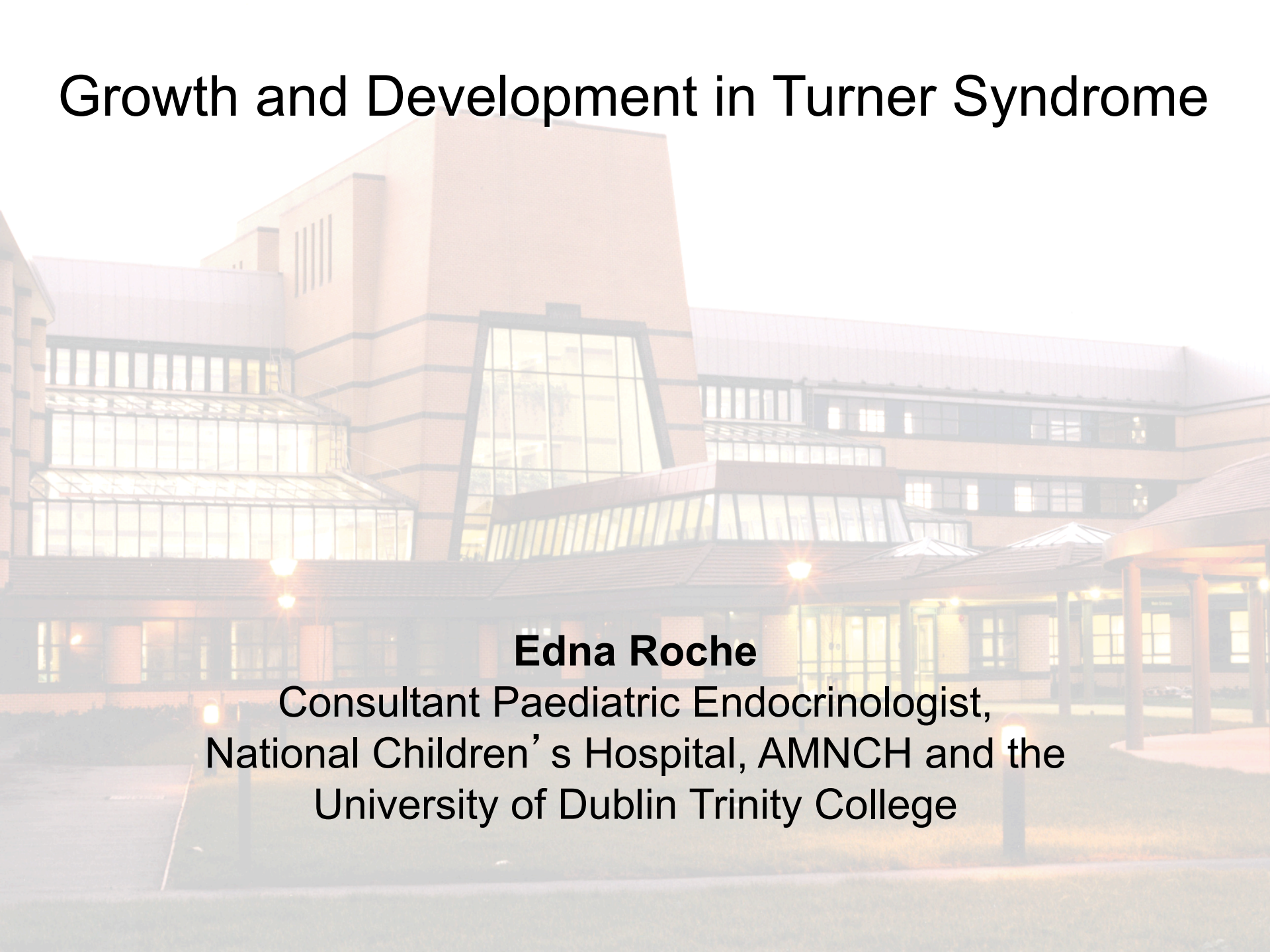
Growth and Development in Turner Syndrome

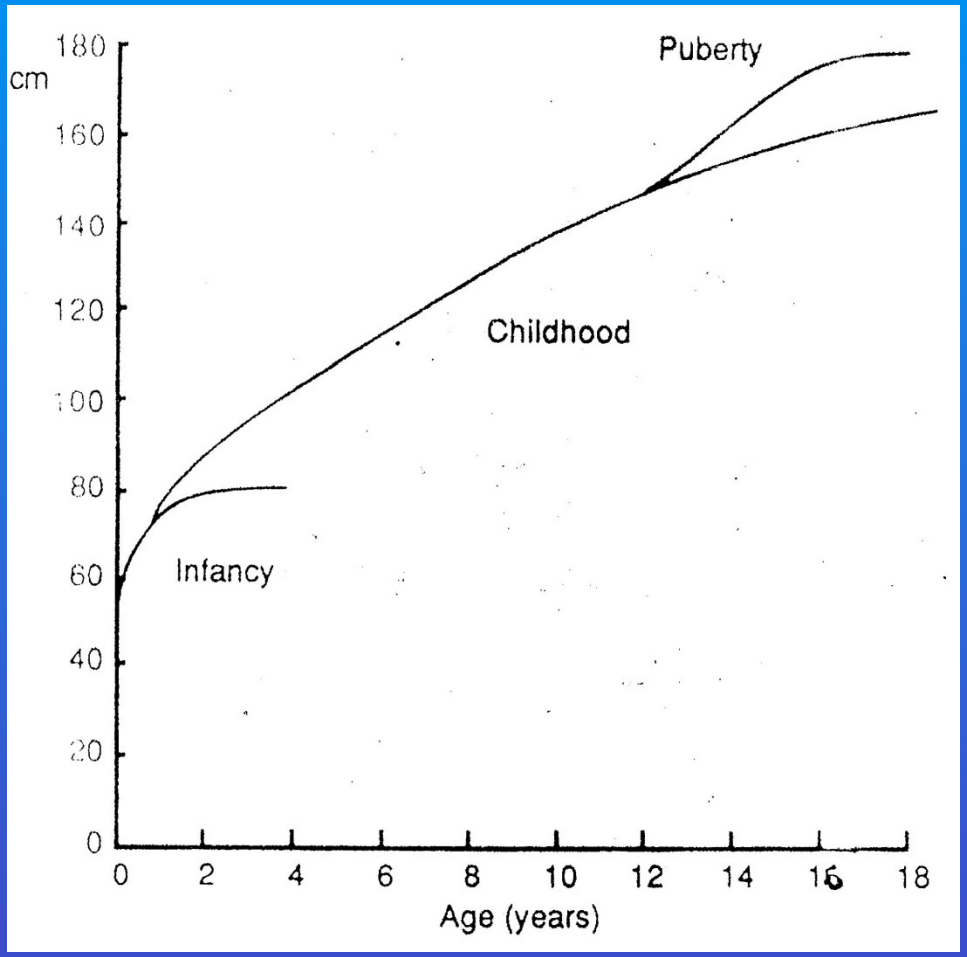


Edna Roche
Consultant Paediatric Endocrinologist,
National Children's Hospital, AMNCH and the
University of Dublin Trinity College

Growth in Turner Syndrome

- Short statue in almost 100%
- Average Final Height 142 – 147 cm (Europe) approx – 20cm
- Influence of parental height
- Increased incidence of Thyroid disease, IBD, RA

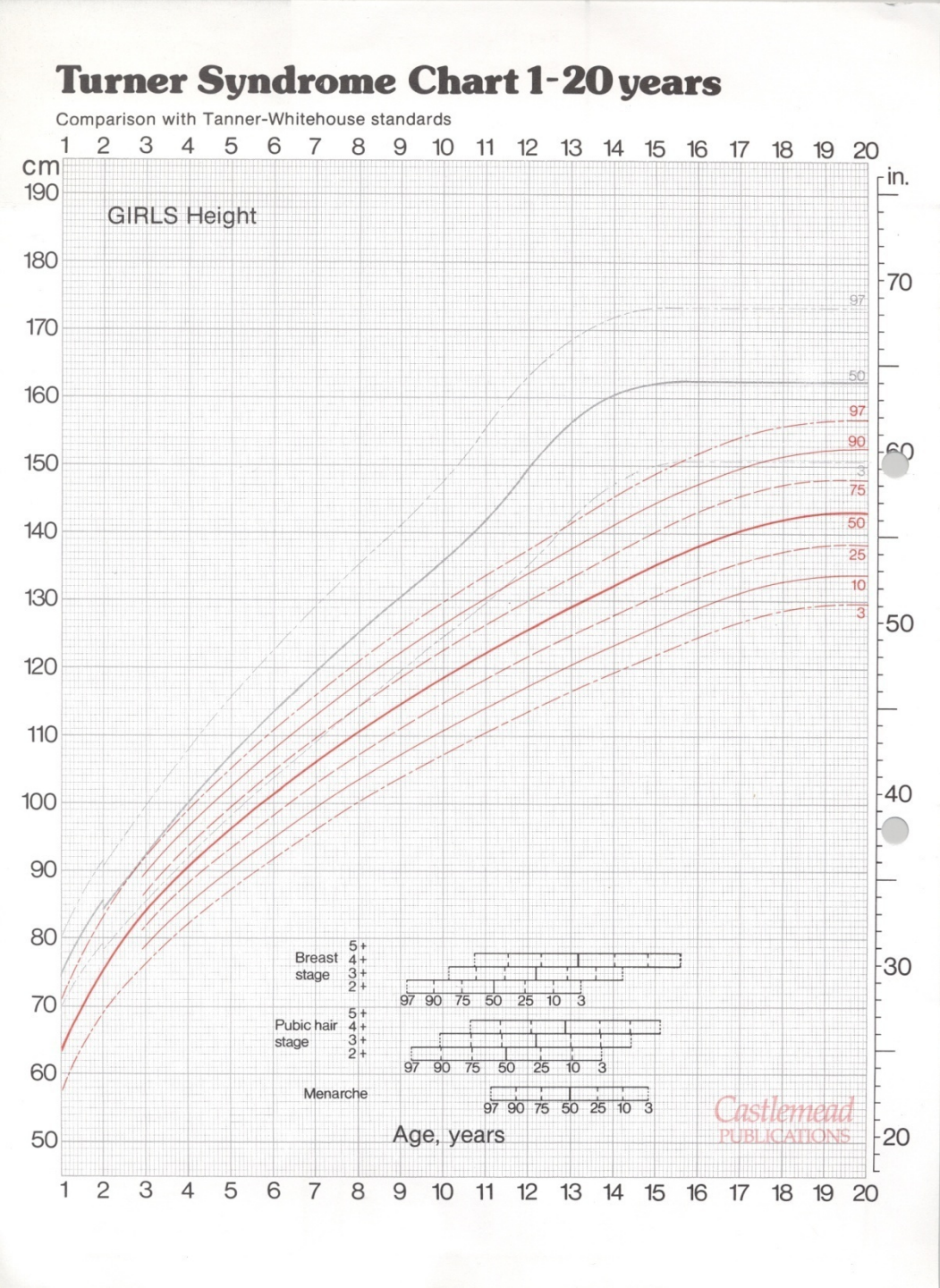
Infancy Childhood Puberty Karlberg growth model



Growth in Turner Syndrome

- Intrauterine growth retardation (Birth length -2.8 cm (-1SD); mean weight 2.18 kg (-1SD))
- Subnormal growth in infancy and childhood (loss of 15cm between 3-12 years)
- Absence of pubertal growth spurt with prolongation of total growth phase

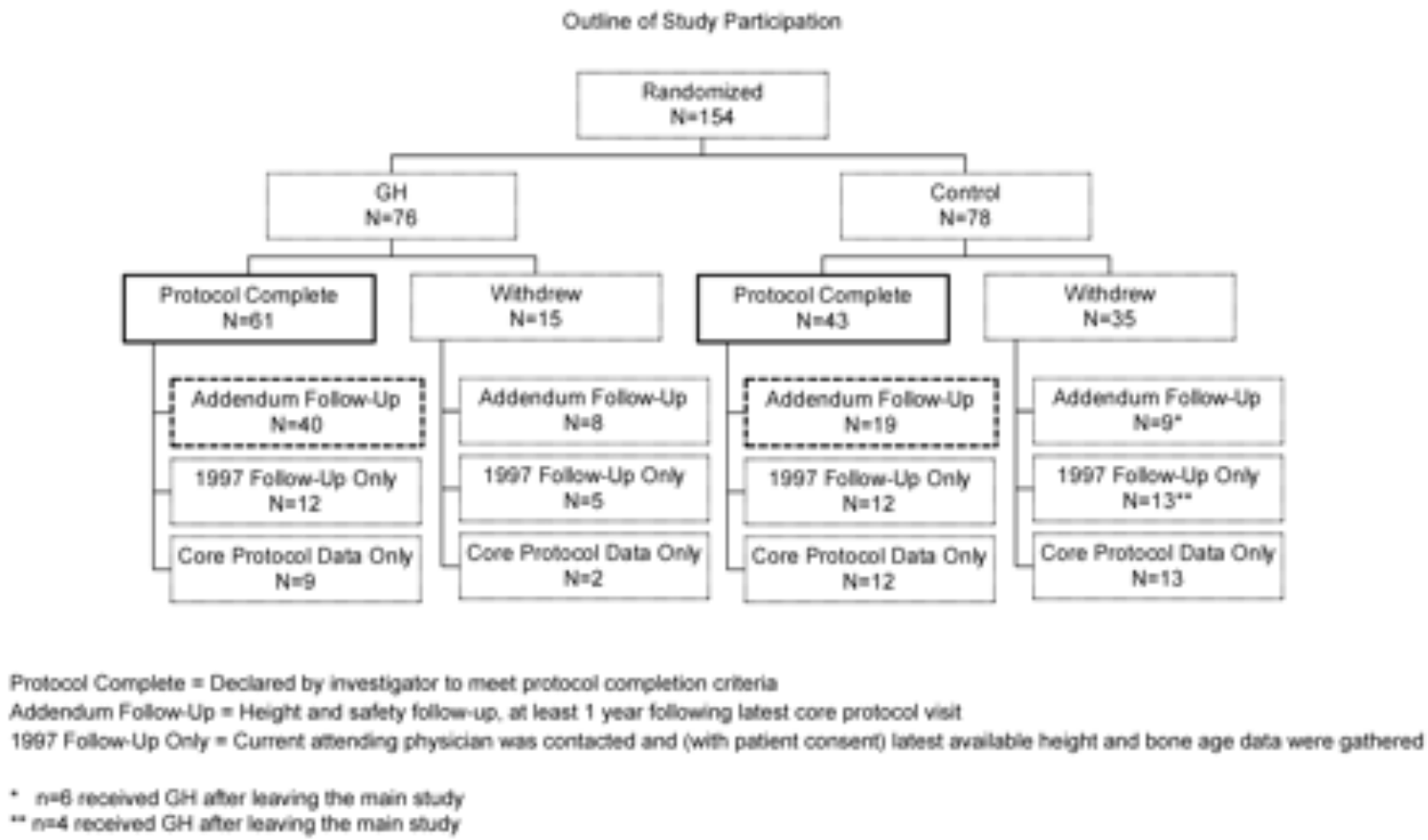
Untreated Final Height 143 cm
(130-157)



Lyon, Preece, Grant ADC 1985; 60: 932-5

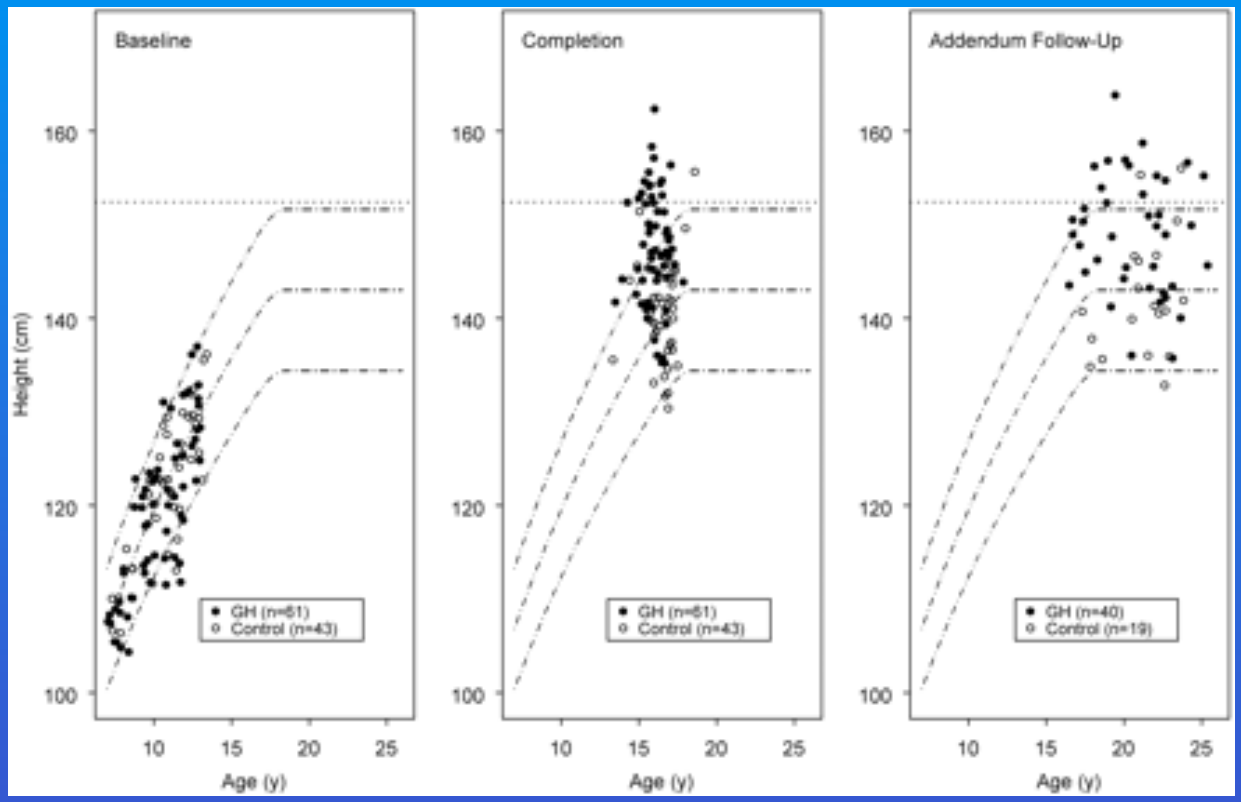
Does Growth Hormone Therapy Improve Final Height in TS?

Impact of GH Therapy in TS



Impact of Growth Hormone Supplementation on Adult Height in Turner Syndrome:
Results of the Canadian Randomized Controlled Trial The Canadian Growth Hormone Advisory Committee
The Journal of Clinical Endocrinology & Metabolism 2005 Vol. 90, No. 6 3360-3366,

Height at baseline, protocol completion, and follow-up *vs.* age



Impact of Growth Hormone Supplementation on Adult Height in Turner Syndrome: Results of the Canadian Randomized Controlled Trial The Canadian Growth Hormone Advisory Committee *The Journal of Clinical Endocrinology & Metabolism* 2005 Vol. 90, No. 6 3360-3366,

Impact of Growth Hormone Supplementation on Adult Height in Turner Syndrome: Results of the Canadian Randomized Controlled Trial

The Canadian Growth Hormone Advisory Committee1

The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 6 3360-3366

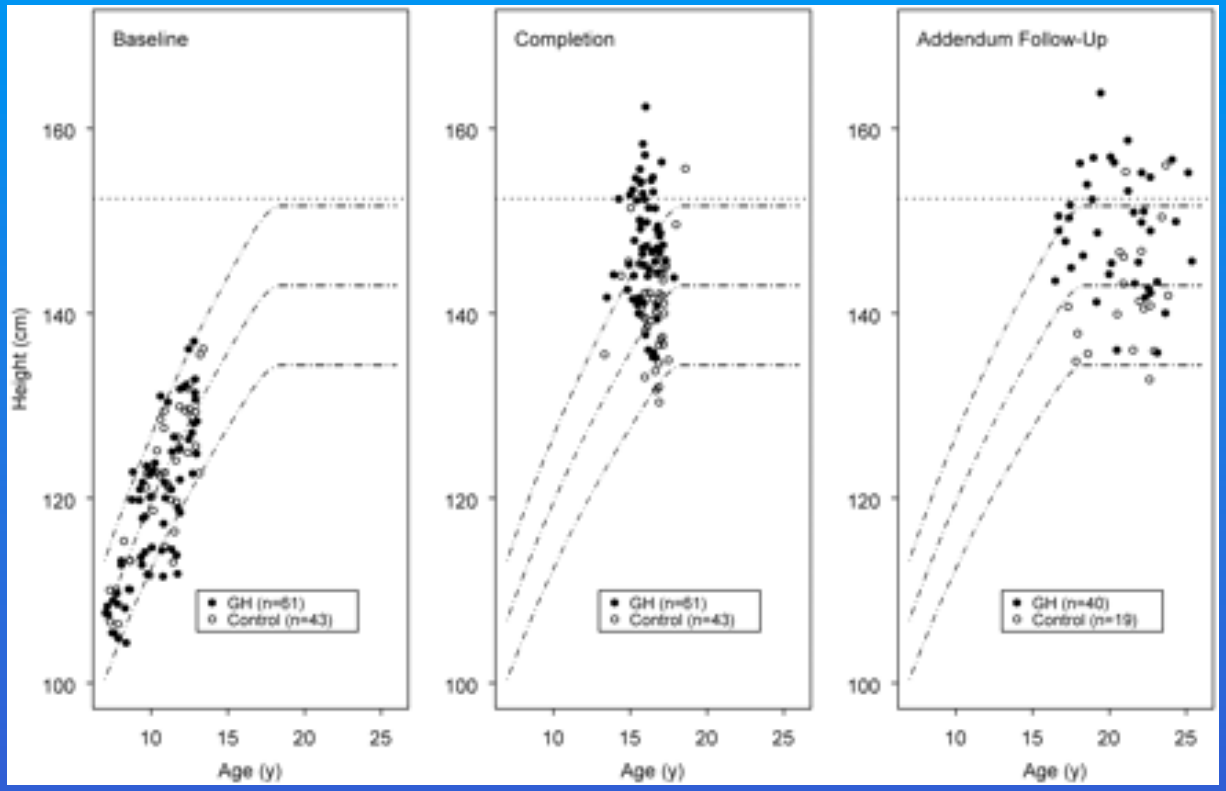
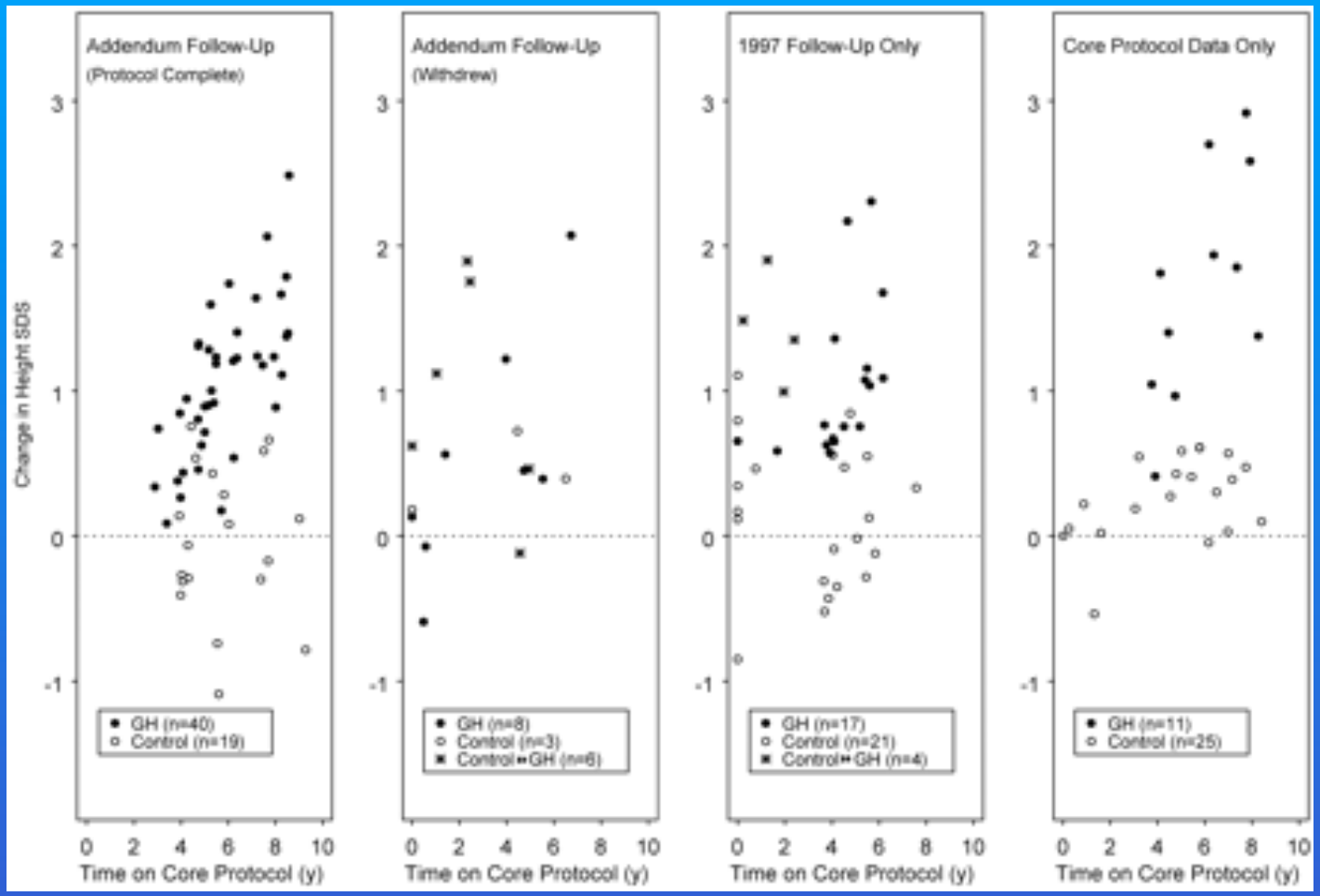


FIG. 2. Height at baseline, protocol completion, and addendum follow-up (at least 1 yr after completion) *vs.* age, plotted with 10th, 50th, and 90th percentile growth curves for Turner syndrome (1) for patients who completed the core protocol. *Horizontal dashed line*, Height of 5 feet (152.4 cm); *open circles*, control subjects; *solid circles*, GH-treated subjects.

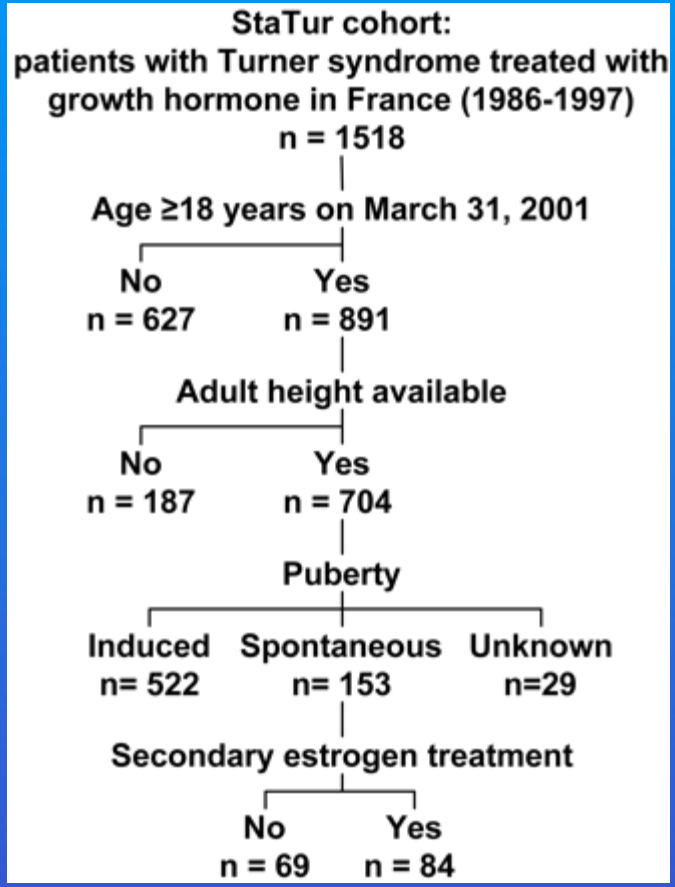
Change in age-specific height SDS for Turner syndrome



Change in age-specific height SDS for Turner syndrome (1) at most recent available height *vs.* time on core protocol for all 154 randomized patients.
Horizontal dashed line, No change in height SDS; *open circles*, control patients; *solid circles*, GH-treated patients; *asterisk*, control patients who received GH after leaving core protocol.

The Journal of Clinical Endocrinology & Metabolism 2005 Vol. 90, No. 6 3360-3366

Adult Height and Pubertal Growth in Turner Syndrome after Treatment with Recombinant Growth Hormone

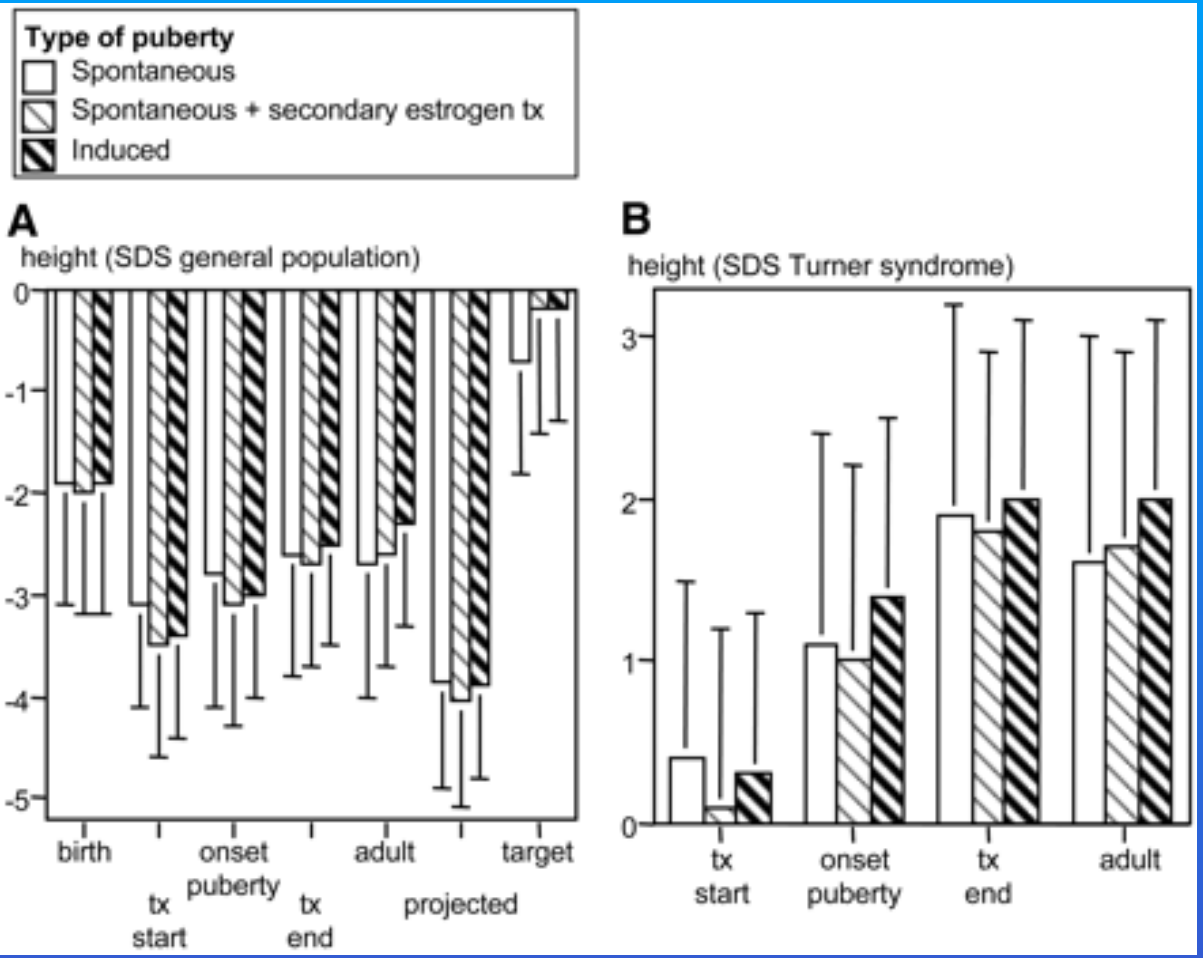


Soriano-Guillen L et al, The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 9 5197-5204

RCT Adult Height

	Growth Hormone	Control	Height gain
Mean Height (completion)	147.5 ± 6.1 cm	141.0 ± 5.4 cm ($p < 0.001$)	+7.2cm (6-8.5) ($p < 0.001$) +1 SD (0.9-1.3)
Mean Height (follow-up)	149.0 ± 6.4 cm	142.0 ± 6.6 cm ($p < 0.001$)	+7.3cm (5.3-9.2) ($p < 0.001$) +1 SD (0.7-1.4)

The Journal of Clinical Endocrinology & Metabolism 2005 Vol. 90, No. 6 3360-3366



Mean AH 149.9 ± 6.1 cm

8.5 cm above projected height

Soriano-Guillen L et al, The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 9 5197-5204

	Growth hormone + oestrogen (Total: 14)	Growth hormone + oestrogen + Oxandrolone (Total: 7)	Growth hormone (Total: 4)	Growth hormone + Oxandrolone (Total: 3)
Mean final height	**149.59cm** (SD 4.8)	**146.11cm** (SD 3.56)	**144.87cm** (SD 2.67)	**142.70cm** (SD 4.65)
Delta (height gain)	**5.27cm** (SD 4.15)	**6.71cm** (SD 2.43)	**0.12cm** (SD 7.6)	**-0.46cm** (SD 3.99)
Mean chronological age starting growth hormone (years)	12.23	12.41	10.57	11.63
Mean duration of growth hormone (years)	4.76	4.66	4.70	4.55
Mean initial dose of growth hormone (units/kg/week)	0.69	0.69	0.50	0.50
Mean final dose of growth hormone (units/kg/week)	0.82	0.95	0.88	0.75
Mean chronological age starting Oxandrolone (years)	Nil	13.11	Nil	13.61
Mean chronological age of starting oestrogen (years)	13.35	14.12	Nil	Nil
Mean bone age of starting oestrogen (years)	11.58 (n = 11)	11.43 (n = 7)	Nil	Nil
Spontaneous menarche	n = 0	n = 1	n = 4	n = 3
Induced menarche	All (n = 14)	n = 6	n = 0	n = 0
Mid parental height	159.10	157.55	156.42	157.00

Treatment outcome in Turner Syndrome Parvin M, Roche E, Costigan C, Hoey H IMJ 2004; 97 (1):12-15

Does Growth Hormone Therapy Improve Final Height in TS?

Yes

BUT

Growth Promoting Therapy

- When to start - ? when falling off in height or earlier
- What GH dose - ? 0.045 - 0.05 mg/kg/day or higher
- ? Add Oxandrolone 0.0625 mg /kg/day

When Should Treatment with Growth Hormone Begin?

Early Treatment with GH

	Growth Hormone	Control
Baseline Mean length/height SDS	- 1.4 ± 1.0	-1.8 ± 1.1
2years Mean length/height SDS	0.3 ± 1.1	-2.2 ± 1.2
Mean Height Gain/Loss	+ 1.1 SDS	-0.5 SDS

2 year Between group difference 1.6 ± 0.6 SDS ($P < 0.0001$)

Davenport et al, Journal of Clinical Endocrinology and Metabolism 2007; 92 (9):3406-16

When to Start GH therapy

"consider as soon as growth failure (decreasing height percentiles on the normal curve) is demonstrated and its potential risks and benefits have been discussed with the family"

Care of Girls and Women with Turner Syndrome: A guideline of the Turner Syndrome Study Group
Carolyn A Bondy for the Turner Syndrome Consensus Study Group
J Clin Endocrinol Metab 92: 10-25, 2007

Height Gain

- Minimal gain to make GH treatment worthwhile 8 cm in 64% Carel, JCEM 2005; 90 (6):3793-94
- Canadian RCT gain 7.2/7.3 cm *JCEM* 2005; 90 (6): 3360-66
- StaTur Cohort gain 8.5 cm above projected height Soriano-Guillen L et al, JCEM 2005; 90 (9):5197-5204

Factors Associated with Final or Near Final Height

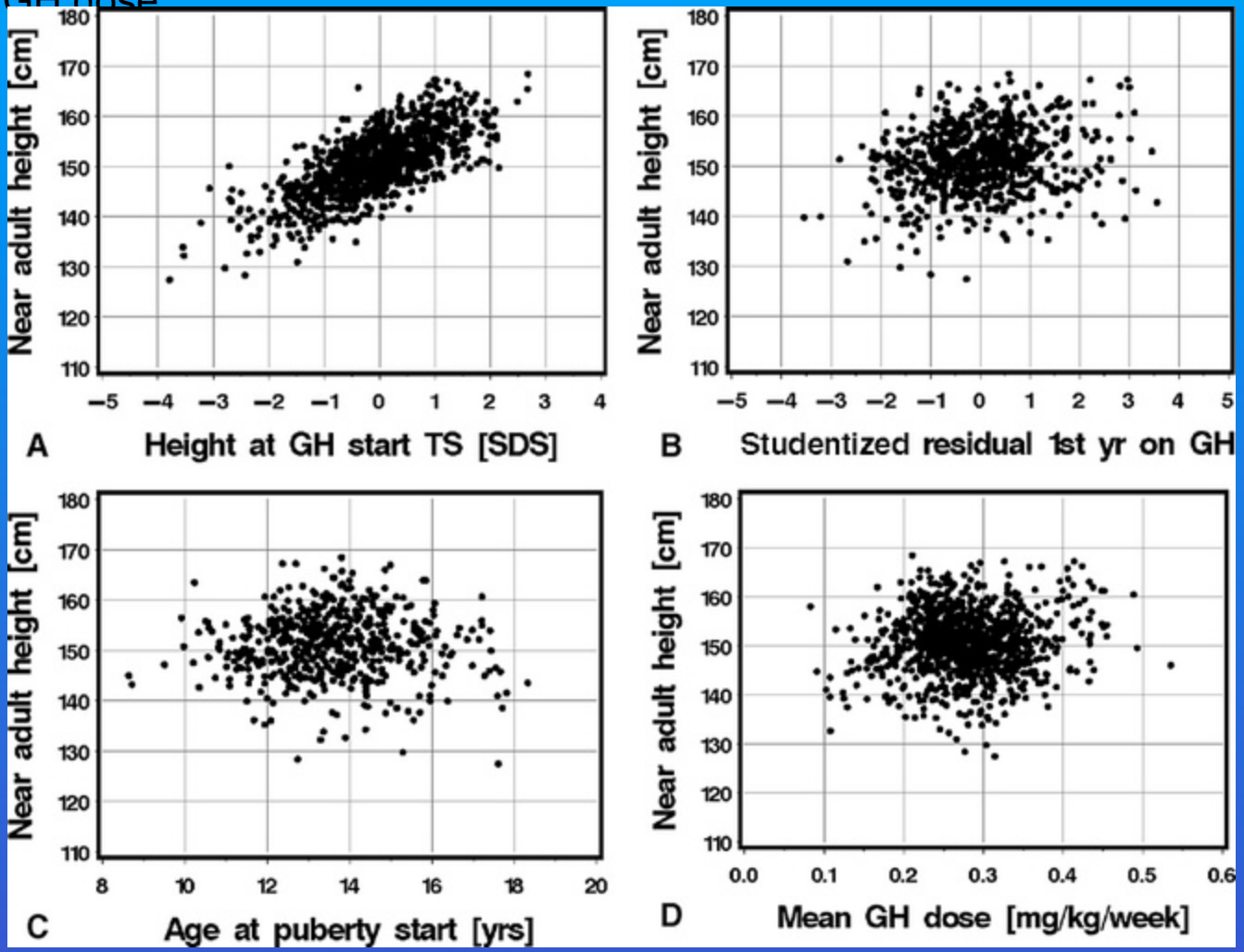
Factors associated with adult height in TS patients treated with GH

Variable	Regression coefficient[a]	95% Confidence interval	*P value*	% Variance explained
Regression toward the mean				
Height at baseline (*a*, cm)	0.13	0.01/0.25	0.033	1.1
Total duration of follow-up (*b*, year)	1.54	0.24/2.84	0.020	1.3
Interaction (*a* × *b*)	−0.01	−0.02/0.00	0.051	0.9
Constitutive				
Birth length (SDS)	0.28	0.07/0.50	0.011	1.5
Target height (SDS)	0.56	0.28/0.84	<0.0001	3.6
Baseline				
Age at baseline (year)	**−3.06**	**−3.49/−2.63**	**<0.0001**	**44.6**
Weight at baseline (SDS)	−0.47	−0.76/−0.17	0.002	2.3
Bone age delay (year)	0.87	0.57/1.17	<0.0001	7.4
Puberty and treatment related				
Age at onset of puberty (year)	0.28	0.08/0.49	0.006	1.7
Duration of GH (year)	**1.54**	**1.22/1.85**	**<0.0001**	**21.3**
Log GH dose (IU/kg wk)	2.42	0.99/3.86	0.001	2.5
No. of injections per week >6 (yes = 1, no = 0)	0.81	1.36/0.26	0.004	1.9

Soriano-Guillen L et al, JCEM 2005; 90 (9):5197-5204

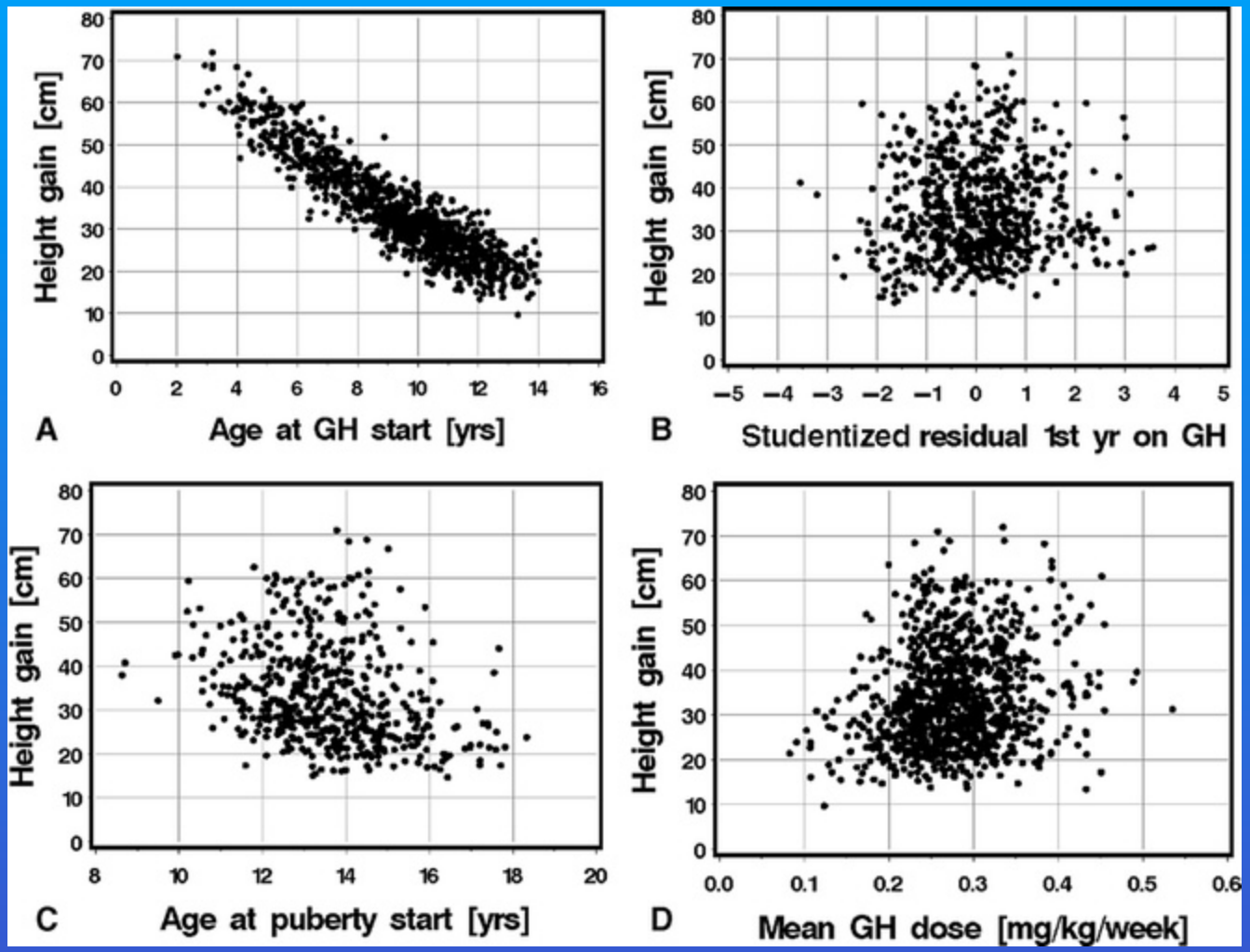
Near adult height (cm) in 987 patients with Turner syndrome.

Correlation with (*A*) HT at GH start, (*B*) Studentized residual 1*st* yr on GH, (*C*) age at puberty onset, and (*D*) mean GH dose



Pediatric Research :Volume 61(1)January 2007pp 105-110, Ranke MB et al
Major Determinants of Height Development in Turner Syndrome (TS) Patients Treated With GH: Analysis of 987 Patients From KIGS

Total gain in height (cm) on GH in 987 patients with Turner syndrome. Correlation with (*A*) age at GH start, (*B*) Studentized residual 1*st* yr on GH, (*C*) age at puberty onset, and (*D*) mean GH dose.



Pediatric Research :Volume 61(1)January 2007pp 105-110, Ranke MB et al
Major Determinants of Height Development in Turner Syndrome (TS) Patients Treated With GH: Analysis of 987 Patients From KIGS

Factors Determining NAH

- height at GH start (the taller, the better)
- age at GH start (the younger, the better)
- the responsiveness to GH (the higher, the better) - variability
- age at puberty (the later, the better) determine NAH.

Pediatric Research :Volume 61(1)January 2007pp 105-110, Ranke MB et al
Major Determinants of Height Development in Turner Syndrome (TS) Patients Treated With GH: Analysis of 987 Patients From KIGS

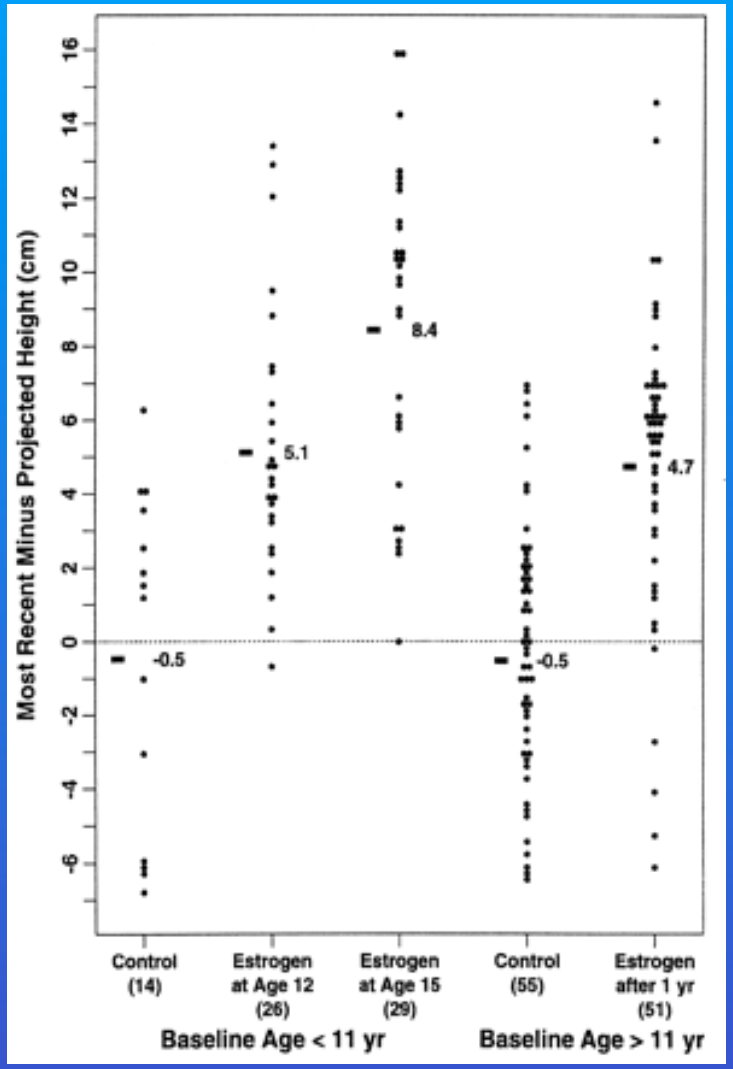
Pubertal Development in Turner Syndrome

- Gonadal failure common - process of oocyte loss is accelerated
- Spontaneous onset of puberty variable (Pasquino et al, 14% Monosomy X; 32% with additional cell lines)
- Many will need support to induce/maintain pubertal development – measure gonadotrophins

Induction of Puberty

- Different preparations available (oral, depot, transdermal)
- Timing varies
- Early GH therapy permits more physiological age induction of puberty
- Slow induction of puberty over 2-4 years
- Physiological age induction of puberty to optimise self-esteem, social adjustment and initiation of sex-life (Carel et al, JCEM 91:2972-2979, 2006)

Growth Hormone Therapy of Turner Syndrome: The Impact of Age of Estrogen Replacement on Final Height

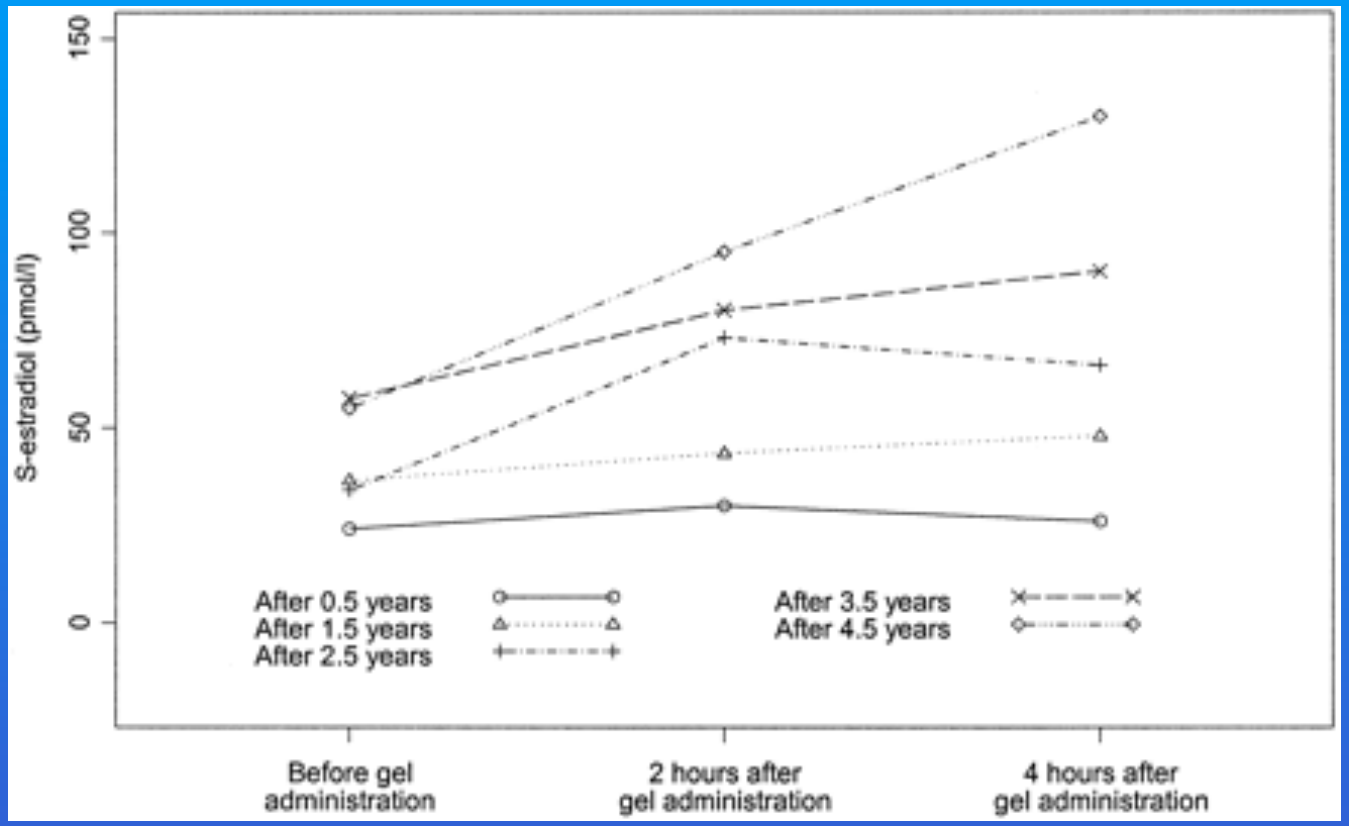


Steven D. Chernausek, Kenneth M. Attie, Jose F. Cara, Ron G. Rosenfeld, James Frane and and the Genentech Inc. Collaborative Study Group
The Journal of Clinical Endocrinology & Metabolism 2000; 85 (7): 2439-24452

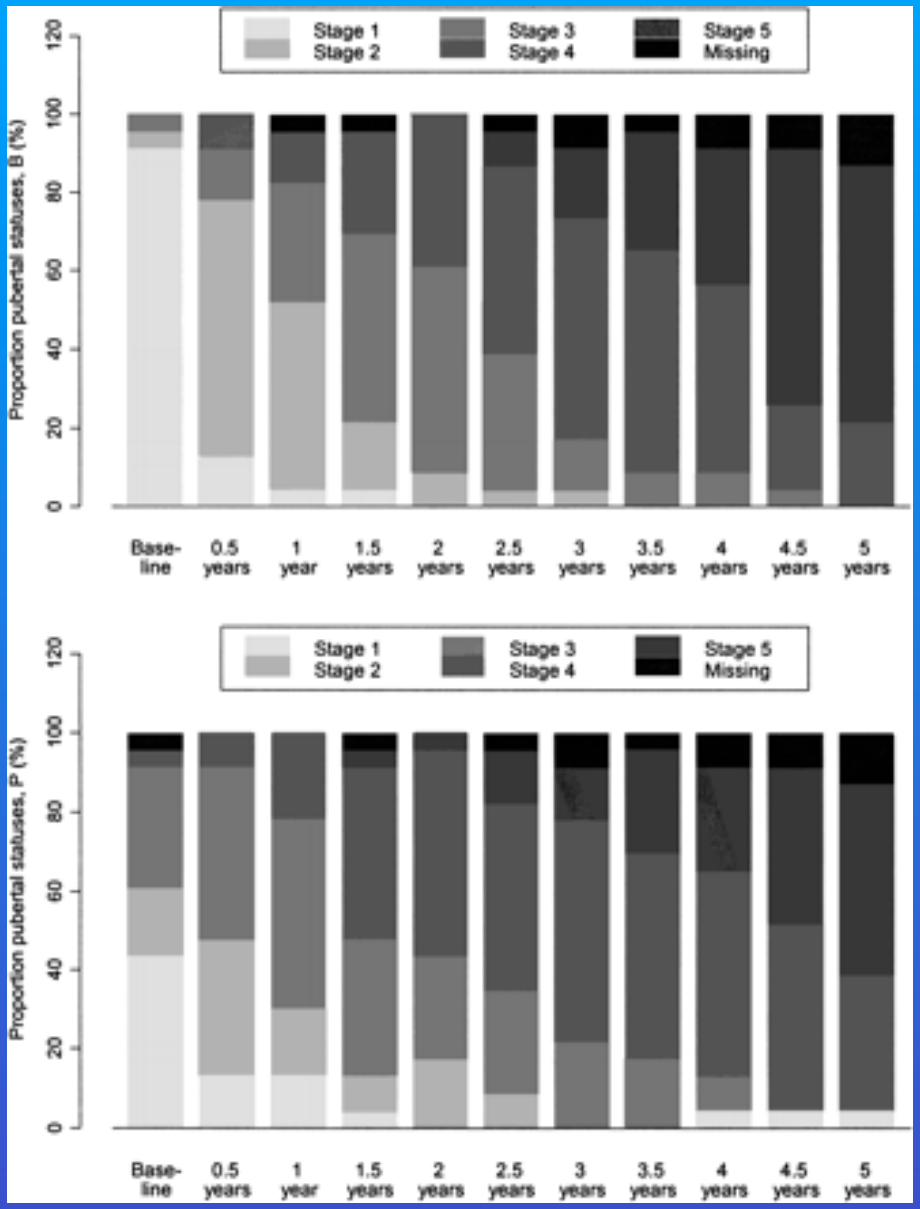
Induction of Puberty

- Early GH Tx induce puberty at age appropriate time variation 11-13 years
- Slow introduction of oestrogens
- Maintain on low dose OCP
- OCP v HRT

Serum oestradiol after percutaneous gel administration



Use of Percutaneous Estrogen Gel for Induction of Puberty in Girls with Turner Syndrome
S. Piippo, H. Lenko, P. Kainulainen and I. Sipilä
The Journal of Clinical Endocrinology & Metabolism 2004 Vol. 89, No. 7 3241-3247

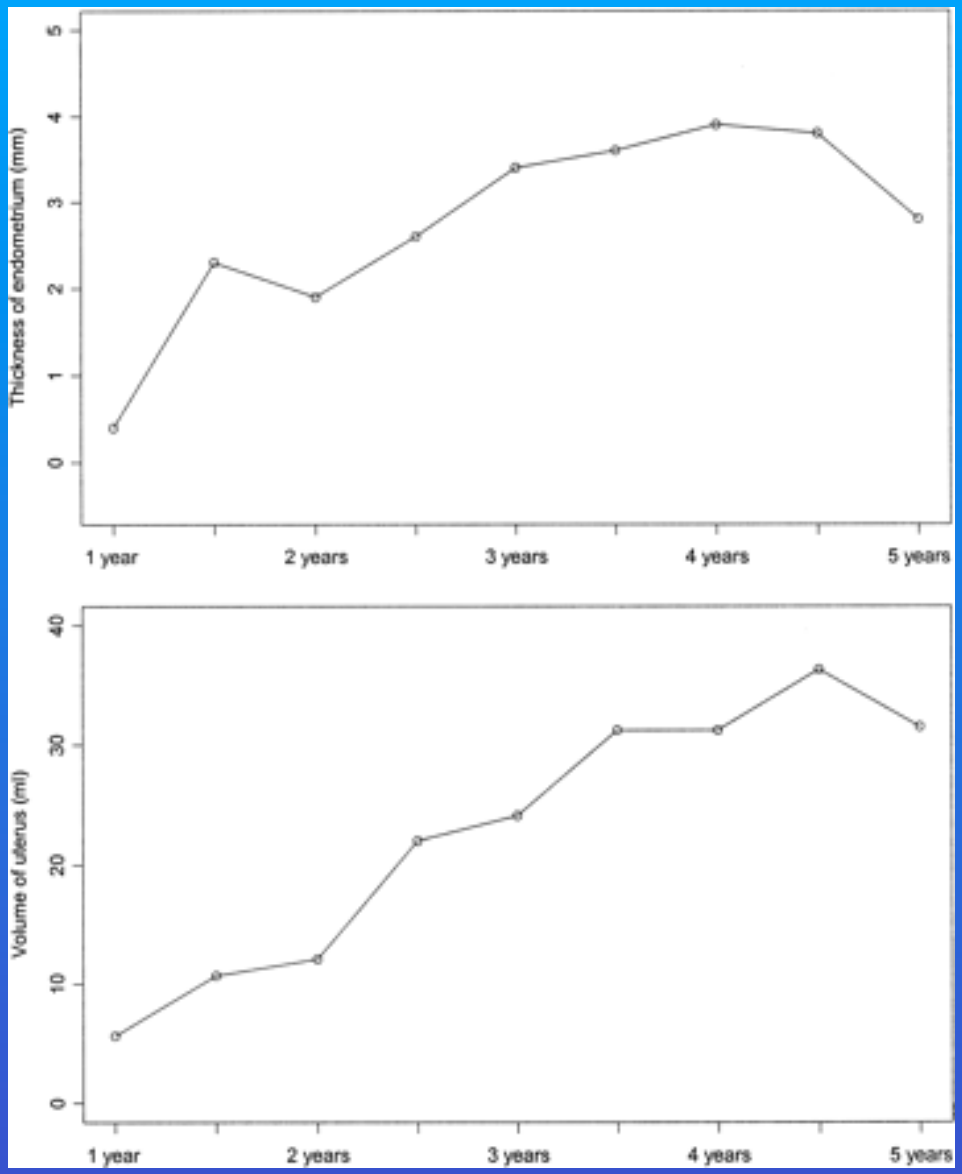


Breast and uterine development proceeded gradually

Normal uterine devt at age 16

Use of Percutaneous Estrogen Gel for Induction of Puberty in Girls with Turner Syndrome
S. Piippo, H. Lenko, P. Kainulainen and I. Sipilä
The Journal of Clinical Endocrinology & Metabolism
2004 Vol. 89, No. 7 3241-3247

Development of the uterus and endometrium.



Uterine length increased
33mm (15-66mm) baseline

67mm (48-91mm) year 5

Uterine volume increased
5.5 mls (1.7 – 12.6 ml) Yr 1
31.5 ml (8.2-82.8ml) year 5

Use of Percutaneous Estrogen Gel for Induction of Puberty in Girls with Turner Syndrome
S. Piippo, H. Lenko, P. Kainulainen and I. Sipilä
The Journal of Clinical Endocrinology & Metabolism 2004 Vol. 89, No. 7 3241-3247

Growth and Puberty in TS

- Growth Hormone is effective in TS but for maximum impact:

- Early detection of TS required
  Counsel patients re growth expectation
  Start Growth Hormone early
  Maximise GH years prior to pubertal induction, potential for very low dose oestrogen
  dose variation in GH to response?

  a variety of methods exist to induce puberty in TS

  QOL a key issue

Thank You

Screening at Diagnosis

Bondy JCEM 2007;92 (1):10-25

All Ages

- Specialist CVS exam
- Renal U/S
- Hearing (Audiologist)
- Evaluate Growth and puberty
- Evaluate Knowledge of TS

Age 0-4 years

- Evaluation Hip Disclocation
- Opthalmologist assess (> 1)

Age 4- 10 years

- Thyroid & Coeliac Screen
- Educational/Psychosocial
- Orthodontic evaluation(> 7)

Age > 10 years (as 4-10 plus)

Evaluation ovarian function/oes Tx

Lipids, RLB,FBC, Glucose

BMD if > 18

Ongoing Monitoring Bondy JCEM 2007;92 (1):10-25

All Ages

- Cardiology Evaluation as reqd
- Annual BP
- ENT and Audiology every 1-5 years

Under 5's

- Social skills age 4-5

School Age

- Annual liver and thyroid
- Coeliac every 2-5 years*
- Annual education & social progress
- Dental & orthodontic prn

Ongoing Monitoring Bondy JCEM 2007;92 (1):10-25

All Ages

- Cardiology Evaluation as reqd
- Annual BP
- ENT and Audiology every 1-5 years

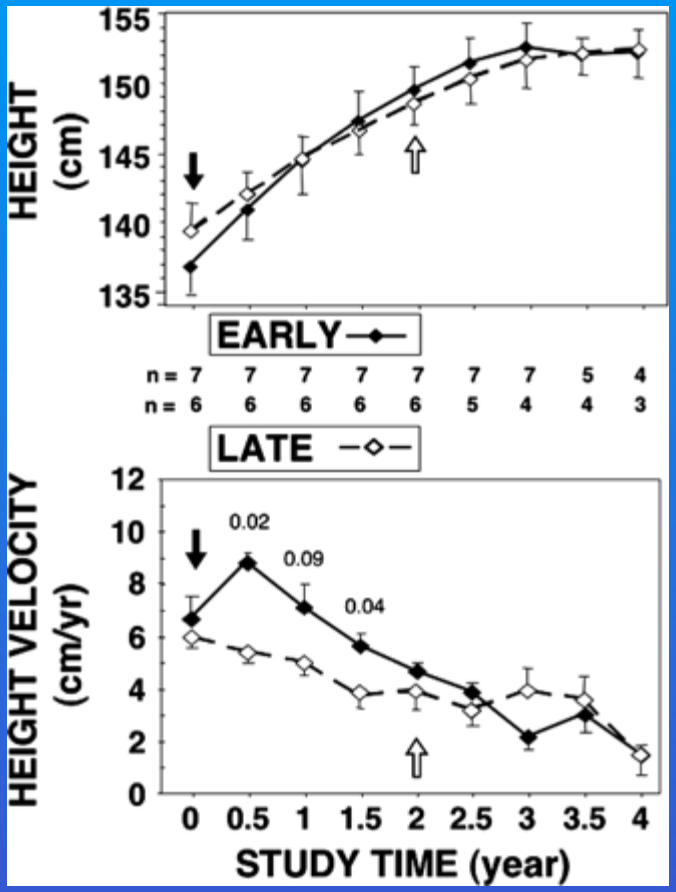
Older Girls and Adults

- Annual Fasting lipids and blood sugar
- Annual liver and thyroid
- Coeliac “as indicated”*
- Age-appropriate evaluation of Pubertal development and psychosexual adjustment

	Oral ethinyl estradiol	Oral estradiol	Percutaneous estradiol	E/P combinations
No. of patients[1]	315	144	45	7
Age at estrogen treatment (yr)	14.6 ± 1.9	15.4 ± 1.8	16.0 ± 1.5	16.8 ± 1.7
Delay between estrogens and progestin (yr)				
<1	13%	29%	35%	
1–2	36%	50%	49%	
>2	51%	21%	16%	
Duration of GH before estrogens (yr)	2.5 ± 1.9	4.0 ± 2.1	3.6 ± 1.9	3.6 ± 2.1
Duration of GH after estrogens (yr)	2.3 ± 1.5	1.6 ± 1.0	1.3 ± 1.1	0.4 ± 1.6
Height at initiation of estrogen treatment (SDS, general population)	–3.1 ± 1.0	–2.7 ± 1.0	–2.8 ± 1.1	–2.7 ± 1.3
Height at initiation of estrogen treatment (SDS, Turner syndrome)	1.2 ± 1.1	1.9 ± 1.1	1.7 ± 1.1	1.8 ± 1.4
Pubertal growth (cm)	10.1 ± 6.5	6.8 ± 3.6	6.4 ± 4.3	5.0 ± 4.2
Pubertal growth on GH (cm)	8.0 ± 6.4	5.3 ± 3.8	4.6 ± 4.0	2.5 ± 4.8
AH (cm)	150.0 ± 5.8	151.4 ± 6.0	152.4 ± 5.2	151.8 ± 6.0
Gain over projected height (cm)	**8.4 ± 4.5**	**9.6 ± 4.0**	**11.2 ± 3.6**	**8.4 ± 3.6**

Salutary Effects of Combining Early Very Low-Dose Systemic Estradiol with Growth Hormone Therapy in Girls with Turner Syndrome

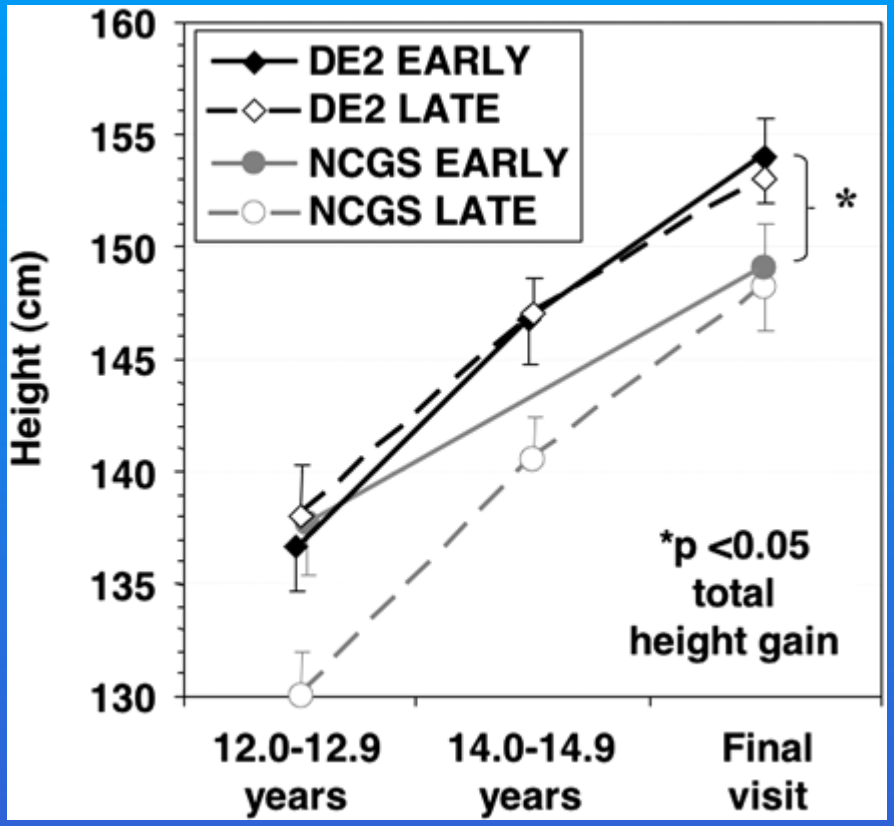
Robert L. Rosenfield, Nancy Devine, Joanne Julius Hunold, Nelly Mauras, Thomas Moshang, Jr. and Allen W. Root
The Journal of Clinical Endocrinology & Metabolism2005 Vol. 90, No. 12 6424-6430



Depot estradiol (estradiol cypionate; Depo-Estradiol), which consists of 67% estradiol, was administered locally as single monthly im injections The starting dose of depot estradiol was 0.2 mg; the dose was then increased at successive 6-month intervals by 0.2 mg initially and by 0.5 mg after a dose of 1.0 mg was reached, to a maximum of 3.0 mg monthly

Early 12 – 12.9 yr

Late 14 – 14.9 yr



Early:
Total height gain from 12.0–12.9 yr of age for subjects treated from that age

Late:
Total height gain from 14.0–14.9 yr of age
to adult or near-adult height

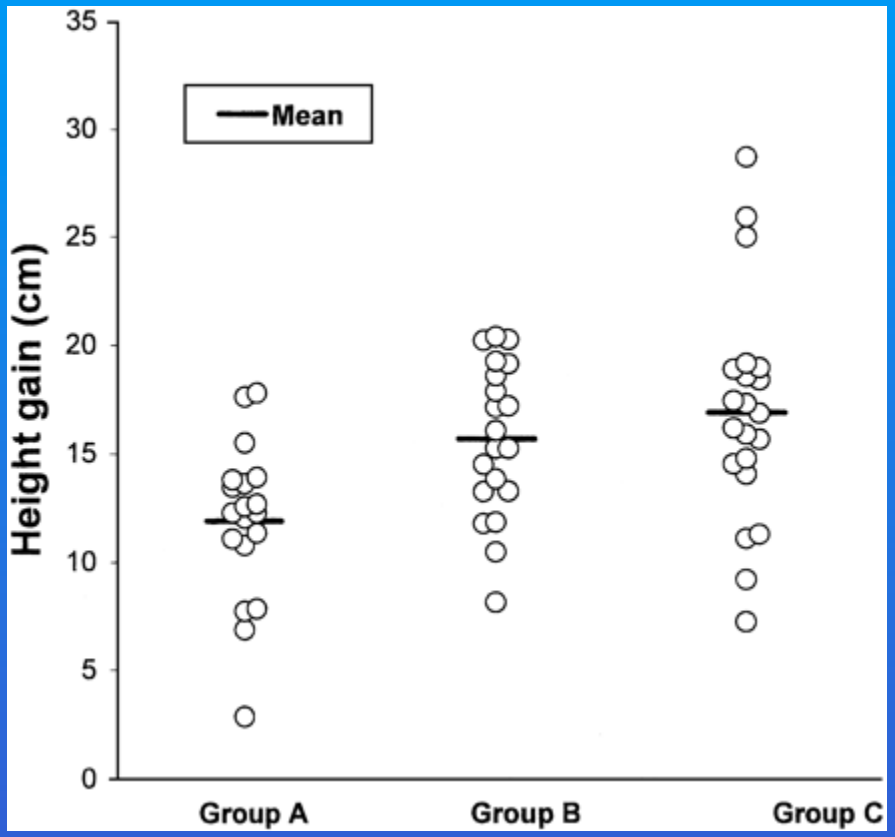
with either depot estradiol (DE2) or conjugated estrogen (NCGS) in conjunction with GH.

Those treated early with DE2 experienced an average of 5.9 cm more linear growth than those treated early with conjugated estrogen ($P < 0.05$).

The Journal of Clinical Endocrinology & Metabolism2005 Vol. 90, No. 12 6424-6430

Robert L. Rosenfield, Nancy Devine, Joanne Julius Hunold, Nelly Mauras, Thomas Moshang, Jr. and Allen W. Root

Final Height in Girls with Turner Syndrome after Long-Term Growth Hormone Treatment in Three Dosages and Low Dose Estrogens



Group A 157.6 ± 6.5 cm

-1.6 ± 1.0 SD

Group B 162.9 ± 6.1 cm

-0.7 ± 1.0 SD

Group C 163.6 ± 6.0 cm

-0.6 ± 1.0 SD

50/60 (83%) normal height SD >-2

Estrogen treatment was started at a mean age of 12.7 ± 0.7 yr.

Final Height in Girls with Turner Syndrome after Long-Term Growth Hormone Treatment in Three Dosages and Low Dose Estrogens van Pareren et al , Journal of Clinical Endocrinology & Metabolism 2003 ;88 (3) :1119-1125

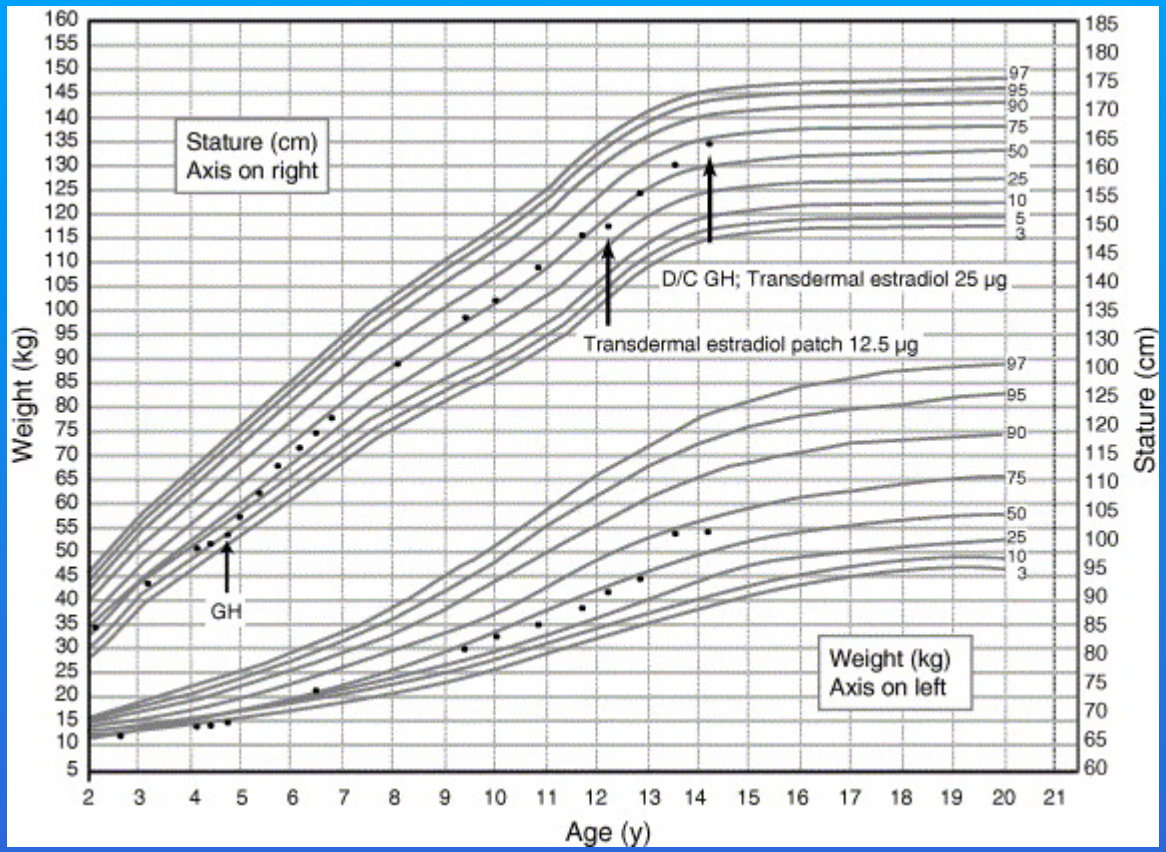


Fig. 1. represents the exceptional growth of a patient with 45,X TS plotted on the CDC chart for normal American girls. Growth hormone therapy was initiated when the patient's height was measured at the 7th percentile and averaged 0.37 mg/kg/wk over 9 years. Transdermal estradiol was initiated at 12.2 years of age and maintained at a relatively low dose (12.5 µg/day) until 14.3 years of age, when the patient demonstrated Tanner III breast development and had reached her target height of 167 cm. At that time, GH was discontinued, and the estradiol dose increased to 25 µg/day.

Recent studies of GH and estrogen in TS patients

Definition of adult height	**GV < 2.0 cm/year and BA > 14 years**		**GV < 1 cm/year or BA > 16 years**	**GV < 1.25 cm/year**	
Baseline					
Treatment groups	GH	No GH	N/A	Early estrogen	Late estrogen
Subjects (no.)	61	43	522	7	7
45,X karyotype	62%	58%	49%	86%	50%
Age at study entry (years)	10.3	10.9	11.9	12.4	12.4
Ht (cm)	119.1	122.0	126.0	136.7	138.0
Ht SDS (general population)	−3.15	−3.03	−3.4	−2.33	− 2.16
Age at GH initiation (years)	10.3	10.9	11.9	10.0	9.5
GH dose (mg/kg/wk)	0.3		0.233	0.0375	0.0375
Age at estrogen initiation (years)	13.0		Doctor's discretion	12.0–12.9	14.0–14.9
Estrogen type	Ethinyl estradiol		Various	Depot 17B estradiol	Depot 17B estradiol
Interval between initiation of estrogen and progestin (years)	2		2.5	>4	>4
Predicted adult ht	–	–	141.5	150.3	150.8
End of study					
Age (years)	16	16.5	21.4	16.4	16.5
Ht (cm)	147.5	141.0	150.5	154.0	152.9
Ht-projected height (cm)	–	–	8.5	2.7[a]	2.1[a]
GH effect (cm)[b]	7.2	–	–	–	–

Height gain from initiation of puberty.

b ANCOVA model with treatment, baseline height SDS, baseline height SDS by treatment interaction, baseline age, and baseline age by treatment interaction. Explanatory variables were removed from the model when not significant. GH effect is estimated by differences of least-squares means for treatment.

The second study, by Soriano-Guillen et al., was observational in design and included all TS patients treated with GH in France between 1986 and 1997 (*n* = 1518) who were 18 years of age by March 31, 2001 (*n* = 891), and for whom final heights were known (*n* = 704) [10]. Mean (±SD) height SDS at baseline was −3.4 ± 1.0. Of these patients, 95% began GH therapy between the ages of 7 and 16 years with a relatively low GH dose (0.26 mg/kg/wk) for an average of 5.0 years. Mean (±SD) adult height of the cohort was 149.9 ± 6.1 cm (8.5 cm above the projected height) after a mean follow-up period of 9.3 ± 2.9 years. For analysis, patients were grouped according to pubertal status: induced (*n* = 522), unknown (*n* = 29), and spontaneous (*n* = 153). Girls with spontaneous puberty were further subdivided into those who required secondary estrogen therapy (*n* = 84) and those who did not (*n* = 69). Age at estrogen initiation was variable, with 93% of patients starting estrogen between the ages of 12 and 18 years. Girls who did not require estrogen entered spontaneous puberty at a mean (±SD) age of 12.5 ± 1.6 years, while those with spontaneous puberty who required secondary estrogen entered puberty at 13.6 ± 1.7 years. Those without pubertal development began estrogen at a mean age of 15.0 ± 1.9 years. Of these patients, 62% received oral ethinyl estradiol; 28%, oral estradiol; 9%, percutaneous estradiol; and 1% combined estrogen and progestin.

Multivariate analyses were used to build a model that accounted for 90% of the variance in adult height (*n* = 547) (Table 2). Age at estrogen initiation and GH treatment duration were independently associated with outcome and, together, were responsible for two thirds of the variance observed in adult height. For each year that estrogen treatment was delayed, 0.3 cm in height was gained. However, repeat analyses restricted to patients with induced puberty only revealed that percutaneous estradiol had a uniquely positive independent effect, resulting in a mean adult height 2.1 cm higher than that obtained with other preparations.

Importance of Estrogen on Bone Health in Turner Syndrome: A Cross-Sectional and Longitudinal Study Using Dual-Energy X-Ray Absorptiometry

Wolfgang Högler, Julie Briody, Bin Moore, Sarah Garnett, Pei Wen Lu and Christopher T. Cowell

Institute of Endocrinology and Diabetes (W.H., B.M., S.G., P.W.L., C.T.C.) and Department of Nuclear Medicine (J.B.), The Children's Hospital at Westmead, NSW 2145 Sydney, Australia; and Department of Pediatrics and Adolescent Medicine (W.H.), University of Innsbruck, 6020 Innsbruck, Austria

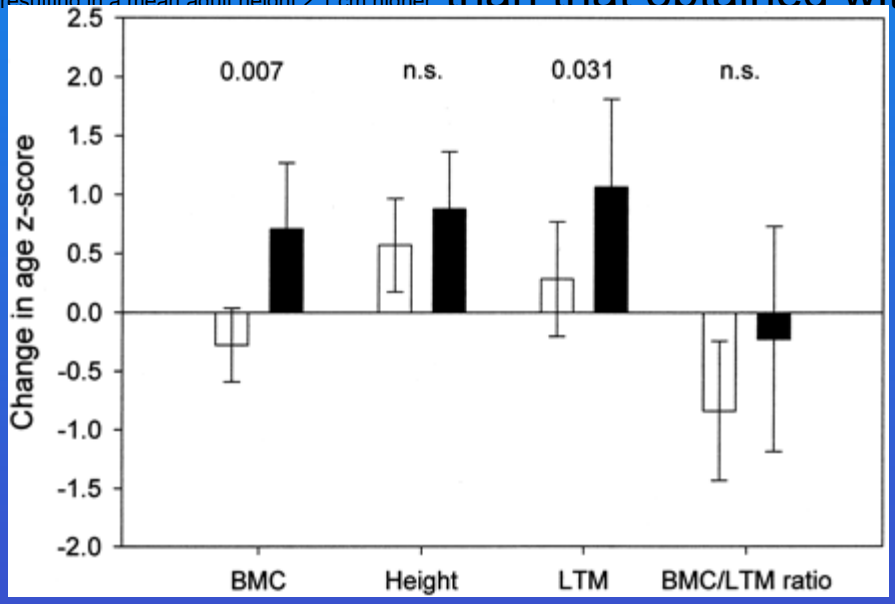
Height gain from initiation of puberty.

b ANCOVA model with treatment, baseline height SDS, baseline height SDS by treatment interaction, baseline age, and baseline age by treatment interaction. Explanatory variables were removed from the model when not significant. GH effect is estimated by differences of least-squares means for treatment.

The second study, by Soriano-Guillen et al., was observational in design and included all TS patients treated with GH in France between 1986 and 1997 (*n* = 1518) who were 18 years of age by March 31, 2001 (*n* = 891), and for whom final heights were known (*n* = 704) [10]. Mean (±SD) height SDS at baseline was −3.4 ± 1.0. Of these patients, 95% began GH therapy between the ages of 7 and 16 years with a relatively low GH dose (0.26 mg/kg/wk) for an average of 5.0 years. Mean (±SD) adult height of the cohort was 149.9 ± 6.1 cm (8.5 cm above the projected height) after a mean follow-up period of 9.3 ± 2.9 years.

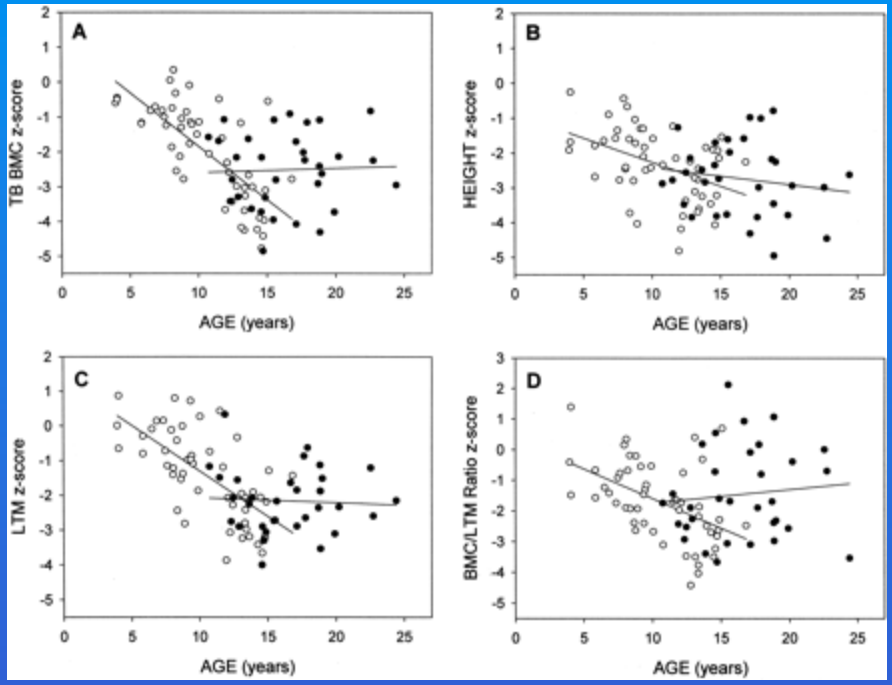
For analysis, patients were grouped according to pubertal status: induced (*n* = 522), unknown (*n* = 29), and spontaneous (*n* = 153). Girls with spontaneous puberty were further subdivided into those who required secondary estrogen therapy (*n* = 84) and those who did not (*n* = 69). Age at estrogen initiation was variable, with 93% of patients starting estrogen between the ages of 12 and 18 years. Girls who did not require estrogen entered spontaneous puberty at a mean (±SD) age of 12.5 ± 1.6 years, while those with spontaneous puberty who required secondary estrogen entered puberty at 13.6 ± 1.7 years. Those without pubertal development began estrogen at a mean age of 15.0 ± 1.9 years. Of these patients, 62% received oral ethinyl estradiol; 28%, oral estradiol; 9%, percutaneous estradiol; and 1% combined estrogen and progestin.

Multivariate analyses were used to build a model that accounted for 90% of the variance in adult height (*n* = 547) (Table 2). Age at estrogen initiation and GH treatment duration were independently associated with outcome and, together, were responsible for two thirds of the variance observed in adult height. For each year that estrogen treatment was delayed, 0.3 cm in height was gained. However, repeat analyses restricted to patients with induced puberty only revealed that percutaneous estradiol had a uniquely positive independent effect, resulting in a mean adult height 2.1 cm higher than that obtained with other preparations.



Importance of Estrogen on Bone Health in Turner Syndrome: A Cross-Sectional and Longitudinal Study Using Dual-Energy X-Ray Absorptiometry

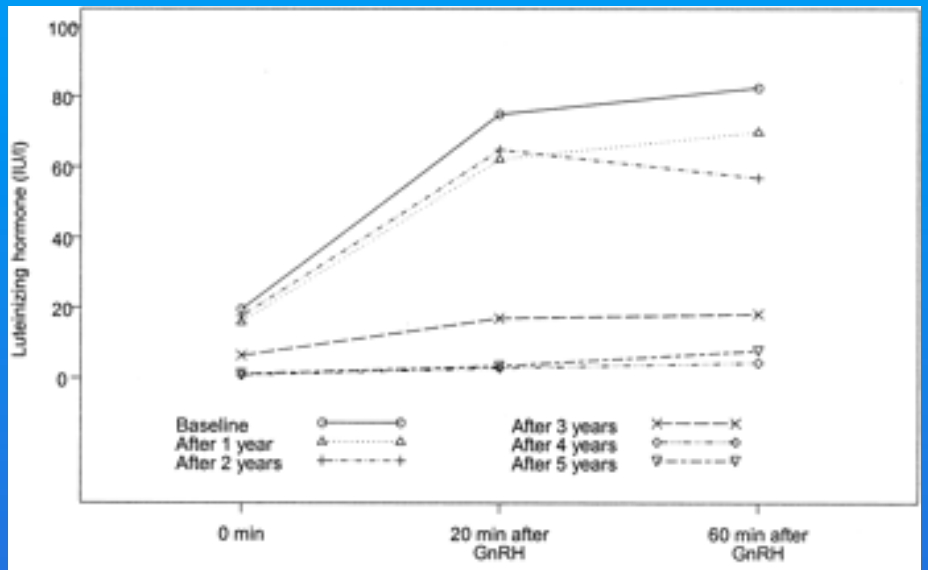
Wolfgang Högler, Julie Briody, Bin Moore, Sarah Garnett, Pei Wen Lu and Christopher T. Cowell



. Growth during the study

Visit	Mean age (yr)	Mean height (cm)			Mean weight (kg)				
			Mean	SD		Mean	SD	Mean	SD
Baseline	13.7	142.0	1.53	1.03	42.6	0.80	1.26	11.3	0.9
1 yr	14.7	147.0	1.85	1.02	46.6	0.78	1.28	12.9	1.1
2 yr	15.8	150.3	1.91	0.98	51.1	0.99	1.28	13.9	1.1
3 yr	16.7	151.4	1.70	1.01	53.3	0.89	1.17	15.2	1.1
4 yr	17.6	152.8	1.61	0.83	56.4	0.92	0.90	16.6	0.9
5 yr	18.5	153.1	1.51	0.86	55.4	0.58	0.78	17.3	0.6

ng to Ranke growth standards for Turner girls.


Luteinizing hormone (IU/l)
100
80
60
40
20
0
Baseline
After 1 year
After 2 years
After 3 years
After 4 years
After 5 years
0 min
20 min after GnRH
60 min after GnRH

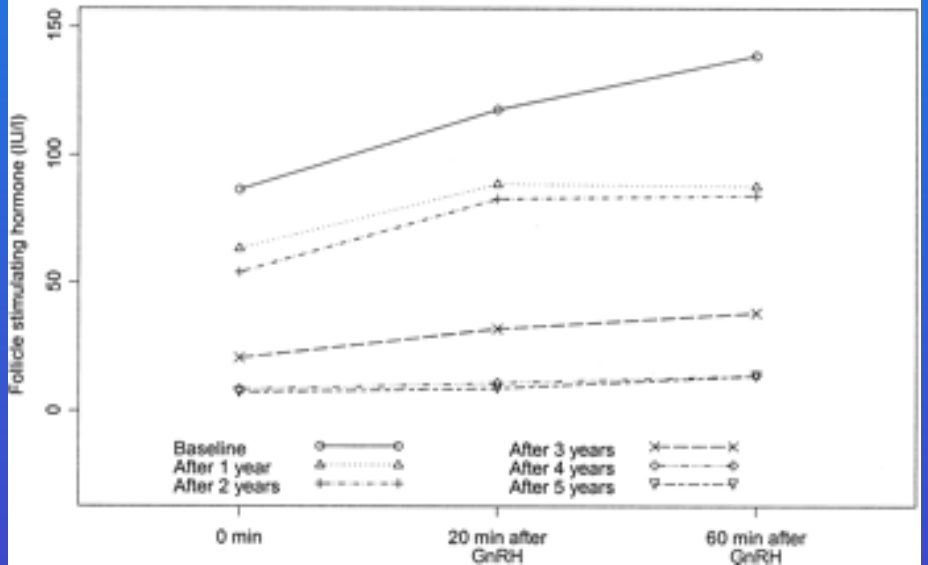

Follicle stimulating hormone (IU/l)
150
100
50
0
Baseline
After 1 year
After 2 years
After 3 years
After 4 years
After 5 years
0 min
20 min after GnRH
60 min after GnRH

Table 3. *Characteristics of patients after one year of GH and at onset of puberty*

Variables	*n*	Median	10th centile	90th centile	Mean	SD
After one year on GH						
Age (years)	904	10.7	6.8	13.2	10.3	2.4
Bone age (years)	471	10.0	6.8	11.5	9.3	2.1
Height (cm)	904	125.2	107.7	137.5	124.0	11.3
Height (Tanner) (SDS)	904	−1.9	−3.0	−0.9	−2.3	1.0
Height TS (Ranke) (SDS)	904	0.7	−0.7	2.0	0.6	1.0
BMI (SDS)	898	0.1	−1.1	1.4	0.1	1.0
Height velocity (cm/yr)	904	7.4	5.4	9.7	7.5	1.7
Predicted height velocity (cm/yr)	752	7.7	6.3	9.1	7.7	1.1
Studentized residual (SDS)	752	0.0	−1.4	1.3	0.0	1.1
Delta height (Tanner) (SDS)	904	0.5	0.2	0.8	0.3	0.3
Delta height (Ranke) (SDS)	904	0.7	0.3	1.1	0.7	0.3
Puberty onset						
Age (years)	540	13.5	11.6	15.7	13.6	1.6
Bone age (years)	183	12.0	10.7	13.0	11.9	1.0
Height (cm)	540	141.8	130.9	151.2	141.3	1.9
Height (Tanner) (SDS)	540	−1.4	−2.5	−0.3	−2.2	1.1
Height TS (Ranke) (SDS)	540	1.6	0.0	3.0	1.5	1.2
Prepubertal delta height (cm)	540	21.2	11.1	43.0	24.1	12.0
Prepubertal delta height (Ranke) (SDS)	540	1.5	0.8	2.5	1.6	0.7
BMI (SDS)	536	0.4	−1.0	1.7	0.4	1.1
GH dose (mg/kg wk)	540	0.28	0.20	0.37	0.28	0.07

Groups

Table II. Characteristics of Turner syndrome (TS) women according to induction of
(median values, range)

Variables				
	45,X	45,X/ 46,XX	45,X/ 46,X,i (Xq)	45,X/ 46,XY
n	59	4	6	6
Age (years) at start of estrogens	14.6 (11.8–21.7)	15.2 (14.4–16.9)	15.0 (14.1–17.3)	14.2 (13.1–17.9)
Age (years) at start of progestins	16.1 (12.8–22.8)	16.9 (14.4–19.3)	16.5 (15.0–18.0)	15.2 (14.2–16.6)
Age (years) at menarche	16.2 (12.5–23.9)	16.0 (13.8–19.3)	17.3 (15.1–24.4)	No data
Duration (years) of	5.3 (1.5–	5.3 (3.6	1.9 (1.6–	2.5 (0.8–

US Multicentre Trial

		Mean Near FH
High Dose GH 0.36 mg/kg/wk	With oestrogen	149.1± 6.0
High Dose GH	Without oestrogen	150.4± 6.0
Low Dose GH 0.27 mg/kg/wk	With oestrogen	145.1 ± 5.4
Low Dose GH	Without oestrogen	149.9 ± 6.0

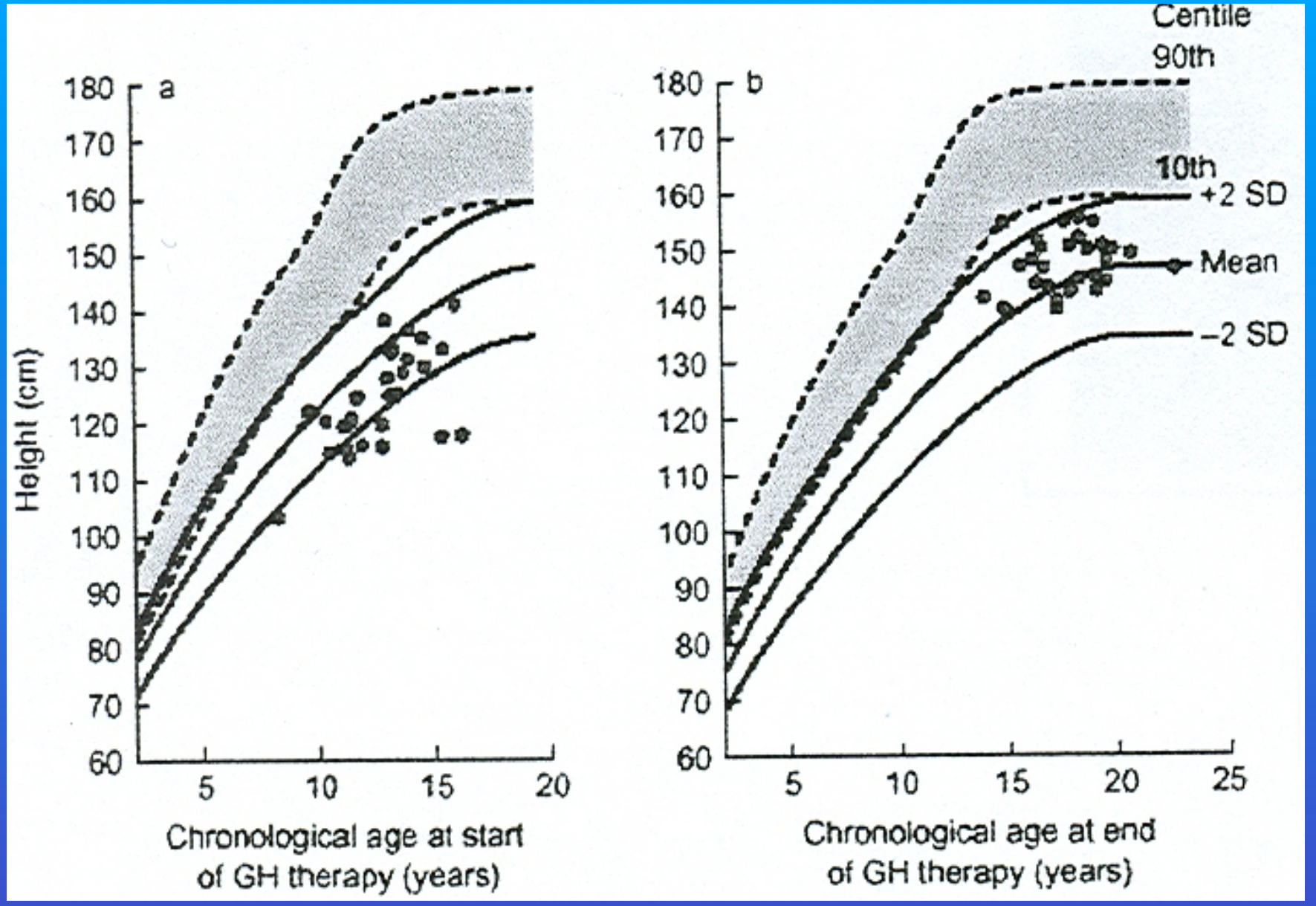
Overall 148.7 ± 6.1 cm after 5.5 ± 1.8 yr GH

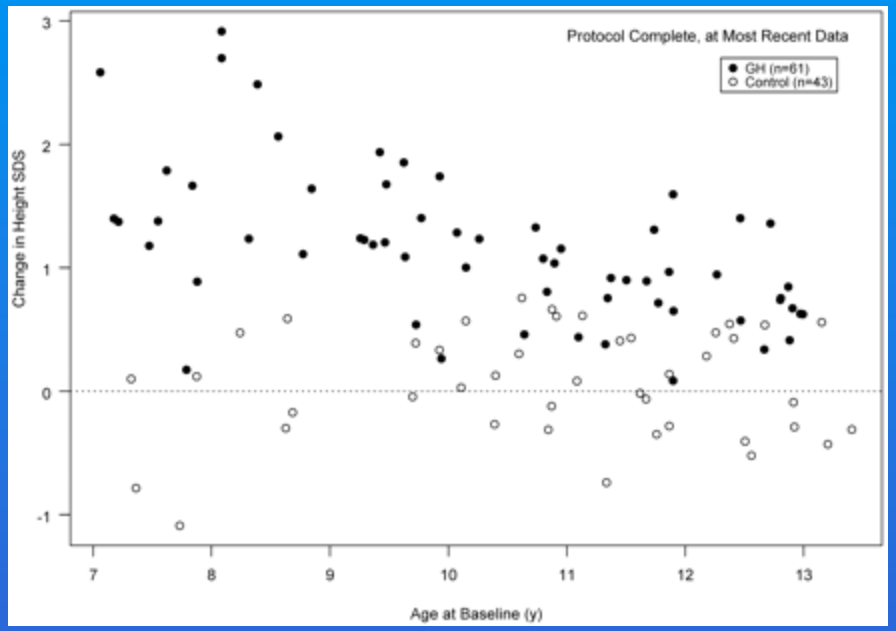
GH and Low Dose Oestrogen In TS Results of a US Multicentre Trial to Near Final Height

Charmian A et al, JCEM 2002; 87: 2033-2041

Table I. Characteristics of Turner syndrome (TS) women at follow-up according to karyotype

Variables	45,X	45,X/46,XX	45,X/46,X, i(Xq)	45,X/46,XY
n	59	4	6	6
Age (years)	19.7 (16.3–30.8)	19.9 (19.3–24.4)	18.0 (16.1–26.0)	18.4 (15.8–21.1)
Height (cm)	152.6 (141.1–167.3)	148.0 (144.6–152.6)	150.8 (143.5–162.6)	151.4 (148.2–157.5)
Height SDS (Ranke)	1.03 (–0.85–3.44)	0.29 (–0.28–1.03)	0.74 (–0.46–2.61)	0.84 (0.31–1.84)
BMI (kg/m^2)	23.7 (17.7–41.5)	27.6 (20.7–36.1)	23.1 (21.8–37.9)	20.1 (19.5–23.5)
Tanner breast stage	B 2 (18.6%) B	B 4	B 4	B 2 (33.3%) B


a
b
Height (cm)
180
170
160
150
140
130
120
110
100
90
80
70
60
5
10
15
20
25
Centile
90th
10th
+2 SD
Mean
−2 SD
Chronological age at start of GH therapy (years)
Chronological age at end of GH therapy (years)



The Journal of Clinical Endocrinology & Metabolism 2005 Vol. 90, No. 6 3360-3366

Canadian RCT	GH	C	GH effect[1] [mean (95% CI)]
Baseline characteristics[2]			
Protocol complete (n)	61	43	–
Baseline age (yr)	10.3 ± 1.8	10.9 ± 1.7	–
Baseline bone age (yr)	8.8 ± 1.4	8.9 ± 1.3	–
Baseline height (cm)	119.1 ± 8.5	122.0 ± 7.8	–
Baseline height SDS (age-specific Turner)	–0.2 ± 0.9	–0.1 ± 0.8	–
Adjusted midparental height (cm)[3]	160.7 ± 6.2	159.3 ± 5.8	–
45, X Karyotype (%)	62.3	58.1	–
Completion characteristics			
Protocol complete (n)	61	43	–
Time since randomization (y)	5.7 ± 1.6	5.7 ± 1.6	–
Age (yr)	16.0 ± 0.8	16.5 ± 0.9	–[4]
Bone age (yr)	14.4 ± 0.8	14.5 ± 0.9	–0.1 (–0.5, 0.3)
Height (cm)	147.5 ± 6.1	141.0 ± 5.4	7.2 (6.0, 8.4)[5]
Height SDS (age-specific Turner)	1.4 ± 1.0	0.2 ± 0.9	1.2 (1.0, 1.5)[5]
Height SDS (adult Turner)	0.7 ± 0.9	–0.3 ± 0.8	1.1 (0.8, 1.3)[5]
Change in height (cm)	28.3 ± 8.9	19.0 ± 6.1	7.2 (6.0, 8.3)[5]
Change in height SDS (age-specific Turner)	1.6 ± 0.6	0.3 ± 0.4	1.3 (1.1, 1.5)[5]
Addendum follow-up characteristics			
Protocol complete with addendum follow-up (n)	40	19	–
Time since randomization (yr)	10.6 ± 1.7	10.7 ± 1.4	–
Age (yr)	20.7 ± 2.5	21.2 ± 2.0	–
Bone age (yr)	15.1 ± 1.0	15.2 ± 1.0	0.0 (–0.6, 0.6)
Height (cm)	149.0 ± 6.4	142.2 ± 6.6	7.3 (5.4, 9.2)[5]
Height SDS (age-specific Turner)	0.9 ± 0.9	–0.1 ± 1.0	1.1 (0.8, 1.4)[5]
Height SDS (adult Turner)	0.9 ± 0.9	–0.1 ± 1.0	1.1 (0.8, 1.4)[5]
Change in height (cm)	30.3 ± 8.3	21.6 ± 6.2	7.3 (5.4, 9.1)[5]
Change in height SDS (age-specific Turner)	1.1 ± 0.5	0.0 ± 0.5	1.1 (0.8, 1.4)[5]

	Historical control baseline age <11 yr (n = 14)	Younger cohort estrogen at 12 yr (n = 26)	Younger cohort estrogen at 15 yr (n = 29)	Historical controls baseline age >11 yr (n = 55)	Older cohort (n = 51)
Duration of GH therapy	N/A	5.6 ± 1.1	6.1 ± 1.3	N/A	3.8 ± 1.1
(yr)		(3.5–7.1)	(2.4–7.6)		(1.1–6.5)
Most recent age (yr)	21.9 ± 2.6	15.8 ± 1.0	16.3 ± 0.9	21.5 ± 2.7	17.6 ± 1.3
	(18.1–26.4)	(13.6–17.4)	(14.7–17.8)	(18.1–27.8)	(14.3–20.5)
Most recent h (cm)	144.1 ± 6.0	147.0 ± 6.1	150.4 ± 6.0	144.1 ± 6.2	148.5 ± 5.5
	(135.5–156.7)	(135.0–155.4)	(141.1–162.0)	(131.5–160.0)	(135.6–159.2)
Pretreatment projected	144.6 ± 5.8	141.9 ± 5.4	142.0 ± 6.1	144.7 ± 7.3	143.8 ± 5.3
adult h (cm) (Lyon)	(134.2–154.4)	(130.9–151.9)	(128.6–153.6)	(132.3–164.0)	(131.9–154.2)
Most recent h minus	-0.5 ± 4.5	5.1 ± 3.6[1]	8.4 ± 4.3[1 2]	-0.5 ± 3.6	4.7 ± 4.0[2]
pretreatment projected adult (cm)	(-7.0–6.1, 95% CI -2.9–1.9)	(-0.9–13.2, 95% CI, 3.7–6.5)	(-0.2–15.8, 95% CI, 6.8–10.0)	(-8.6–6.7, 95% CI, -1.5–0.4)	(-6.3–14.4, 95% CI, 3.6–5.9)
Treated minus controls	N/A	5.9	8.3	N/A	5.0
(cm)		(95% CI, 3.3–8.5)	(95% CI, 5.3–11.3)		(95% CI, 3.7–6.3)

Types of Oestrogen

- Oral ethinyl oestradiol
- oral oestradiol
- Percutaneous oestradiol
- Oestrogen-progestin combinations

Growth Hormone Dose