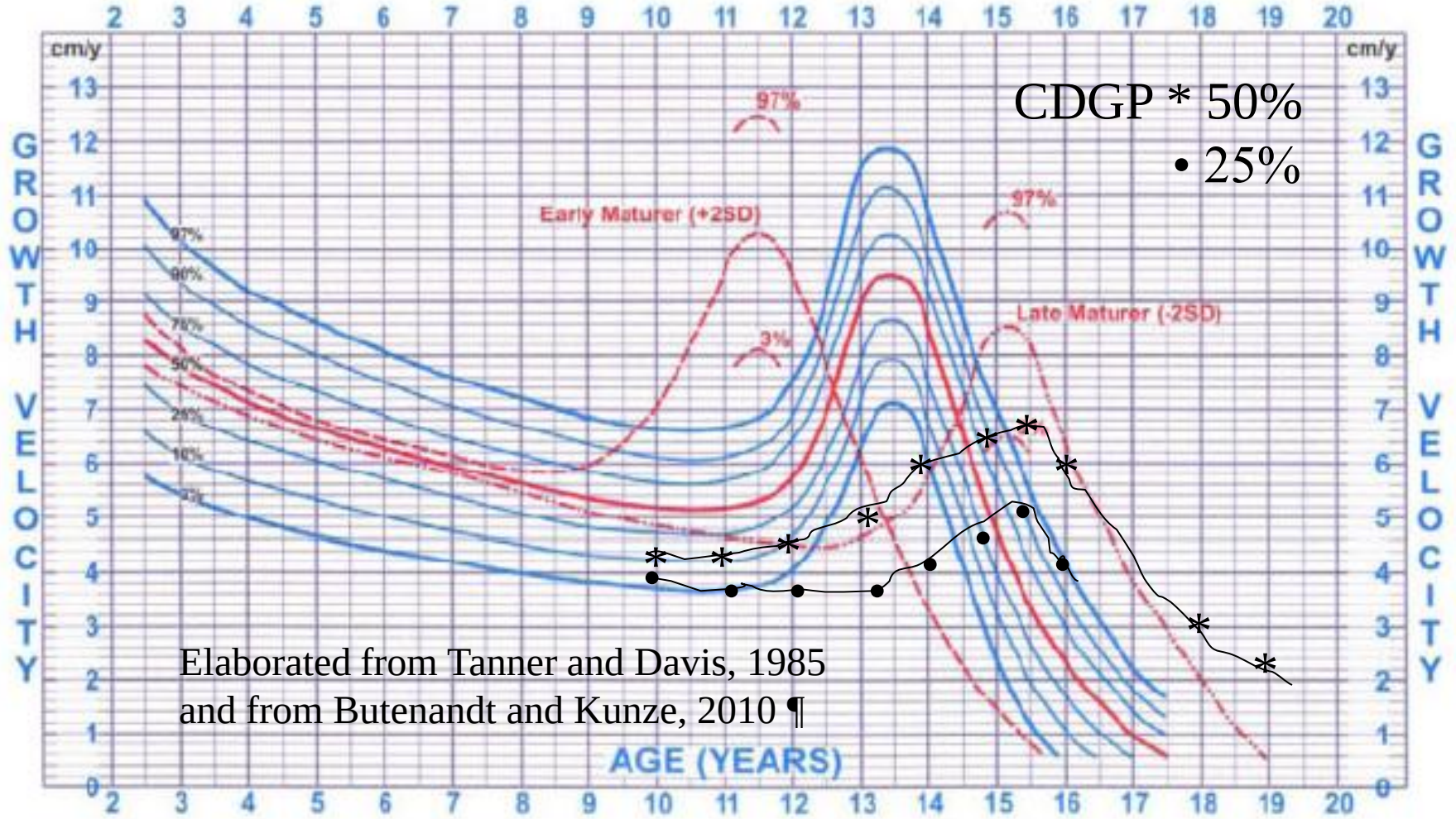
difficult intrepretation in the others :

In ***infancy***, because of "**canalization"**

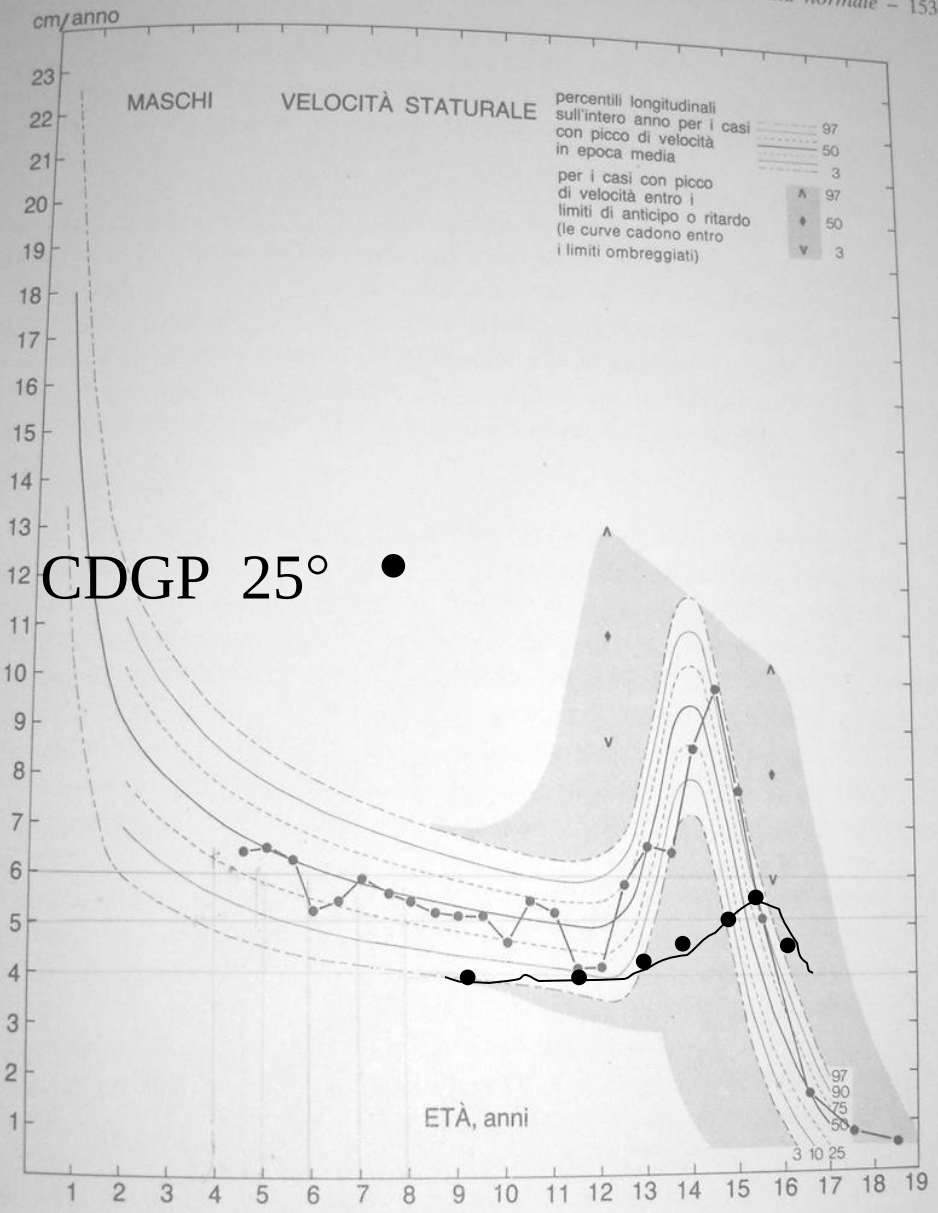
In ***adolescence***, because of "**tempo" of growth** (overall pace of somatic maturation which can include *timing of puberty, rate of growth and bone maturation)*



Smith et al J Pediatr 1976



¶ Journal of Pediatric Endocrinology & Metabolism, 23, 19-25 (2010) VOLUME 23, NO. 1-2, 2010



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weight and are GH sufficient. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of short stature. It is estimated that approximately 60–80% of all short children at or below −2 SDS fit the definition of ISS (7). This definition of ISS includes short children labeled with constitutional delay of growth and puberty (CDGP) and familial short stature. The frequency of referral of these children

Cohen *et al.* Consensus Statement on ISS

J Clin Endocrinol Metab, November 2008, 93(11):4210–4217

Are There Specific Therapies for Various Patient Subtypes?

In children with CDGP, whose puberty and bone age are substantially delayed and who are taller than −2.5 height SDS, testosterone is the appropriate therapy in boys, where this clinical picture is far more prevalent than in girls. In late-maturing girls, low-dose estrogens represent a theoretical option; however, there are no published data to support its use. In ISS children where CDGP is unlikely, GH therapy could be considered.

Cohen *et al.* Consensus Statement on ISS

J Clin Endocrinol Metab, November 2008, 93(11):4210–4217

An Pediatr (Barc). 2011;xxx(xx):xxx.e1–xxx.e11

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ANALES DE PEDIATRÍA

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ARTÍCULO ESPECIAL

Talla baja idiopática. Revisión y puesta al día

A. Carrascosa[a,*], A. Fernández Longás[b], R. Gracia Bouthelier[c], J.P. López Siguero[d], M. Pombo Arias[e] y R. Yturriaga[f], en representación del Grupo Español de Consenso[◊]

Carrascosa A, et al. Talla baja idiopática. Revisión y puesta al día. An Pediatr (Barc). 2011

El consenso de GHRS, LWPES y ESPE sobre TBI, incluyó el RCCD como una más de las entidades clínicas que forman parte de la TBI[2]. Sin embargo, esta consideración es desde nuestro punto de vista discutible, ya que si bien es cierto que en el RCCD existe una talla baja de la que no conocemos su etiología y en este sentido podría ser incluido dentro de la TBI, es también cierto que en su evolución espontánea la talla adulta alcanzada está en los límites de la normalidad, cosa que no ocurre en el resto de situaciones clínicas incluidas en la TBI.

rhGH is frequentely used in CDGP, due to:

1. ….uncertainty inherent in the prediction of final height in a prepubertal state….
2. ….desire by both physician and family to correct the immediate problem…….

Cohen P et al

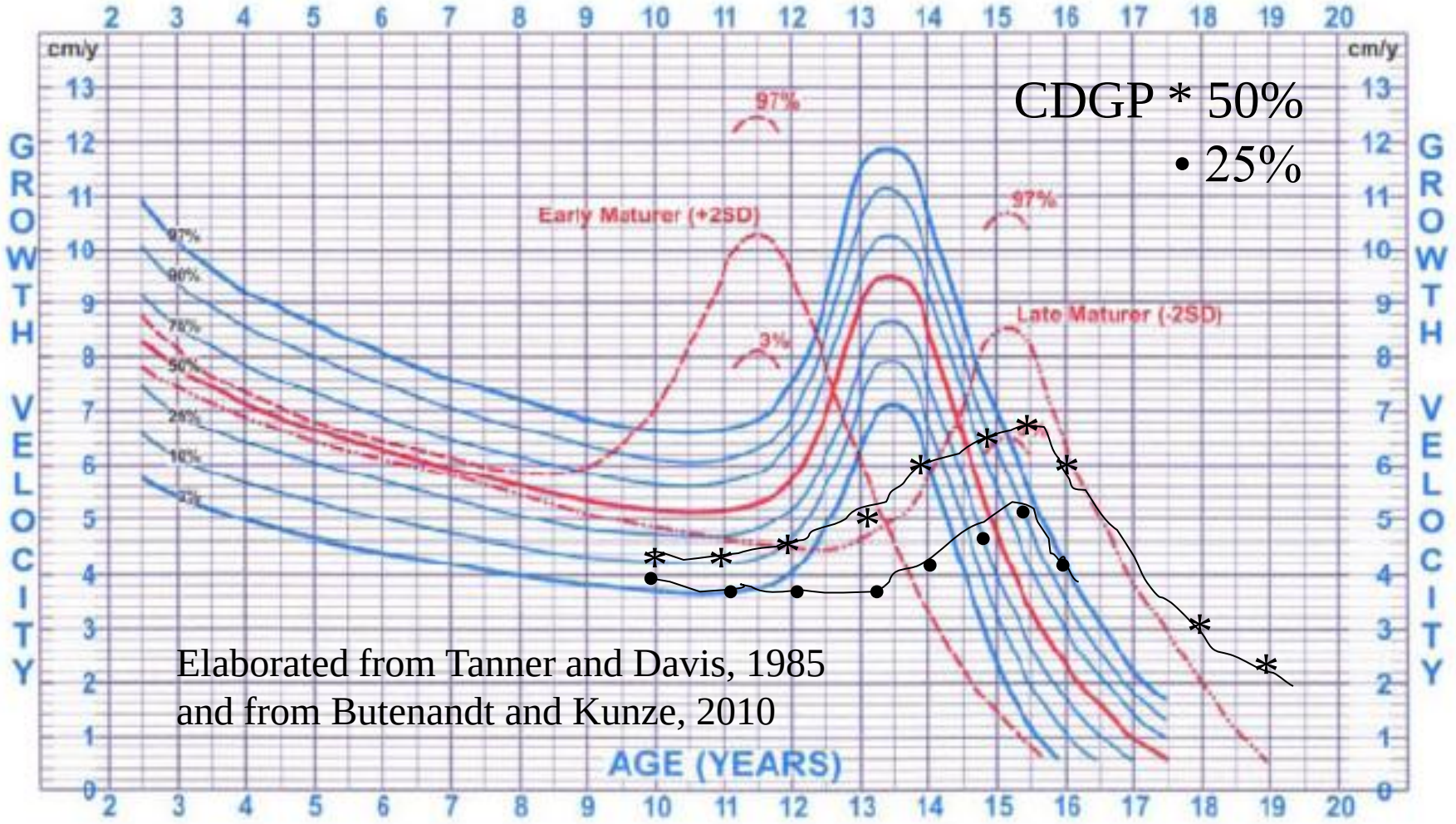
Consensus Statement……on Idiopathic Short Stature

J Clin Endocrinol Metab 2008

CDGP adolescents are concerned about:

- Lack of size and height (*early adolescence*)

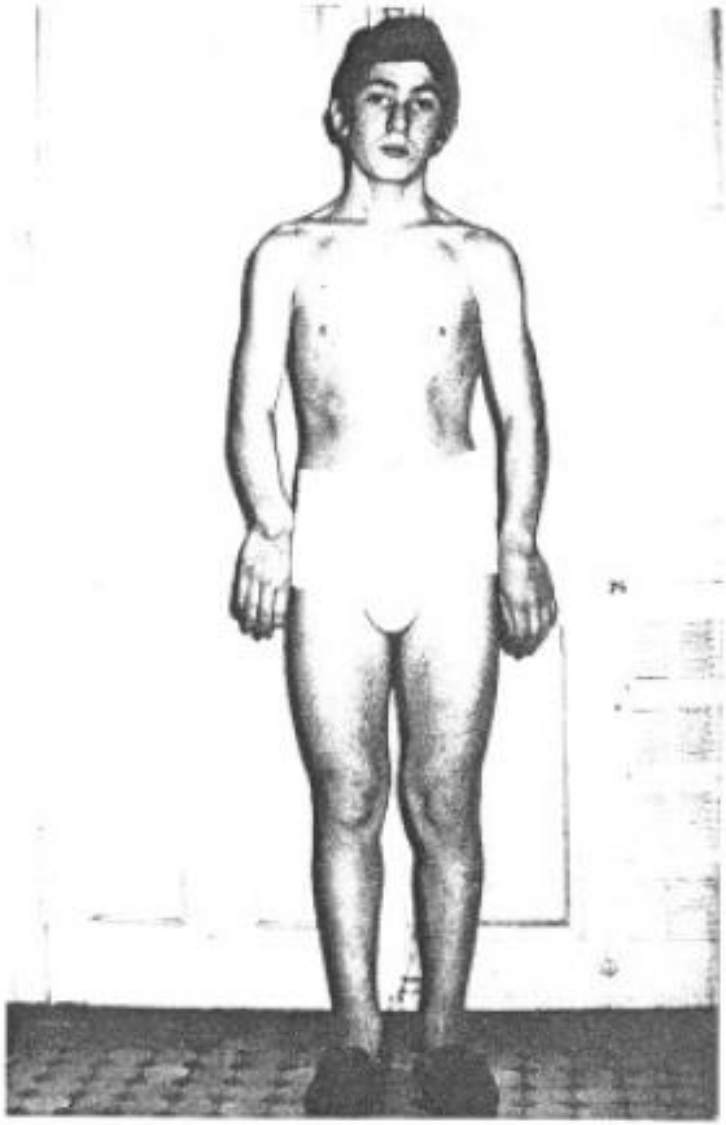
- Lack of secundary sexual characteristics (*middle – late adolescence*)

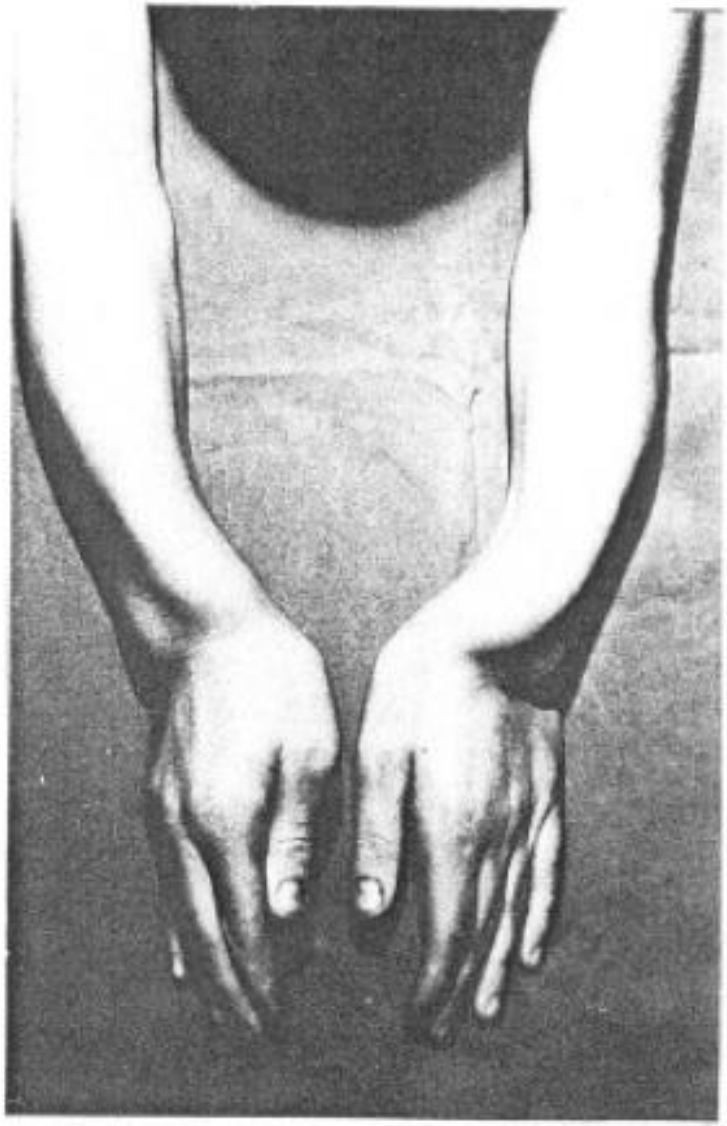

cm/y
GROWTH VELOCITY
AGE (YEARS)
Early Maturer (+2SD)
Late Maturer (-2SD)
97%
90%
75%
50%
25%
10%
3%
CDGP * 50%
• 25%
Elaborated from Tanner and Davis, 1985
and from Butenandt and Kunze, 2010

rhGH non conventional uses *in adolescence*

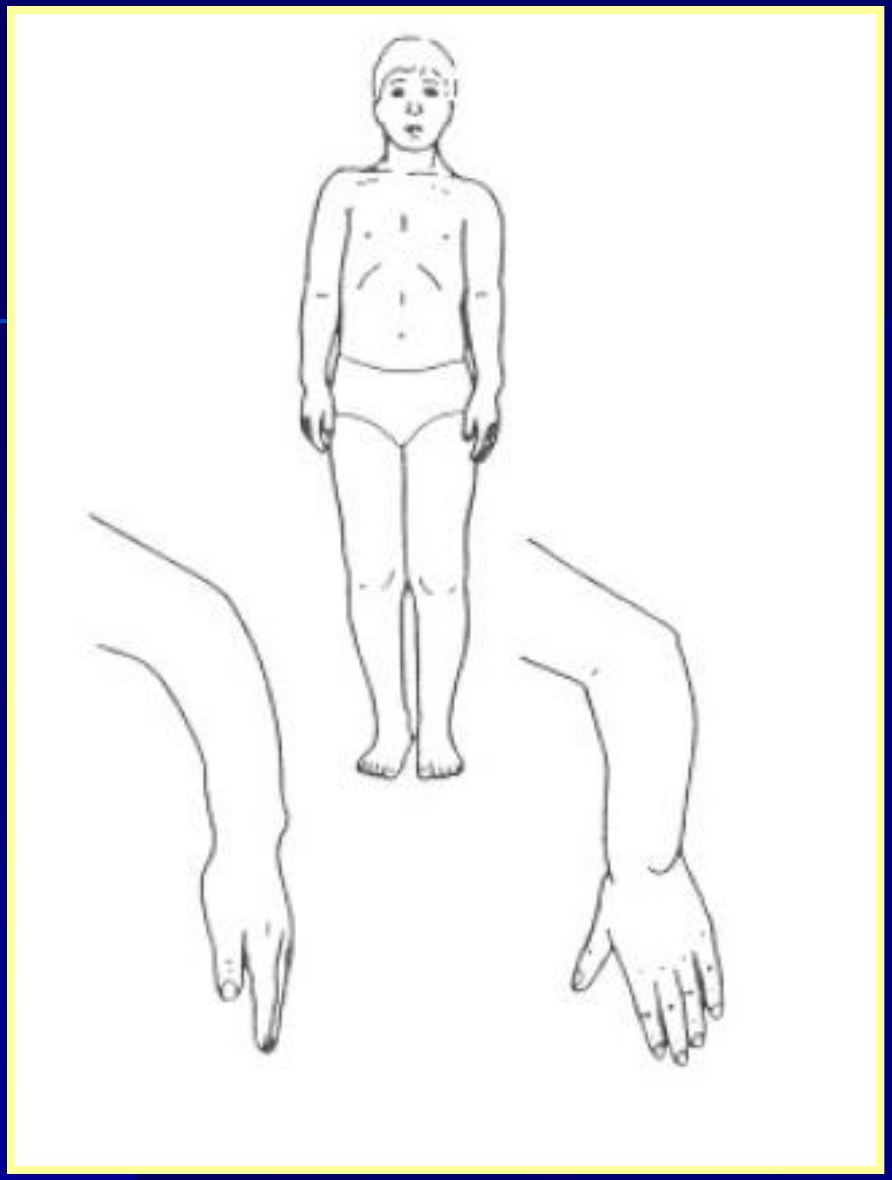
remarks on:

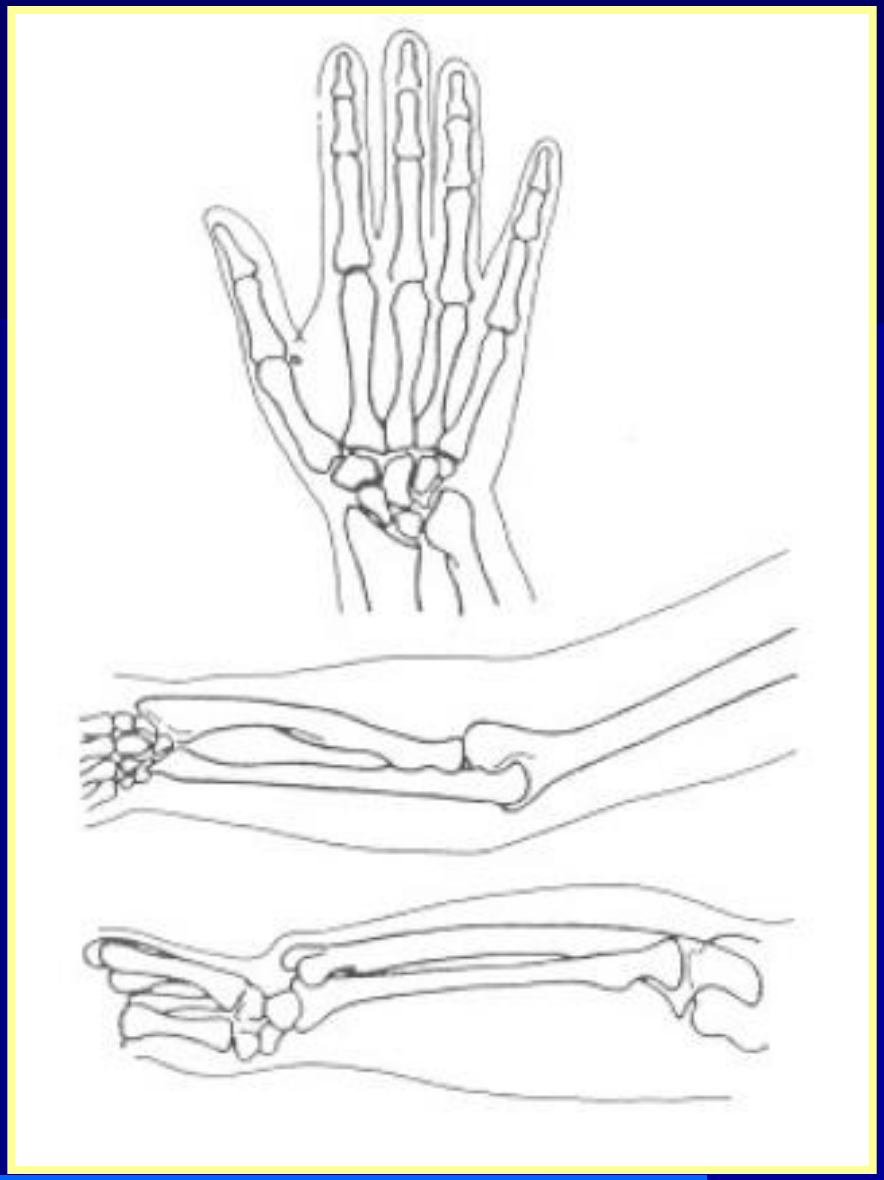
- Constitutional delay of growth and puberty
- **SHOX-deficiency**





Santolaya y Delgado, Displasias oseas, Salvat 1988





DYSCHONDROSTEOSIS

Santolaya y Delgado, 1988

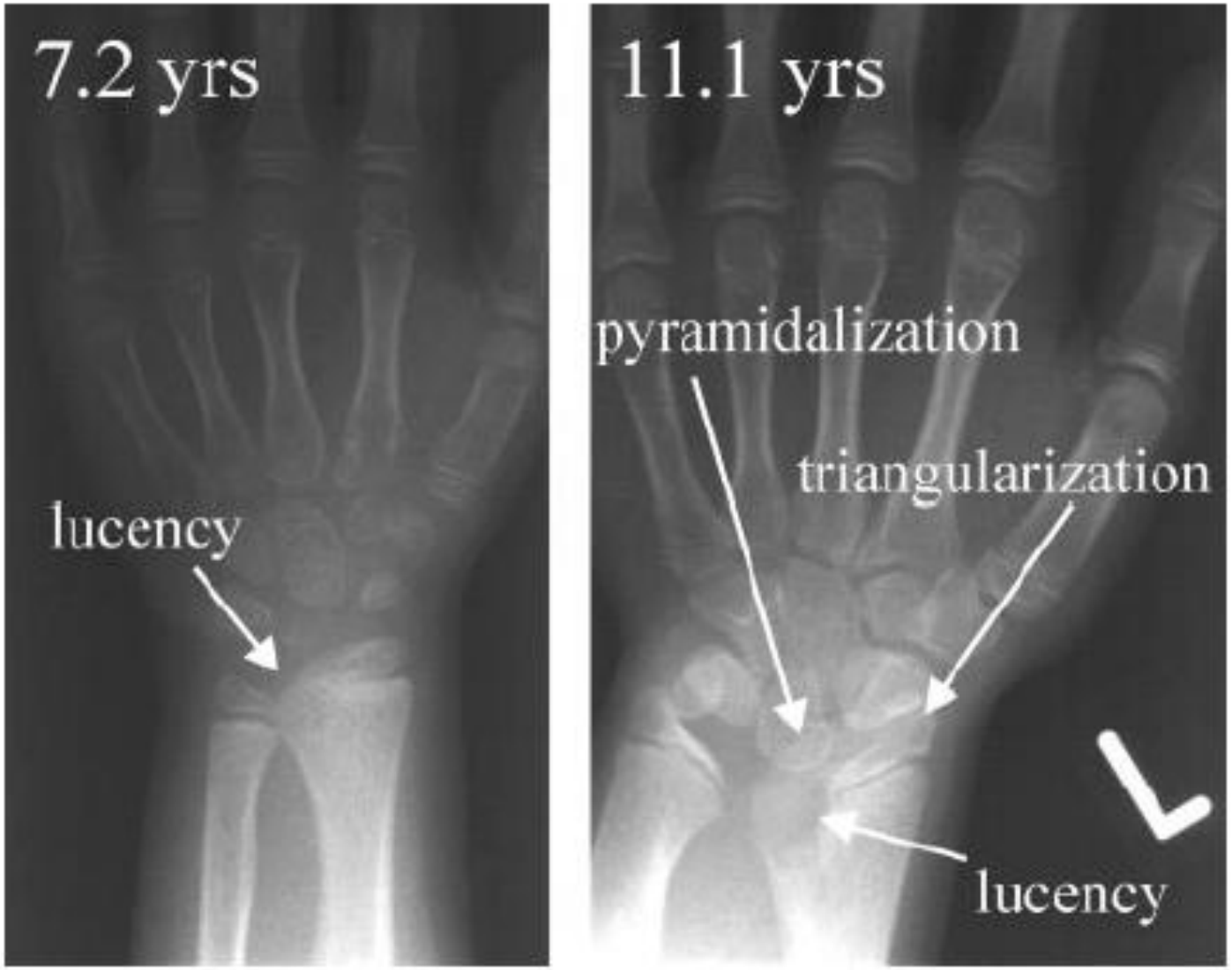


FIG. 4. Radiography of patient 1 (*left*) and patient 2 (*right*) with SHOX haploinsufficiency, showing the main characteristics of mild LWD.

Binder et al JCEM 2003

Natural history in SHOX defects

- A relatively well–preserved prepubertal growth-rate
- Compromised pubertal growth spurt

Kosho et al JCEM 1999

Scalco et al JCEM 2010

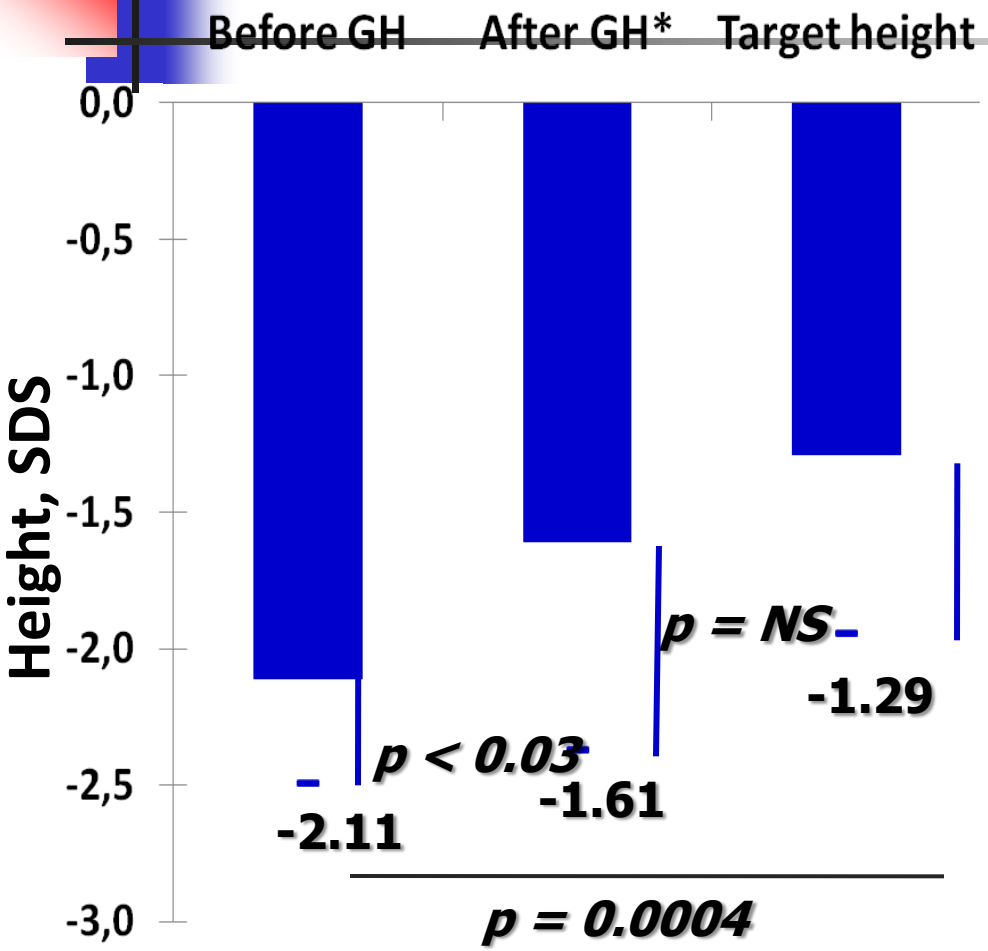
Combined rhGH and GnRHa in SHOX deficiency

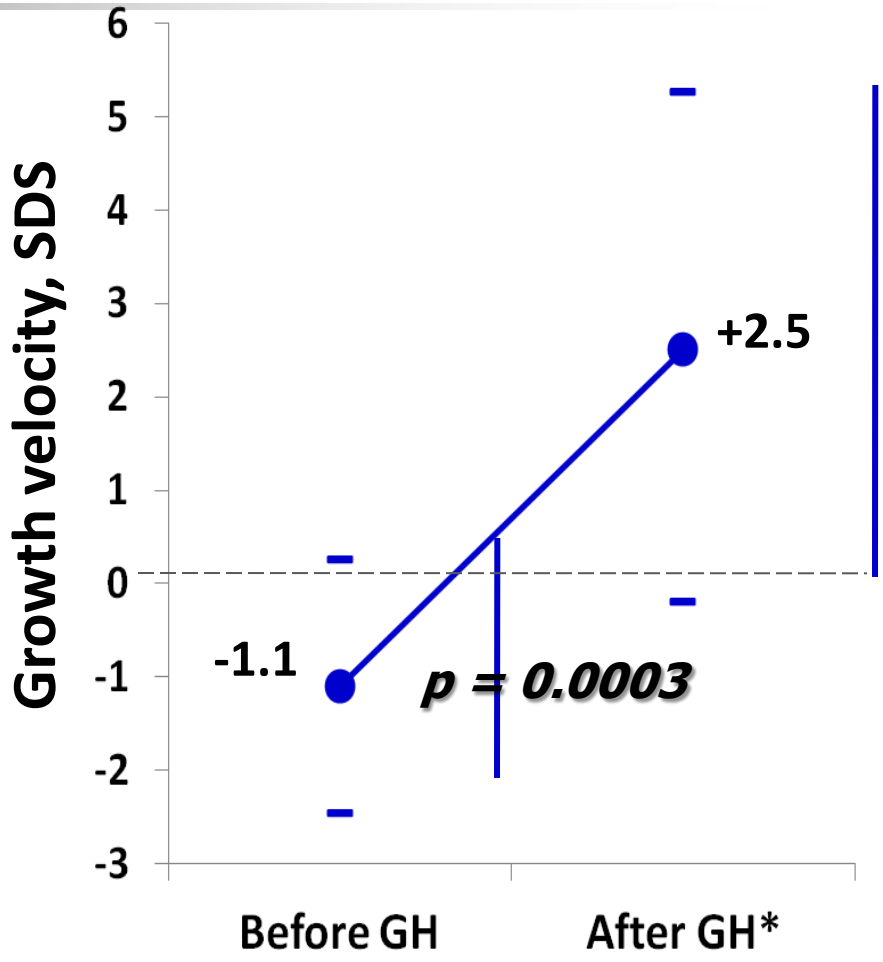
trial to prevent

Loss of growth potential during puberty due to premature growth plate fusion

SHOX Deficiency: rGH Treatment (0.26±0.05 mg/kg/wk) in Italian Patients [n = 13 (6 M/7F), mean age 9.6 yrs (range 4.9 – 14.5 yrs)]

(*Modena, Torino, Bologna, Pisa, Bolzano, Parma*)



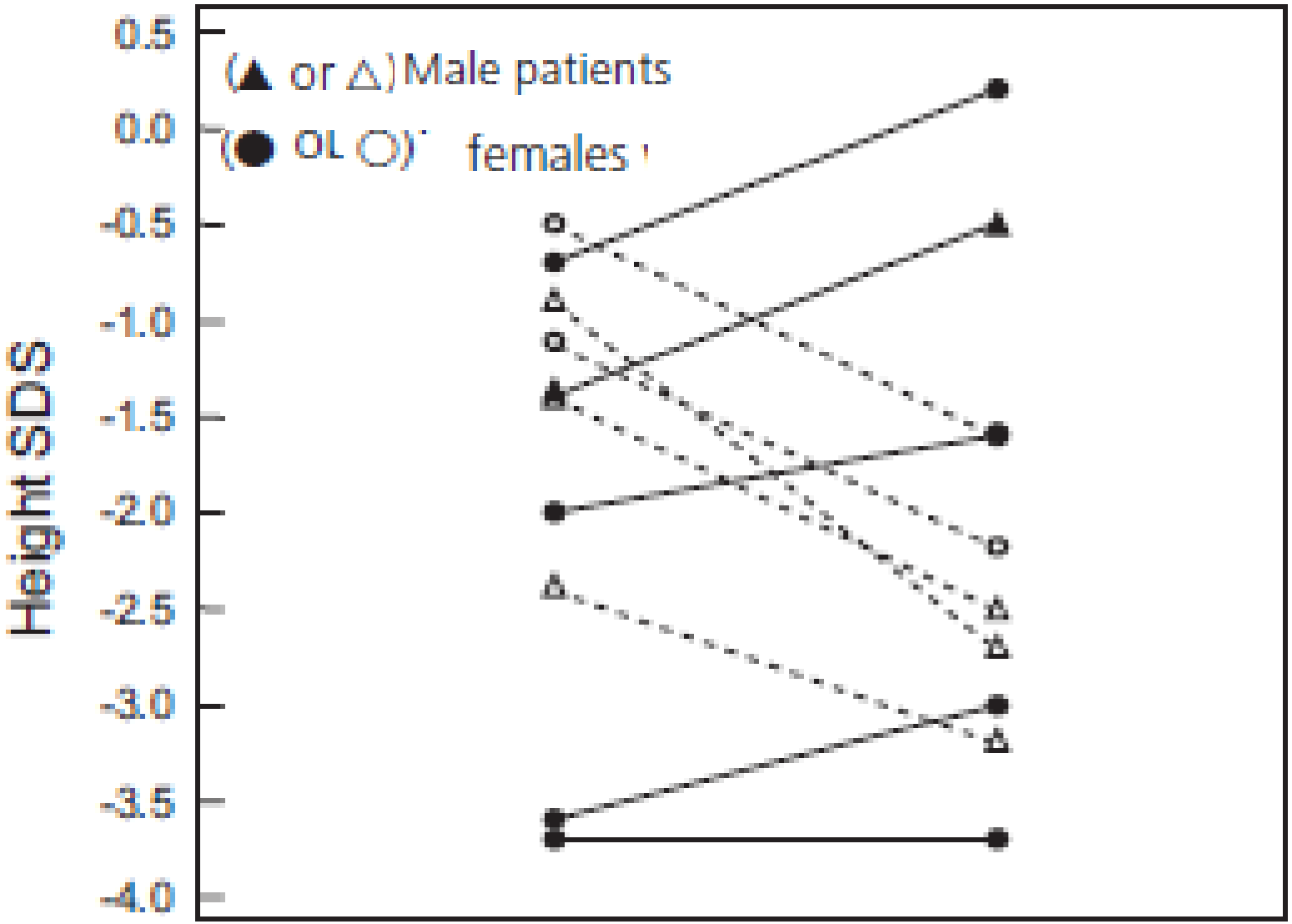


*mean rGH treatment 2.5 yrs (range 1.0 – 6.4 yrs)
mean dose: 0.26 ± 0.055 mg/kg/day

(Iughetti et al, ESPE 2010)

Similar final height benefit from rhGH treatment

	SHOX deficiency n=14, F 12	**Turner** Syndrome n=158	
SDS height gain from baseline to final height p<0,001	**1,1**± 0,7	**1,2** ± 0,8	p=0,708
	Blum et al *Horm Res 2009*		



Scalco *et al.*

treated

filled symbols and *solid lines*.

(*J Clin Endocrinol Metab* 95: 328–332, 2010)

mean difference in adult height between treated and untreated children

- Turner Syndrome 6 cm
- Small for gestational age 7 cm
- Idiopathic short stature 4 cm

reported from

Deodati and Cianfarani *BMJ 2011; 342:e7157*

The amount of gain in adult height by rhGH

- *Clinically significant for a child of disabling short stature*
- *Of marginal benefit for a child of already average height*

Limitations of studies

- Retrospective
- Limited number of patients
- Lack of (metod of) randomisation
- Lack of details of withdrawals, dropouts, blinding
- Weak outcome measures

Adult height is influenced

Negatively by *age at start*

Positively by *midparent height*
height at start
bone age delay
first-year response

response to therapy

- Responses higly variable
- Dose dependent
- Concern on Higher GH doses
  > 53 µg/kg/die

rhGH safety

- rhGH appears to be a relatively safe hormone, at least during the time that it is being administred
- There are few data relating to long-term follow-up and this is a challenge for the future

Targeted adverse events

- Scoliosis
- Slipped femoral proximal epiphysis
- Idiopathic intracraneal hypertension
- pancreatitis

Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk

*Jane Green, Benjamin J Cairns, Delphine Casabonne, F Lucy Wright, Gillian Reeves, Valerie Beral, for the Million Women Study collaborators**

Lancet Oncol 2011; 12: 785–94

	Women	Incident cancers	RR (95% FCI)
<155 cm (mean 152·8 cm)	233 516	15 792	1·00 (0·98–1·02)
155 cm (mean 156·5 cm)	196 773	14 213	1·08 (1·07–1·10)
160 cm (mean 160·4 cm)	388 515	28 806	1·12 (1·11–1·14)
165 cm (mean 164·9 cm)	288 893	22 571	1·20 (1·18–1·22)
170 cm (mean 169·0 cm)	143 289	11 902	1·28 (1·25–1·30)
≥175 cm (mean 173·8 cm)	46 138	4092	1·37 (1·33–1·42)

Analysis stratified by age at recruitment and region and adjusted for socioeconomic status, smoking, alcohol intake, body mass index, strenuous exercise, age at menarche, parity, and age at first birth.

Table 2: Relative risks (RRs) and 95% floated CIs (FCIs) for total cancer incidence, by category of height reported at recruitment (mean measured height)

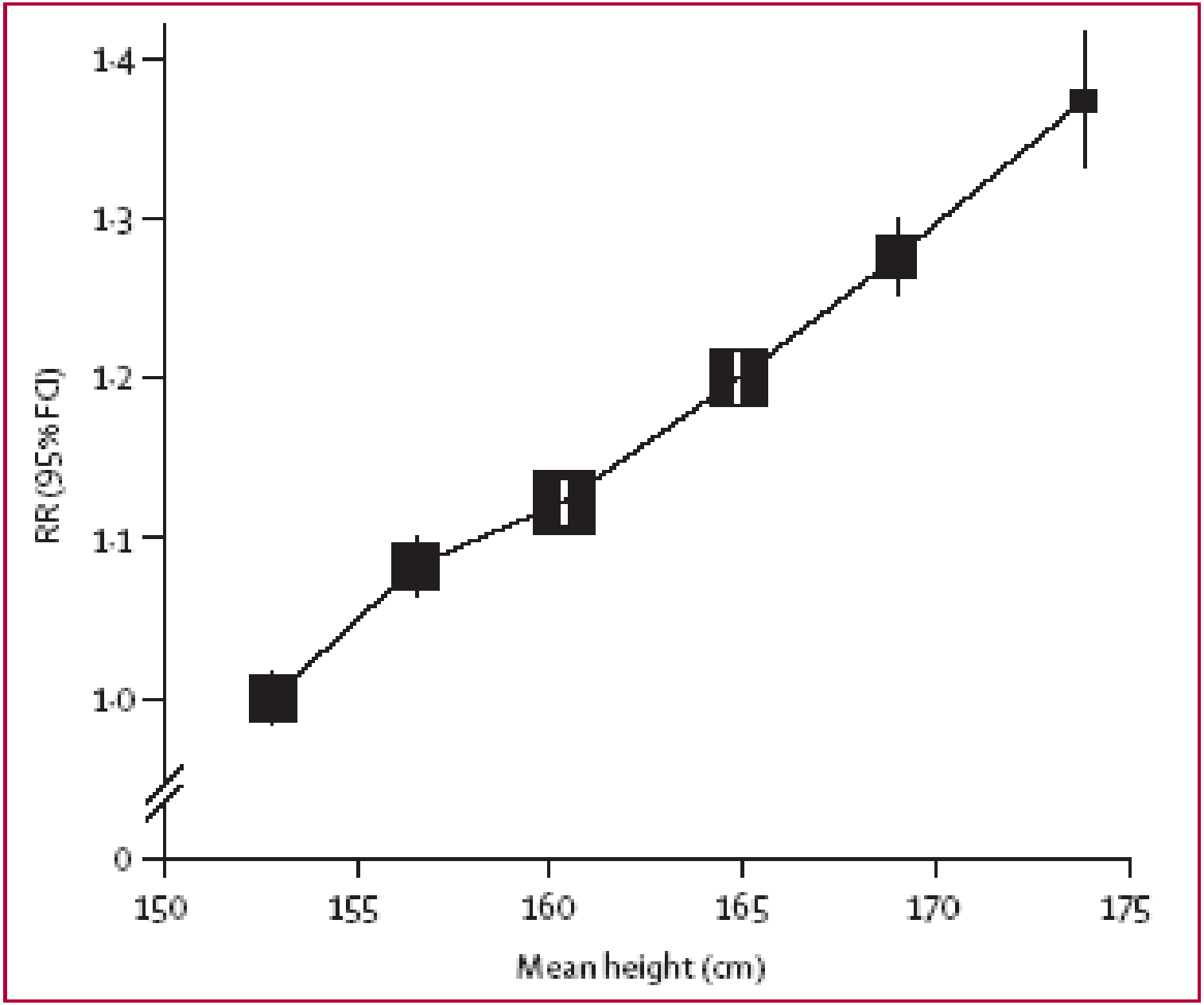


Figure 1: Relative risks (RRs) and 95% floated CIs (FCIs) for total incident cancer, by height

potential adverse events in adult:
caution and ongoing scrutiny of risks

1. Continuing trend toward dose escalation
2. Possibility of delayed post-treatment effects of:

- high insulinemia levels
- heightened GH and IGF-1 exposure to cancer risk

Allen DB *Horm Res Paediatr 2011*