10-year-old Female with Tall Stature

Payal Patel, M.D.
Pediatric Endocrinology Fellow
April 10, 2014

Chief Complaint

- 10 1/12 yo F with Marfan's presents for evaluation of accelerated growth and tall stature.

HPI

- 1st evaluated by endocrine 5 years ago for premature pubarche (at 5 4/12 yrs)
- Labs showed:
  - Prepubertal FSH (1.6 mIU/mL), LH (0.15 mIU/mL), and estradiol (2 pg/mL)
  - Preadrenachal DHEAS (<15 ug/dL)
  - Normal IGF-1 (185 ng/mL)
- Bone age read as 7 10/12 yrs
- Followed up in the Marfan Clinic
- Returned for endo f/u this past year

HPI- over the last 1 year…

- Growth spurt
- Shoe size has increased from 13 to 19
- Significant weight gain
- Increase in pubic hair (first noted at 5 yrs)
- Breast development
- No menses

Review of Systems

- Constitutional: **+ Increased appetite and weight gain x1 yr**
- Eyes: **+ Bilateral lens dislocation, wears bifocals**
- Resp: – cough or shortness of breath.
- CV: – palpitations or chest pain. **+ Mild aortic dilatation**
- GI: **+ Abd pain, recent dx of mesenteric adenitis. +chronic constipation**
- GU: – urgency, frequency or enuresis. **No menses**
- MSK: **+ Back and knee pain. Falls often at school**
- Skin: **+ Darkening around neck, axillae, knees and elbows**
- Neurological: **+ Headaches, occasionally related to hair style**
- Psych: **+ Increasing mood swings.** – sleep problems.

Past Medical History

PMH:

- Marfan's (diagnosed at 6 yrs)
  - Tall stature, lens dislocation, mild aortic root dilation, thoracic scoliosis
- Obesity
- Asthma
- Premature pubarche
- Developmental delay

PSH:

- Retinal tear repair (at 8 yrs)

Family History

- T2DM: mother, maternal family, paternal GM
- Hypertension: maternal family
- Early menarche: Maternal grandmother (at 8yrs)

- Father: 6'1"
- Mother: 5'6", menarche at 15 yrs
- Maternal aunt: menarche at 11-12 yrs

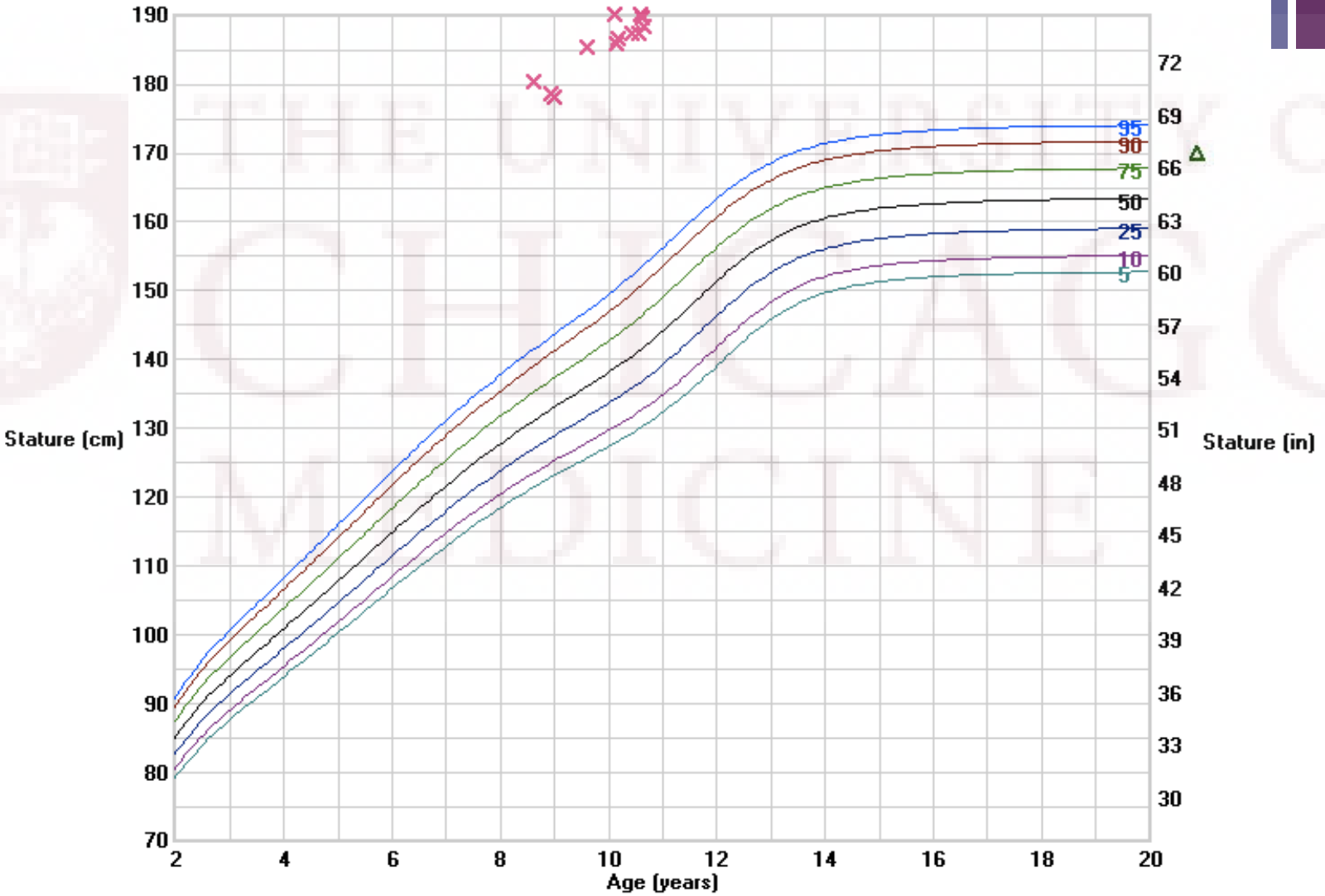
Further History

- SH: Lives parents, 4 younger siblings and maternal GM. In 5th grade, has an IEP for cognitive impairment.
- Meds: losartan, amlodipine, albuterol
- Allergies: NKDA

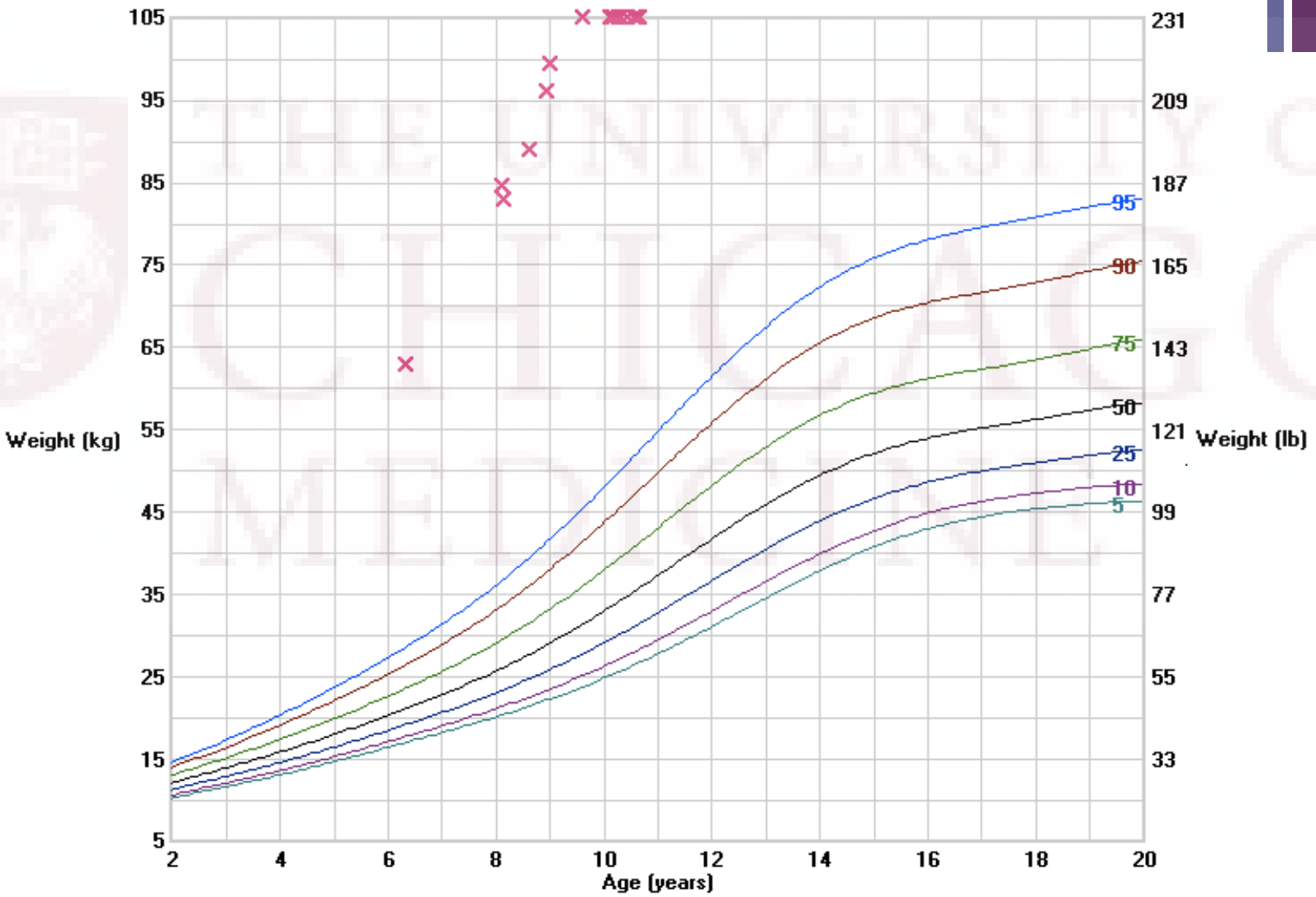
Physical Exam

- Vitals: T 36.4, HR 95, BP 110/64, Ht 185.7 cm (6'1"), Wt 114 kg (252 lbs)
- General: NAD, wide shoulders with abdominal obesity
- Eyes: Conjunctivae and EOM nL, **wears bifocals**
- Neck: No thyromegaly
- CV: nL rate and rhythm, no murmur, strong pulses
- Chest: CTAB, **Tanner 3 breasts, Tanner 1 axillary hair**
- Abd: S/ND/NT. **Thin, vertical purple striae on flanks**
- GU: **Tanner 3 pubic hair**
- MSK: **Genu valgum, slight spinal curvature to left**
- Neuro: Alert, nL muscle tone, 2+ DTRs. No tremor on outstretched hands
- Skin: **Acanthosis on neck & axillae, minimal facial acne, no hirsutism**

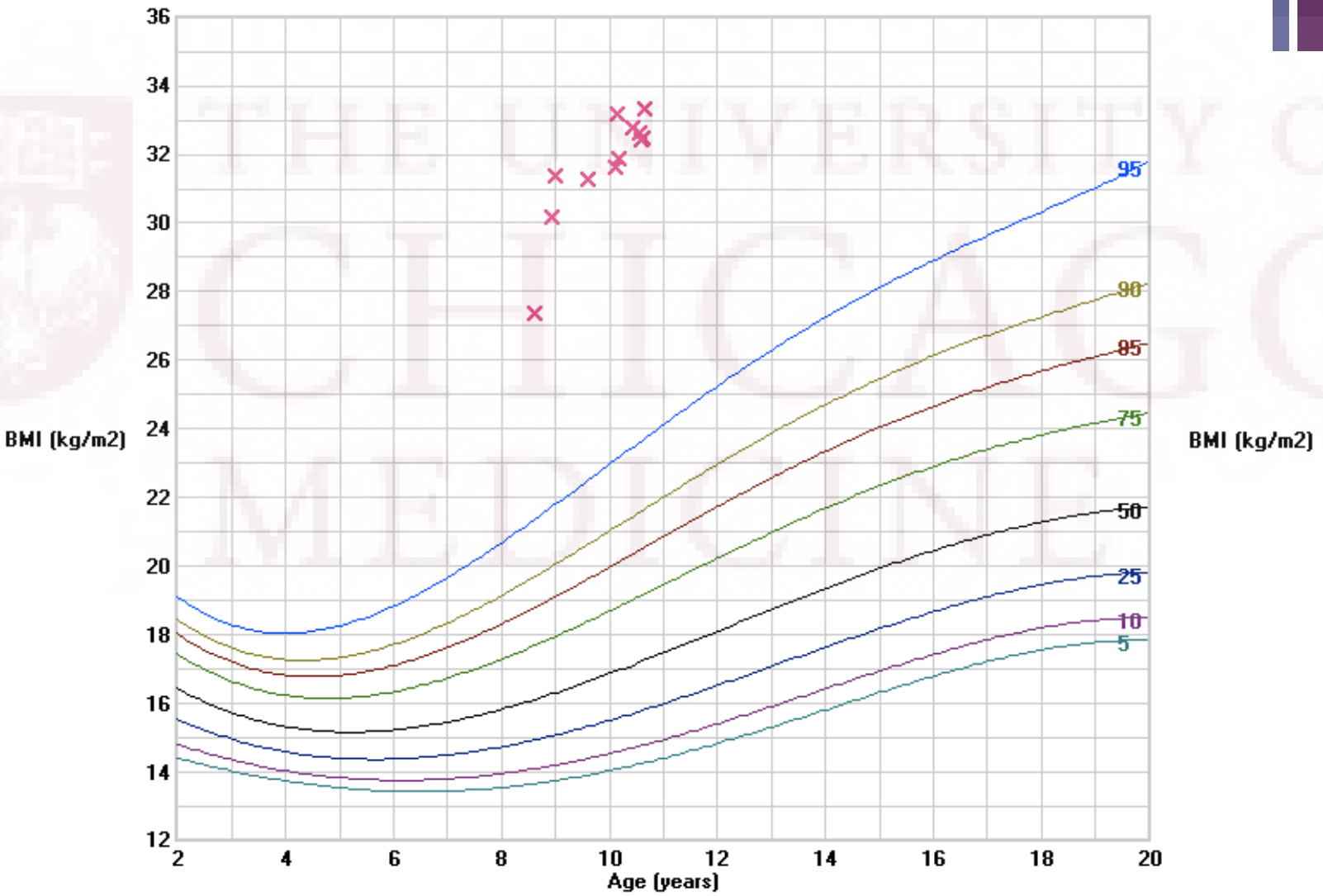
Height


Stature (cm)
190
180
170
160
150
140
130
120
110
100
90
80
70
Stature (in)
72
69
66
63
60
57
54
51
48
45
42
39
36
33
30
95
90
75
50
25
10
5
2
4
6
8
10
12
14
16
18
20
Age (years)

Weight


Weight (kg)
105
95
85
75
65
55
45
35
25
15
5
231
209
187
165
143
121
99
77
55
33
Weight (lb)
95
90
75
50
25
10
5
2
4
6
8
10
12
14
16
18
20
Age (years)

BMI


BMI (kg/m2)
36
34
32
30
28
26
24
22
20
18
16
14
12
2
4
6
8
10
12
14
16
18
20
Age (years)
95
90
85
75
50
25
10
5
BMI (kg/m2)

Labs

- FSH 4.5 (>2.7 mIU/mL)
- LH 1.1 (>0.2 mIU/mL)
- Estradiol 14 (>12 pg/mL)
- DHEAS 27 (32-226 ug/dL)
- Total testost. 12 (<44 ng/dL)
- Free testost. 5 (<9 pg/mL)
- Bone age 13 3/12 yrs
- GH 0.6 (<6 ng/mL)
- IGFBP-3 6.3 (3.1-8.9 ug/mL)
- IGF-1 227 (88-452 ng/mL)
- Insulin 63.4 uIU/mL (BG 118)
- HbA1C 6.3% (<5.7%)
- Cholesterol 134 (<199 mg/dL)
- Triglycerides 245 (<149 mg/dL)
- LDL 51 (60-129 mg/dL)
- HDL 34 (40-80 mg/dL)

Clinical Questions

- What is the role of estrogen in the treatment of tall stature in girls with Marfan's syndrome (in regards to cardiovascular safety)?

Marfan's

- Autosomal dominant connective tissue disorder
- Mutation in the FBN1 gene, which encodes fibrillin-1
- Prevalence = 1 in 3–5,000
  - 15–30% = new mutations
- May have ocular, skeletal, cardiovascular, integumentary, pulmonary, and/or neurological sx
- Diagnosis is primarily clinical
- Formal diagnosis may be made via the Ghent criteria and genetic testing

Review of Estrogen Treatment for Tall Stature

- Ethinyl estradiol (E2) is the most established estrogen preparation used
  - Dose ranges from 100-500 mcg daily
- Two mechanisms:
  - Suppressive effect on IGF-1 → reduced effectiveness of GH
  - Direct effect on epiphyseal cartilage
- Side effects: fluid retention → increase in BP, and increased risk for clots

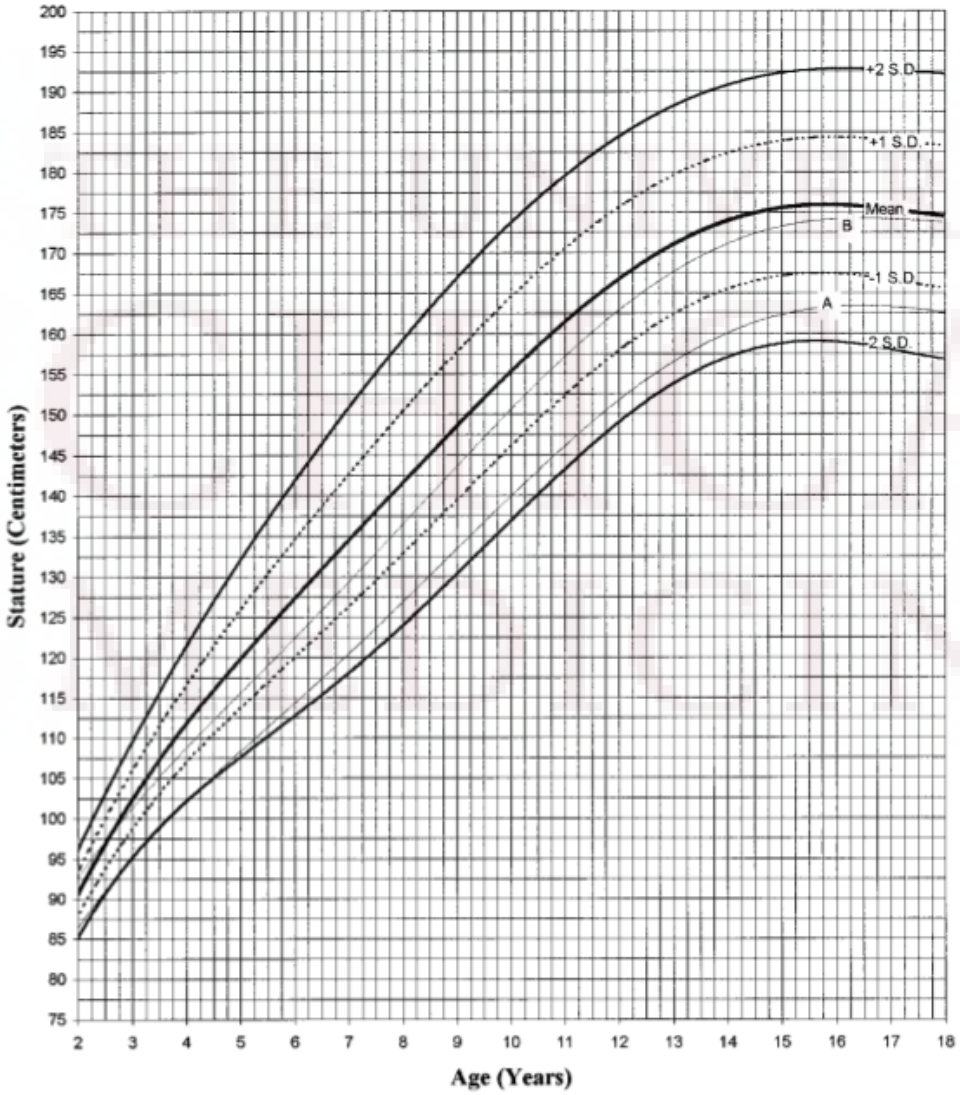
ETHINYL ESTRADIOL TREATMENT FOR GROWTH LIMITATION IN GIRLS WITH MARFAN'S SYNDROME—EXPERIENCE FROM A SINGLE CENTER

Sema Kalkan Uca □ Wendy F. Paterson □ Malcolm D.C. Donaldson □ David Young

	Baseline (Start E_2/Equivalent age)						Stop E_2	Final height/Near final height						
Patient no.	CA (years)	BA (years)	Ht (cm)	Ht SDS	Ht SDS BA	Tanner stage	CA (years)	CA (years)	FHt/NFHt (cm)	PFHt (cm)	PFHt-FHt (cm)	FHt SDS	PFHt SDS	THt SDS
Group A: Treated														
1	10.9	12.1	160.4	2.5	1.4	B2	16.6	15.6	175.1	178.0	2.9	1.9	2.5	1.3
2	12.1	12.7	163.8	1.9	1.4	B1	14.0	14.6	170.6	175.0	4.4	1.2	2.1	0.3
3	10.1	11.0	154.1	2.4	1.4	B1	–	16.4	175.0	177.5	2.5	1.9	2.3	2.0
4	7.1	10.6	141.6	3.8	–0.04	B1	–	14.6	176.6	184.0	7.4	2.1	3.5	–0.8
Mean (SD)	10.0 (2.1)	11.6 (0.9)	155.0 (9.8)	2.6 (0.8)	1.04 (0.7)	–	–	15.3 (0.8)	174.3 (2.6)	178.6 (3.8)	4.3 (2.2)	1.8 (0.4)	2.6 (0.6)	0.7 (1.2)
Group B: Untreated														
5	9.8	12.3	160.8	3.7	1.3	B1	–	15.6	190.3	184.0	–6.3	4.4	3.4	2.4
6	9.8	11.9	158.4	3.3	1.3	B1	–	15.6	185.3	182.5	–2.8	3.6	3.1	2.4
7	11.3	12.1	167.1	3.0	2.4	B1	–	20.1	184.1	194.0	9.9	3.4	5.0	2.4
8	10.2	–	158.1	2.8		NK	–	18.1	183.9	177.5	–6.4	3.4	2.3	0.9
9	9.4	11.9	146.4	1.9	–0.4	B1	–	23.3	171.5	170.0	–1.5	1.3	1.1	0.7
Mean (SD)	10.1 (0.7)	12.0 (0.2)	158.2 (7.5)	2.9 (0.7)	1.15 (1.1)	–	–	18.5 (3.3)	183.0 (6.9)	181.6 (8.8)	–1.4 (6.7)	3.2 (1.1)	3.0 (1.4)	1.8 (0.9)

Abbreviations: CA, chronological age; BA, bone age; Ht, height; FHt/NFHt, final height/near final height; SDS, standard deviation score; PFHt, projected final height; THt, target height.

Marfan's Growth Curve- Females



Cardiovascular Surveillance

TABLE 3 Cardiovascular Surveillance of the Nine Patients

	Pretreatment/Equivalent age					Post- or during treatment/Equivalent age				
Patient	CA	AR	AR/BSA	SP	DP	CA	AR	AR/BSA	SP	DP
Group A: Treated										
1	7.2	22	21.7	100	60	15.5	26	15.1	110	70
2	12.3	31	22.4	110	70	14.2	39	27.8	120	70
3	9.0	33	32.6	95	60	12.3	38	33.0	100	60
4	8.0	25	20.1	90	60	11.6	28	17.0	110	65
Group B: Untreated										
5	11.9	35	22.5	115	70	17.8	37	23.1	120	80
6	11.9	35	24.6	115	70	17.8	38	24.0	125	80
7	13.9	30	19.2	110	70	17.8	34	21.1	130	80
8[a]	8.2	32	16.6	100	60	15.5	43	–	140	85
9	7.0	17	20.0	117	60	23.3	39	24.7	108	67
P		0.9	0.2	0.08	0.6	P	0.2	0.5	0.02[a]	0.02[a]

Conclusions

- Optimal time to start may be at 10-11 yrs of age
- Treatment should be continued until height velocity decreases to < 1 cm/yr
- Echo should be done annually before and during estrogen tx
  - More frequent monitoring (including BP measurements) and preemptive beta blockade for girls with marked aortic dilation
- A prospective study with a larger population is needed

Clinical Questions

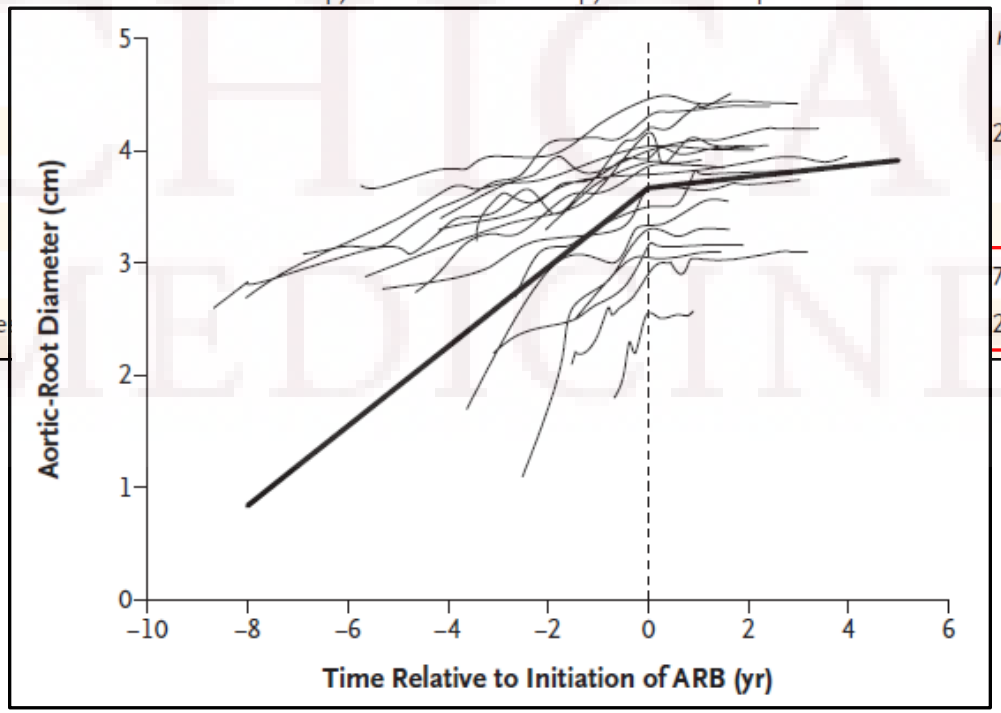
- What is the role of estrogen in the treatment of tall stature in girls with Marfan's syndrome?
- How should aortic dilation be best managed in children with Marfan's?

The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin II Blockade and Aortic-Root Dilation in Marfan's Syndrome

Benjamin S. Brooke, M.D., Jennifer P. Habashi, M.D., Daniel P. Judge, M.D., Nishant Patel, B.A., Bart Loeys, M.D., Ph.D., and Harry C. Dietz III, M.D.

Variable	Severe Marfan's Syndrome (N=18)			Mild Marfan's Syndrome (N=65)	
	Before ARB Therapy	After Initiation of ARB Therapy	P Value†	After Initiation of Therapy with Beta-Blockers	P Value‡
				mean	
Aortic-root-diameter z score					
Cohort average§				25±1.52	<0.001
Last measurement¶				NA	
Change in aortic-root diameter					
Absolute change (mm/yr)				71±1.24	<0.001
Normalized change (z score				24±0.50	<0.001



Affect of ARB on Linear Growth

Variable	Pre-ARB Median	Pre-ARB Mean(±SD)	Post-ARB Median	Post-ARB Mean(±SD)	P-value†
Change in Body Mass					
Weight (kg/yr)	3.4	3.62(1.59)	2.6	3.05(1.49)	0.42
Weight Z-score/yr	+0.3	+0.61(2.54)	+0.4	+0.61(2.05)	0.45
BMI (kg/m^2/yr)	0.3	0.48(1.10)	0.4	0.47(0.54)	0.47
BMI Z-score/yr	+0.1	+0.21(0.53)	+0.4	+0.54(0.70)	0.28
Change in Linear Growth					
Height (cm/yr)	9.0	9.63(7.47)	4.4	5.01(3.31)	<0.05
Height Z-score/yr	-0.1	+0.14(0.61)	-0.2	-0.06(0.69)	0.06
Height Velocity Z-score	+0.7	+0.98(1.64)	-1.3	-1.02(2.16)	<0.05

Brooke BS, et al. *N Engl J Med* 2008.

Patient Update

- Underwent a 3-hr OGTT– confirmed impaired glucose tolerance
  - Started Metformin
  - Check BGs at home
  - Diet modifications, increase physical activity
- Plan to start estrogen tx with Premarin 30 mcg daily

Summary

- Research supports the use of estrogen as a safe tx for tall stature in girls with Marfan's (regarding CV risks)
  - More frequent monitoring is recommended for girls with marked aortic dilation
- Studies have shown no significant changes in the aortic root size post-estrogen tx
- Estrogen may aid in decreasing systolic and diastolic BPs in these patients
- For tx of aortic dilation, recent research suggests ARBs are superior to using a beta-blocker alone
- ARBs have been show to decrease the rate of aortic dilation
  - Efficacy thought to be due to decreased expression of TGF- beta

References

- Erkula G, Jones KB, Sponseller PD, Dietz HC, and Pyeritz RE. Growth and Maturation in Marfan Syndrome. Am J Med Gen 2002;109:100–115.
- Ucar SK, Paterson WF, Donaldson MDC, and Young D. Ethinyl Estradiol Treatment for Growth Limitation in Girls with Marfan's Syndrome- Experience from a Single Center. *Endocrine Research* 2009;34(4):109-120.
- Knudtzon J and Aarskog D. Estrogen Treatment of Excessively Tall Girls with Marfan Syndrome. *Acta Pcediatr Scand 1988;*77:537-541.
- Yetman AT. Cardiovascular Pharmacotherapy in Patients with Marfan Syndrome. *Am J Cardiovasc Drugs* 2007;7(2):117-126.
- Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC. Angiotensin II Blockade and Aortic-Root Dilation in Marfan's Syndrome. *N Engl J Med* 2008;358:2787-2795.