



Diagnosing and Managing Late Blooming Teenagers

Paul Hofman 2016

Definition

- Failure of breast development by 13 years age in girls
- Failure of testicular enlargement $>3\text{ml}$ by 14 years in boys



13.9 yr old boy presents with short stature &
poor growth

What history is relevant?

Birth and antenatal hx:

Birth weight 3450gm at term.

Past Medical Hx:

Otherwise well

Family Hx.:

Mother's menarche 14 years

Father - probably normal pubertal onset

Mid Parental Height (Parents height $\pm$ 13cm/2)

- 165cm (-1.3 SDS or 10th %ile)

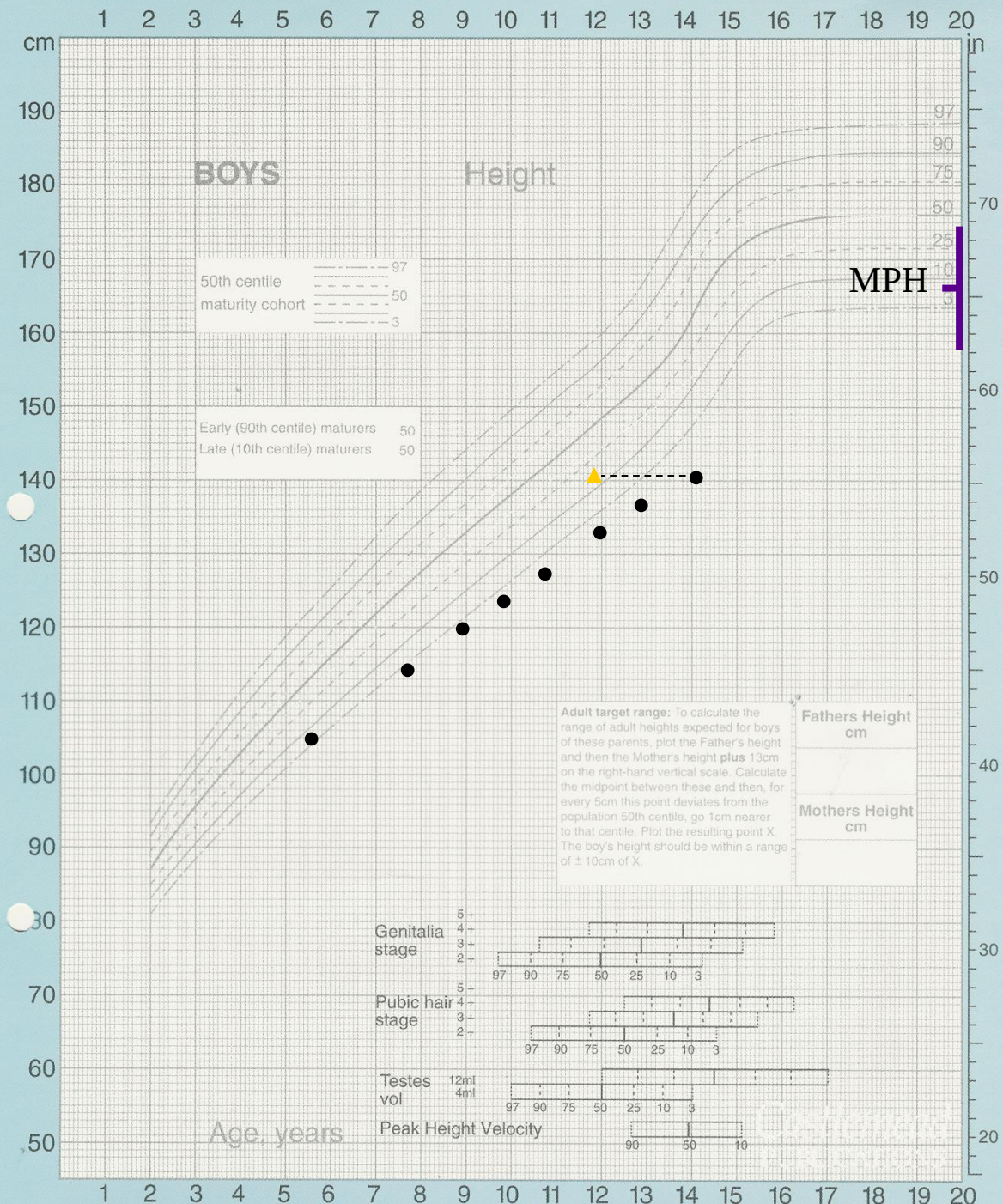
Other signs of constitutional delay

Delayed dental eruption (first teeth eruption
>9 months age)

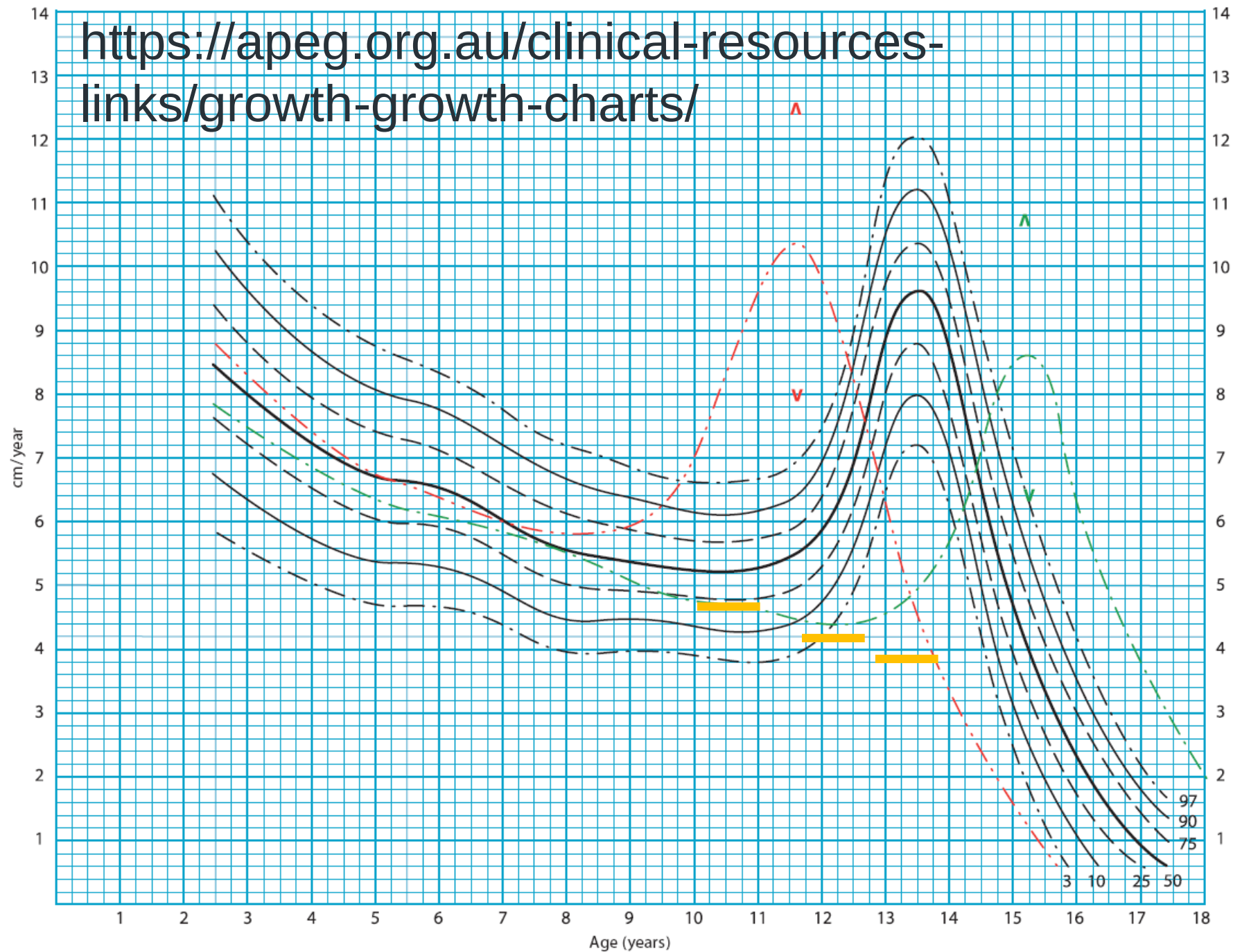
Catch down growth in early childhood

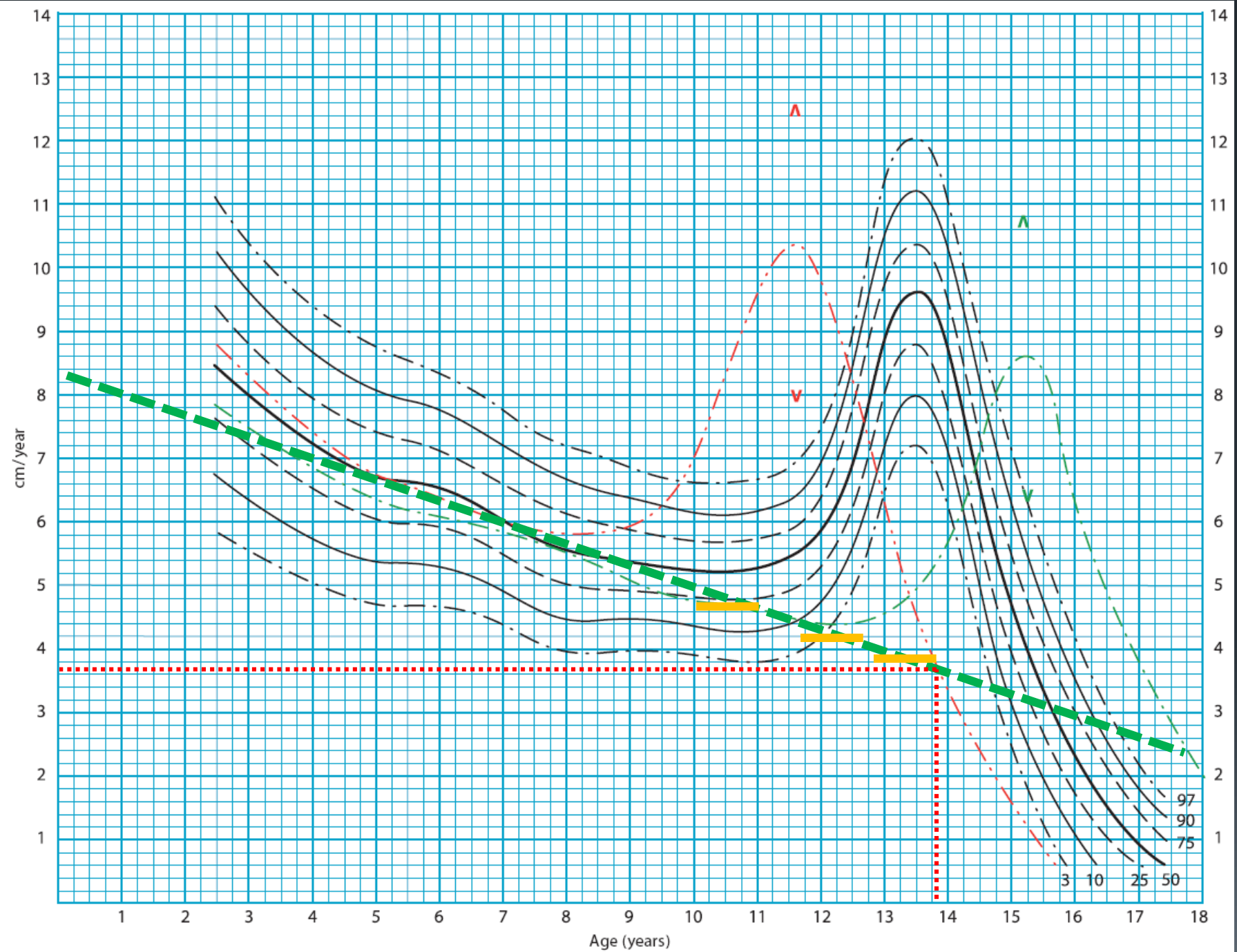
Height for bone age close to MPH

Family hx of delayed puberty



<https://apeg.org.au/clinical-resources-links/growth-growth-charts/>





What examination findings are relevant?

Growth:

Height -3.4 SDS

Weight -2.1 SDS

Height velocity 3.8 cm/ year (last 6 months)

Arm span=height

Sitting height 54%ile (normal)

Signs of syndromic short stature, occult illness or pubertal assessment:

No neurocutaneous stigmata

Not dysmorphic

Organs system examination normal

Tanner 2 pubic hair and 2ml testis bilaterally

Differential Diagnosis

- 1) Constitutional delay of growth and development plus familial short stature
- 2) Undiagnosed occult illness
- 3) Central defect in the hypothalamus/pituitary
 - 1) Kallmanns etc.
 - 2) Anorexia
 - 3) Extreme exercise
- 4) Primary defect in gonads

Investigations?

It depends on your perspective:

If the child is healthy with a family history of delayed puberty then a trial of testosterone is not unreasonable.

However if you believe pathology needs excluding then a much wider range of tests are required

A bone age is the only mandatory test required (X-ray left hand and wrist)

Investigations

Bone Age	11 years
U&Es	Normal
Ca & PO ₄	Normal
FBC&ESR	Normal
LH	0.2 IU/L
FSH	1.1 IU/L
Free T ₄	13 pmol/L
TSH	1.4 IU/L
Urinalysis	Normal
Urine pH	6.0



Summary of history, examination and investigations

- Familial short stature
- Probably normal growth velocity for a prepubertal boy
- Height for bone age close to MPH

How would you manage
this boy?

Potential Strategies

Wait and watch

Puberal Induction

Growth Hormone Tx?

Wait and Watch

This is a reasonable option if teenager not too concerned about height or lack of secondary sexual characteristics

Consider psychological issues of being prepubertal and short though.

Even if therapy doesn't increase final height, getting there more quickly can be beneficial.

Peak growth velocity occurs late in male puberty (ie at least 18 months away for this boy if he has constitutional delay and develops 4 ml testis now)

Pubertal Induction

If you feel you want to exclude a central pubertal cause for the delayed puberty AND the bone age is >10 years consider a buserelin stimulation test either before or after 6 months of testosterone.

Perform earlier if there evidence of CNS damage (previous tumour, radiotx etc), anosmia (Kallmann's syndrome) or other syndromic features.

Note LH 4 hours post buserelin should be >10 IU/L and considered abnormal if <5 IU/L

Pubertal Induction



Treatment Options

Testosterone Undecanoate (Panteston)

Testosterone Esters (Sustanon)

Testosterone patches and gels

Testosterone Undecanoate

PO administration, **lymphatic transp.**

40 mg daily, 15-21 mos

At 12 mos:

G3, PH 2-3

HV 3.2 to 7.2 cm/yr

Puberty onset 12-24 mos

dBA = dCA

Butler GE et al, J Clin Endocrinol Metab 1992;75:37

Testosterone Enanthate (similar to esters)

N=15 boys

14.1 +/-1.0 yrs

TE 50 mg monthly for 1.2 yrs

HV from 3.8 to 10.0 cm/yr

Testes from 5.9 to 11.3 ml

Final ht = pretreatment predicted ht

Richman and Kirsch, N Engl J Med, 1988;319:1563

Androgen Regimens

Consider when testes <5 ml

3-6 months of:

Tesosterone undecanoate 40 mg/day

Testosterone esters (250mg/ml) 50 mg
monthly x 3 months then 100mg monthly
x3 months (IM)

DP Treatment Summary

3-6 mos of androgens are safe and effective in

- Promoting virilisation

- Promoting growth

- Precipitating puberty

- Not compromising final height

Close follow up essential if testosterone trialed

Watch growth velocity – in 6 months should be $>8\text{cm/year}$

Watch spontaneous puberty – increasing testicular size should begin within 6 months

Poor post testosterone growth velocity (GV <8cm/year)

Consider:

- Occult illness (including steroid meds)

- Skeletal dysplasia

- GH deficiency/ hypopituitarism

- Compliance with medication!

No evidence of entering puberty spontaneously

Consider:

- Central or primary gonadal defect

- Arrange buserelin stimulation test (which should be positive after 6 months of testosterone priming)

 - High baseline LH indicates primary gonadal failure

 - Flat LH response to buserlin indicates a central problem

Growth Hormone Tx in this boy?

If he is GH deficient then this is a no-brainer.

HOWEVER he is much more likely to be normal.

Can GH benefit non-GH deficient idiopathic short stature?

Wit JM. Rekers-Mombarg LT. Dutch Growth Hormone Advisory Group. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. *Journal of Clinical Endocrinology & Metabolism*. 87(2):604-11, 2002 Feb.

	FSS				Non-FSS				IUGR			
	Treated	n	Untreated	n	Treated	n	Untreated	n	Treated	n	Untreated	n
FH SD score	-2.1 (0.7)	5	-2.2 (0.9)	10	-2.0 (1.0)	36	-2.4 (0.8)	45	-2.4 (0.9)	12	-2.5 (0.7)	9
FH SD score - height SD score baseline	0.8 (0.6)	5	0.3 (0.5)	10	1.5 (0.8) ^c	36	0.8 (0.6)	45	0.8 (1.0)	12	0.6 (0.6)	9
FH SD score - height SD score for BA baseline	-1.5 (1.4)	4	-1.1 (0.7)	9	-0.7 (1.1) ^b	36	-1.4 (1.2)	40	-0.7 (1.1)	12	-1.0 (0.6)	9
FH - PAH baseline (cm)	2.2 (3.5)	2	-0.6 (3.7)	7	4.0 (6.2) ^a	33	0.9 (6.0)	29	4.4 (4.6)	10	1.7 (3.7)	9
FH - TH (cm)	-2.1 (5.0)	5	-4.3 (3.9)	10	-7.1 (5.6) ^a	34	-9.6 (4.6)	45	-12.1 (9.1)	12	-10.3 (5.8)	9

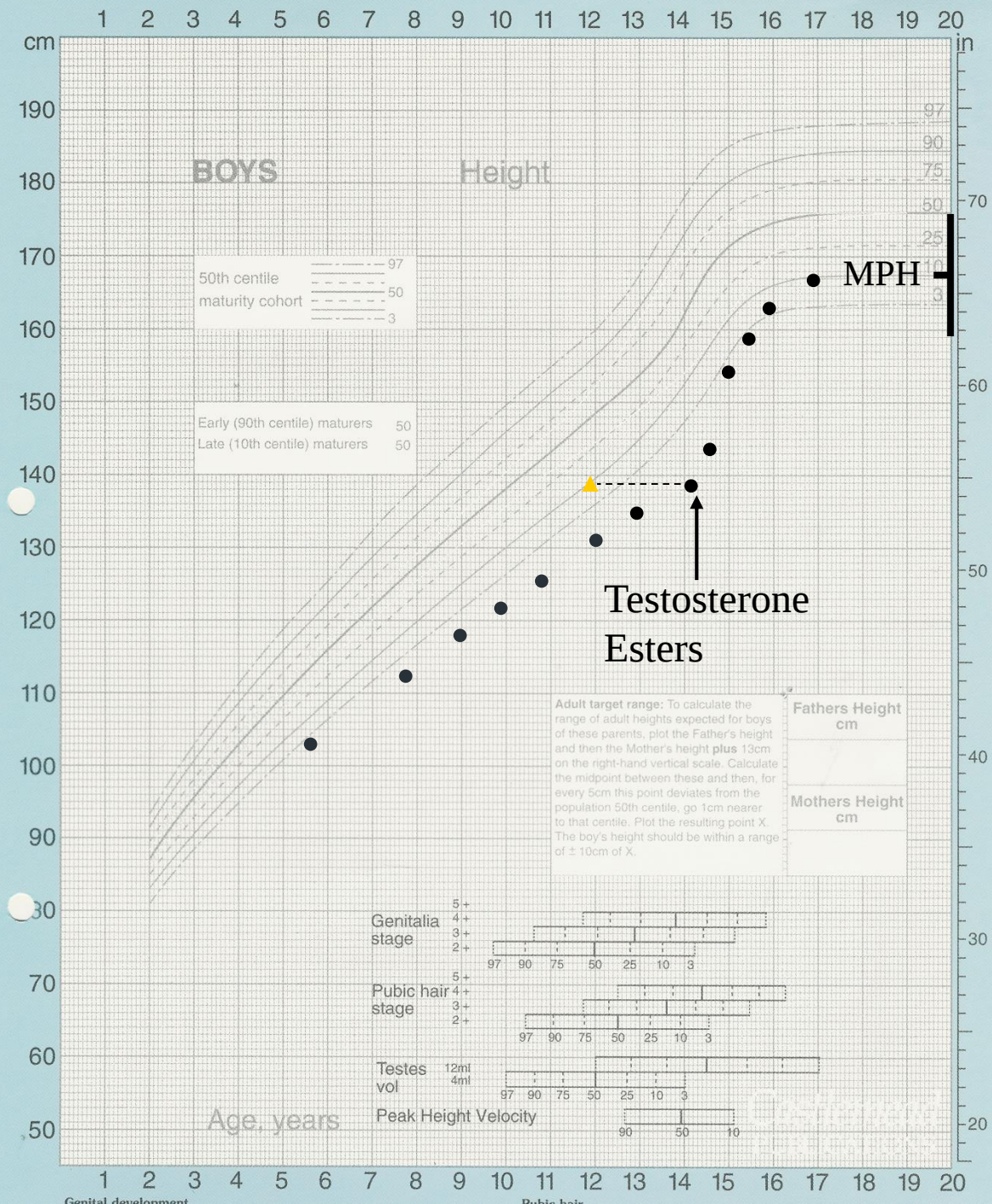
Mean (SD).
Difference between treated and untreated subjects: ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$.

Mean duration of GH Tx 5.9 years and mean age of starting 10.5 years

Follow-up in this case....

Treated with testosterone esters 50 mg monthly IM

Good growth and testis 6 ml after 6 months of therapy



What about girls?

- Trickier as oestrogen replacement has a greater impact on the growth plate
 - More rapid epiphyseal fusion
 - Greater risk of reducing final height
- Suggest always excluding other differential diagnoses in girls before starting tx.
- If everything points to a diagnosis of Constitutional delay in growth and development
 - Consider low dose oestrogen patches (1/4 of a 25mcg oestradiol patch weekly X6 months).
 - Try to avoid oral therapy as more likely to impact on growth

Summary

- Most adolescents will have CDGD and while it is a diagnosis of exclusion it can generally be made from history and examination
- Beware those who do not respond to treatment appropriately
 - Failure to recognise this can lead to delayed therapy for the underlying cause and short stature
- A bone age is the only mandatory investigation
- A trial of Testosterone (preferably IM) is safe and effective at managing this problem in boys
- Oestradiol patches are a reasonable alternative in girls



Thank you