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

rhGH therapy use

- in GHD *"as replacement therapy"*
- in non-GH-deficient states
  "as augmentation therapy"

Indications for GH use

- Approved indications
- Potential indications:
  a. Height-related
  b. Non-height-related
  c. Both height-related and anabolic

Table 1 Approved indications for GH use in the USA and Europe

Indication	Year of FDA approval
GH-deficiency states	
Childhood growth-hormone deficiency	1985 (E)
Adult growth-hormone deficiency	1996 (E)
Pubertal dosing	2000
Non-GH-deficiency states	
Chronic kidney disease	1993 (E)
Turner syndrome	1996 (E)
AIDS wasting	1996
Prader–Willi syndrome	2000 (E)
Small for gestational age	2001 (E)
Idiopathic short stature	2003
Small bowel syndrome	2004
SHOX deletion	2006 (E)
Noonan syndrome	2007

Abbreviations: E, Europe; FDA, US Food and Drug Administration; GH, growth hormone.

Approved for use in Pediatrics in non-GH-deficient states

- Chronic renal insufficiency
- Genetic disease with severe short stature
- IUGR/SGA without catch-up growth
- Abnormal body composition and short stature

Approved for use in pediatrics in non-GH-deficient states

- Chronic renal insufficiency
- ***Genetic disease with severe short stature***
- IUGR/SGA without catch-up growth
- Abnormal body composition and short stature

Genetic disease with severe short stature

- Turner Syndrome
- Noonan Syndrome
- SHOX mutations

Approved for use in pediatrics in non-GH-deficient states

- Chronic renal insufficiency
- Genetic disease with severe short stature
- IUGR/SGA without catch-up growth
- ***Abnormal body composition and short stature***

Abnormal body composition and short stature

Prader-Willi Syndrome

Non conventional uses of rhGH in adolescence

1. Idiopathic short stature as **a paradigm** of approved indications

2. Remarks on specific issues in adolescence

Growth retardation in puberty

- Important clinical challenge
- Potential strategy to improve growth :

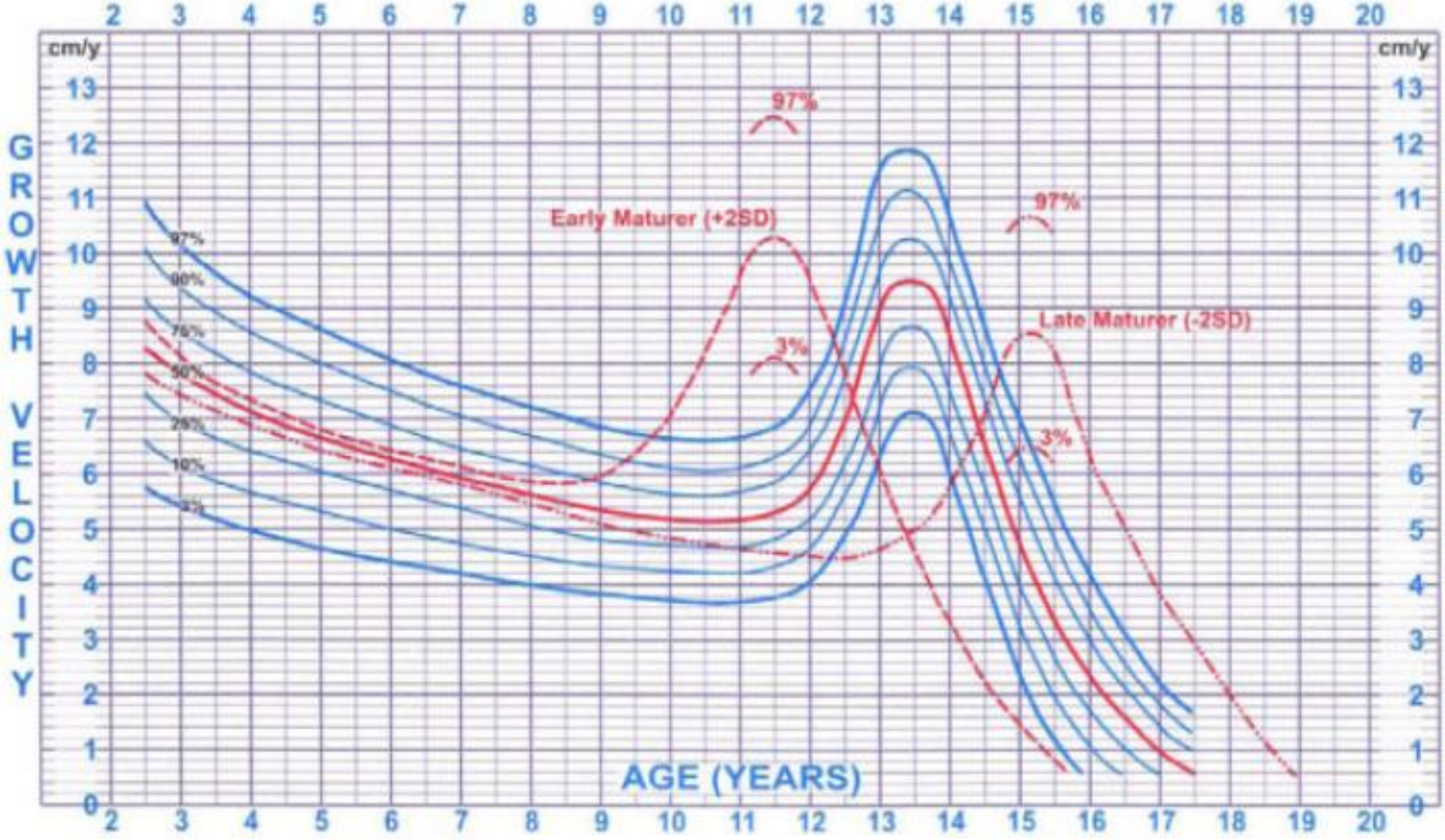
  a. High dose rhGH

  b. Suppression of puberty with GnRHa in combination with GH

  c. Aromatase inhibitors

Mauras N

Pediatr Clin North Am 2011



From Tanner JM, Davis PSW. J Pediatr. 1985; 107:317–329.

Growth measures

- "***Size*** of growth"
- "***Tempo*** of growth"

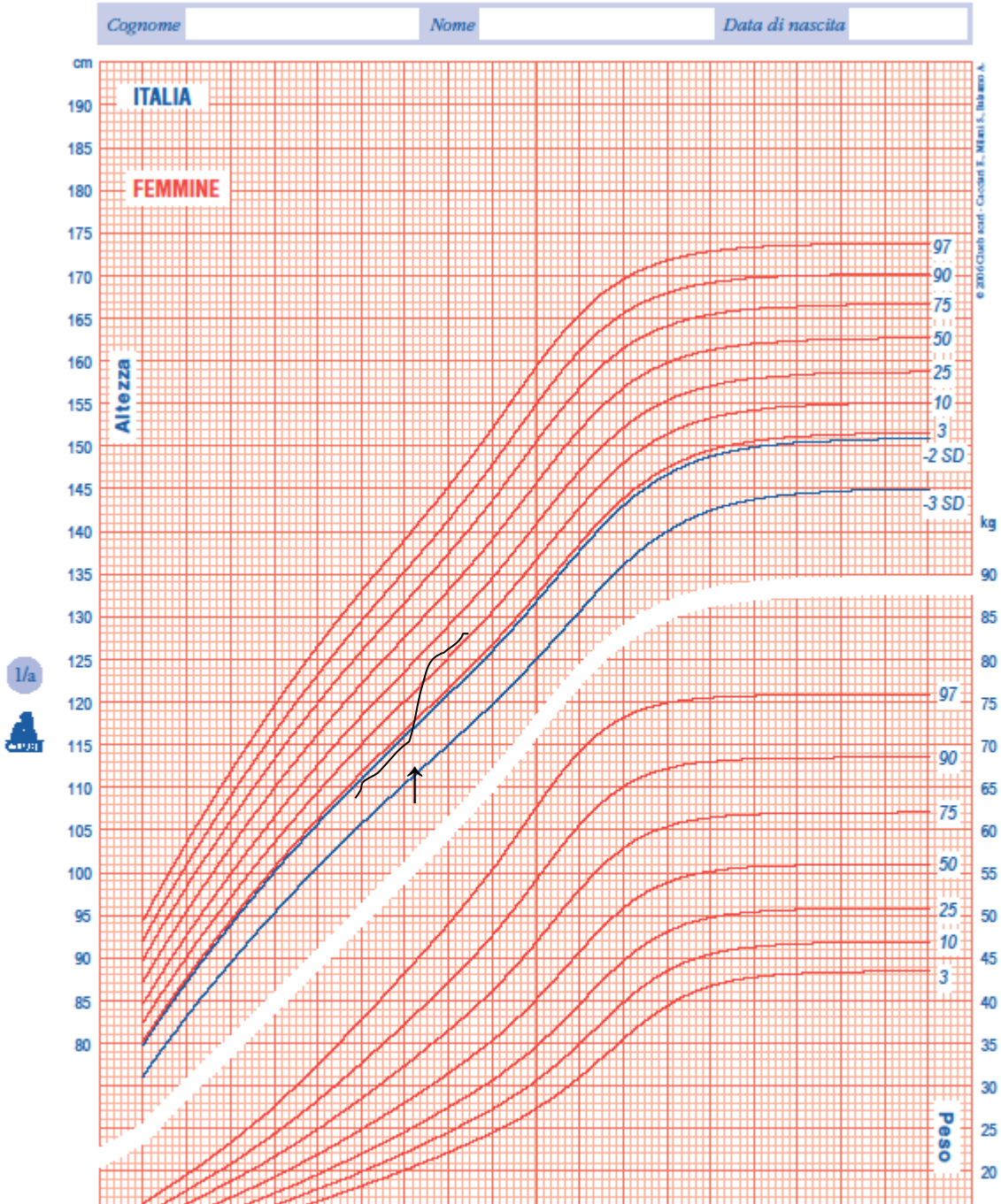
why families seek growth promoting treatment ?

- Diminished height compared to peers that is presently viewed as disabling
- Concern about possibility of marked short stature as an adult

To improve child's current state

- Acute increase in growth velocity
- A rate faster than peers results in upward crossing of percentiles on the growth curve to restore position in normal range

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



Frequency of ISS amongst short children in most studies

- Percentage of pathology 5%
- Hystory of SGA 15%
- No pathology can be detected 80%

Voss LD et al BMJ 1992
Ahmed ML et al Arch Dis Child 1993
Lindsay R et al J Pediatr 1994
Grote FK Leiden University 2007
Cianfarani S et al J Clin Res Ped Endo 2009

Short children without patology detected (80 %)

- Vast majority normal variants (FSS or CDGP)
- Adult height within the target height range

ISS, a heterogeneous group

- **F**amilial **S**hort **S**tature
- **C**onstitutional **D**elay of **G**rowth and **p**uberty
- Partial or transient GH deficiency or resistence
- Unidentified conditions (intrinsic short stature)

Non conventional uses of rhGH in adolescence

1. **Idiopathic short stature as a paradigm of approved indications**

2. Remarks on specific issues in adolescence

rhGH in Idiopathic short stature

- Three randomised controlled trials (115 children, 79 cases, 36 controls)
- Mean duration of therapy 5,4±1,5 years

randomised and controled studies up 2009

McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomized trial of growth hormone in short normal girls. *Lancet* 1998;351:940-4.

Leschek EW, Rose SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, et al. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, doubleblind, placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:3140-8.

Recombinant growth hormone for idiopathic short stature in children and adolescents (Review)

Bryant J, Baxter L, Cave CB, Milne R

THE COCHRANE COLLABORATION®

The Cochrane Library 2009, issue 1

randomised and controled studies up 2011

McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomized trial of growth hormone in short normal girls. *Lancet* 1998;351:940-4.

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Albertsson-Wikland K, Aronson AS, Gustafsson J, Hagenäs L, Ivarsson SA, Jonsson B, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. *J Clin Endocrinol Metab* 2008;93:4342-50.

Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review

Annalisa Deodati, research fellow, Stefano Cianfarani, associate professor

BMJ 2011;342:c 7157

Study and group	No	Mean (SD) age at start of therapy (years)	Growth hormone dose (mg/kg/day)
McCaughey et al 1998[9]:			
Treated	8	6.24 (0.38)	0.04
Untreated	6	6.14 (0.62)	—
Leschek et al 2004[10]*:			
Treated	22	12.5 (1.6)	0.03
Untreated	11	12.9 (1.1)	—
Albertsson-Wikland et al 2008[11]:			
Treated	49	11.5 (1.3)	0.033 to 0.067
0.033 mg/kg/day	18	11.5 (1.3)	0.033
0.067 mg/kg/day	31	—	0.067
Untreated	19	12 (1.6)	—

*Placebo controlled trial.

Mean (SD) years of therapy	Mean (SD) height at baseline (SD score)	Mean (SD) adult height (SD score)	Mean (SD) height gain (SD score)	Difference (cases −controls) in adult height (SD score)	Quality
6.2 (range 5.5-6.5)	−2.52 (0.26)	−1.14 (1.06)	1.38 (0.7)	1.23	Low
—	−2.55 (0.32)	−2.37 (0.46)	0.18 (0.4)	—	
4.4 (1.6)	−2.7 (0.6)	−1.77 (0.80)	0.93 (0.75)	0.57	Moderate
4.1 (1.7)	−2.8 (0.6)	−2.34 (0.56)	0.46 (0.23)	—	
5.64 (1.37)	−2.84 (0.56)	−1.6 (0.68)	1.24 (0.82)	0.6	Moderate
—	—	−1.7 (0.68)	1.20 (0.82)	0.5	
—	—	−1.5 (0.84)	1.30 (0.73)	0.7	
—	−2.76 (0.39)	−2.2 (0.75)	0.40 (0.62)	—	

Deodati e Cianfarani

BMJ 2011;342:c7157

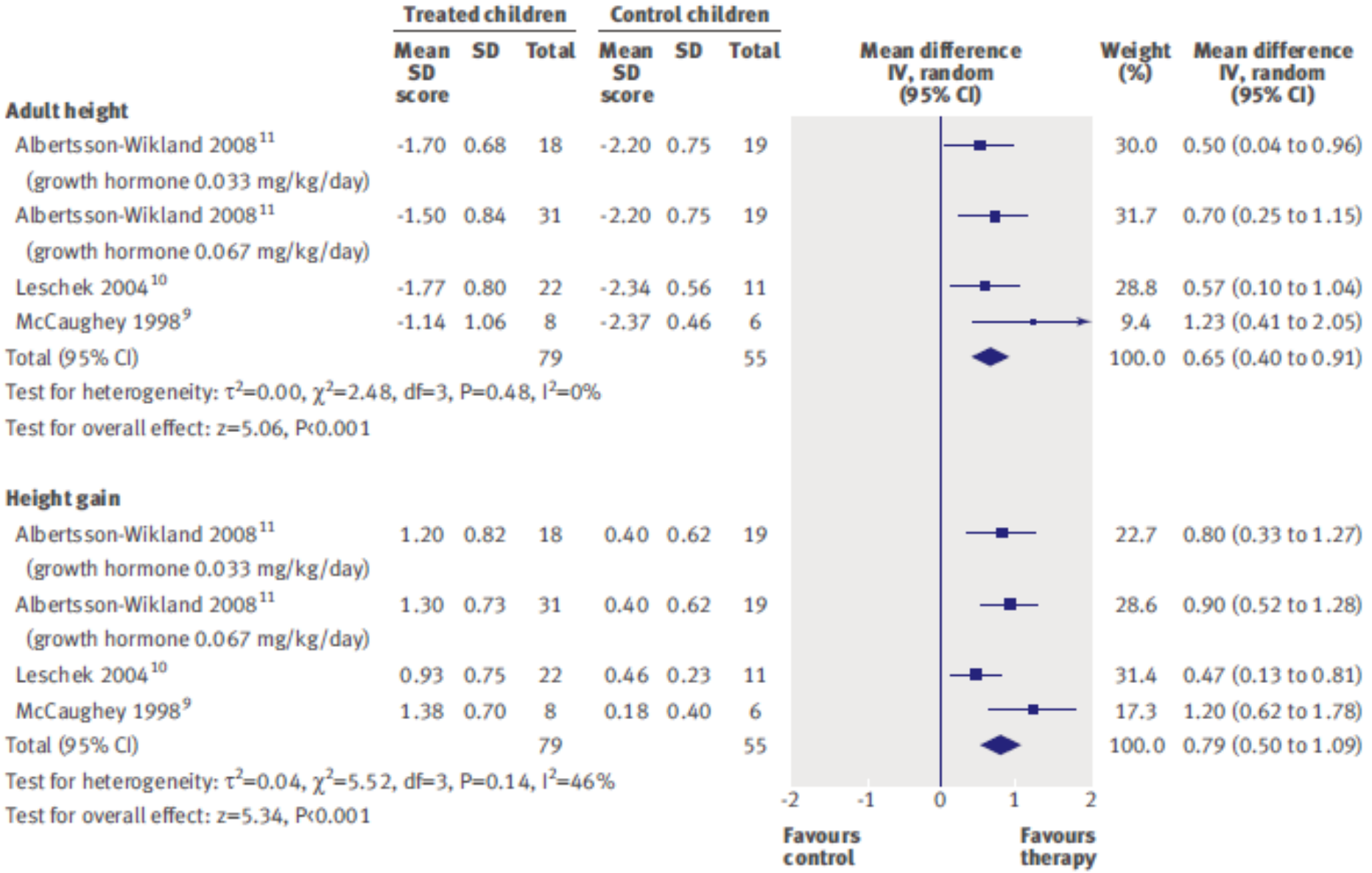

Fig 2 | Effect of long term growth hormone therapy at conventional doses on adult height and height gain in randomised controlled trials. Results of meta-analysis according to random model

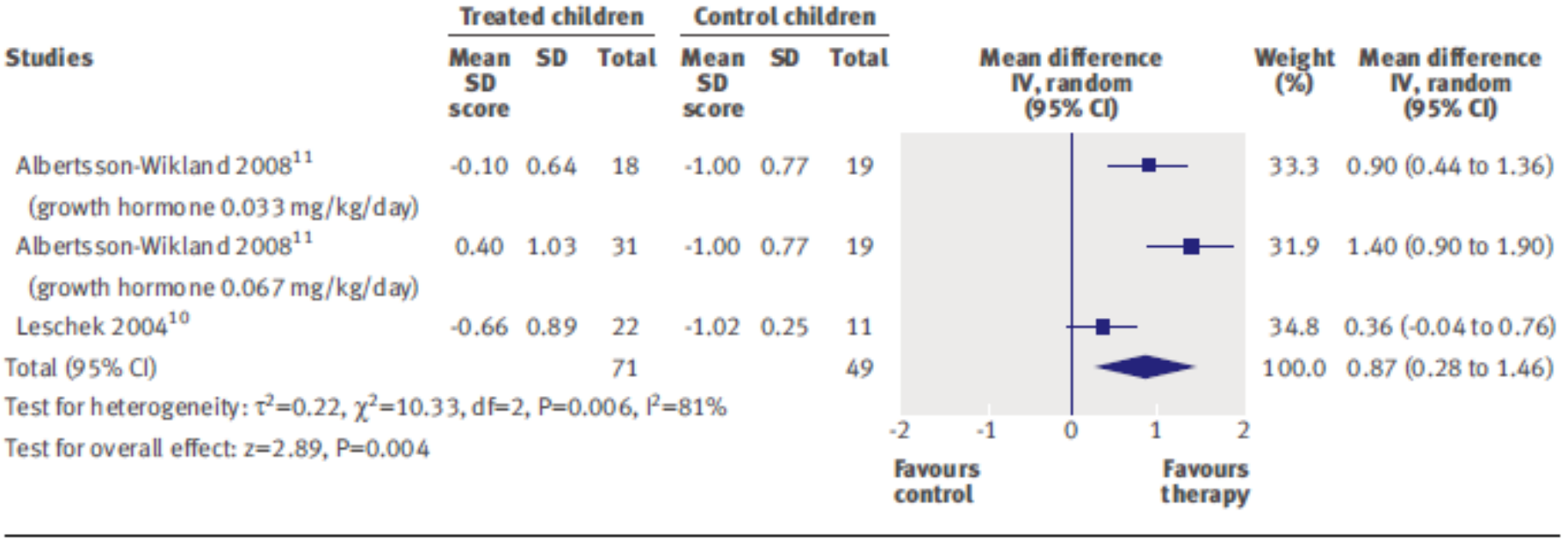

Fig 3 | Effect of long term growth hormone therapy at conventional doses on adult height corrected for mid-parental height in randomised controlled trials. Results of meta-analysis according to random model

Deodati e Cianfarani

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ISS: Authors' conclusions 1

Implications for practice:

- rhGH improves growth and final height
- Individual become taller, but still relatively short
- Small gains in height merit daily injections for a number of years**?**
- No evidence on quality of life
- Height gains justify the expense?
- Adverse effects must be taken in consideration

ISS: Authors' conclusions 2

Implications for research:

- **R**andomised **C**ontrolled **T**rials are required that focus on clear outcomes such as final height; analysed on an *intent-to-treat* basis
- To be addressed: adverse effects, quality of life and psychological outcomes, age of onset, optimal dose, heterogeneity of participants

Non conventional uses of rhGH in adolescence

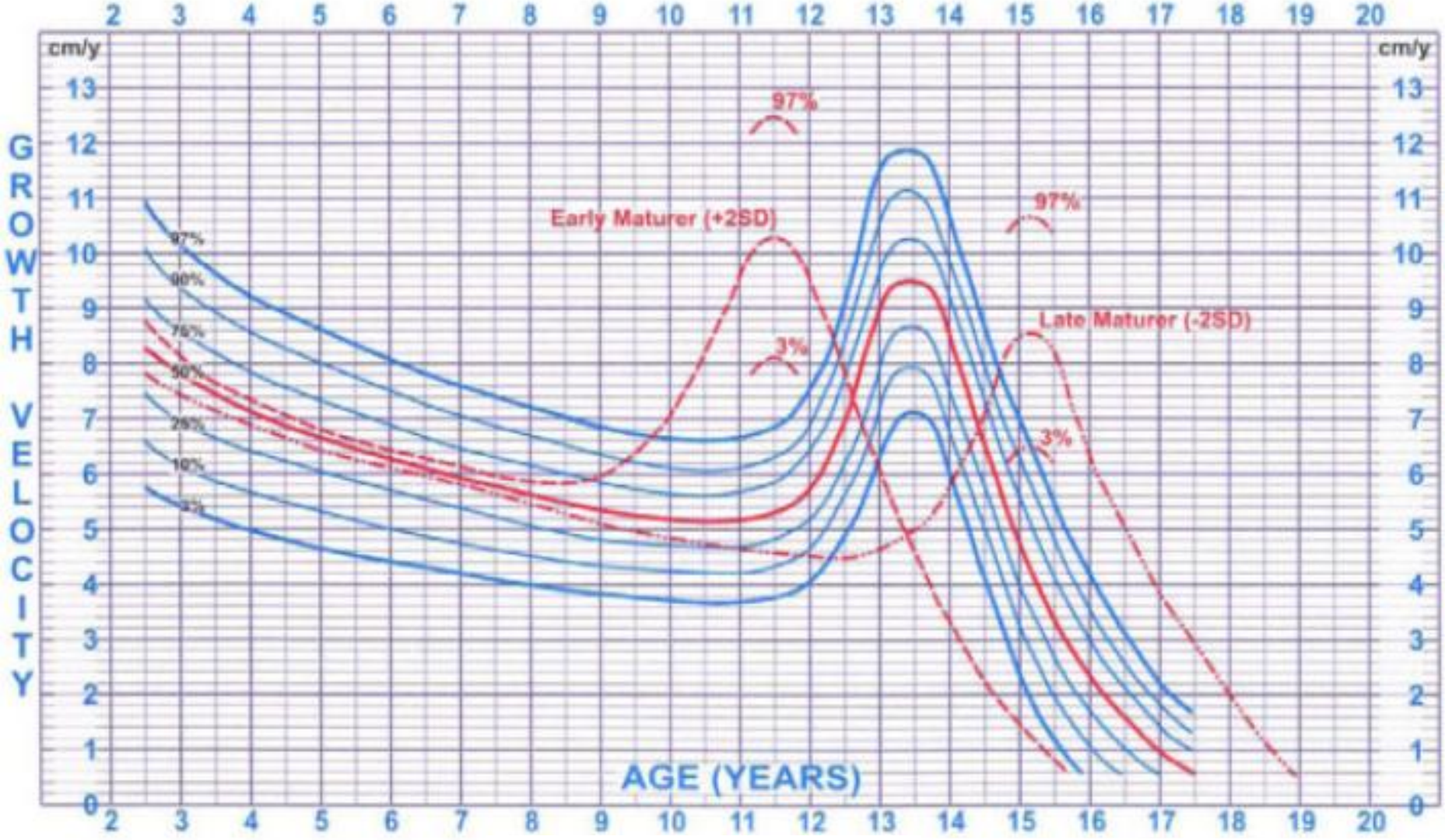
- Idiopathic short stature as paradigm of approved indications

- **Remarks on specific issues in adolescence**

rhGH non conventional uses *in adolescence*

remarks on:

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



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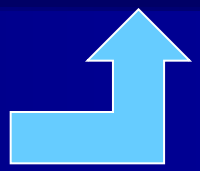
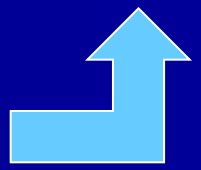
Normal growth velocity





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