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
Weight
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

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CA (years)</th>
<th>BA (years)</th>
<th>Ht (cm)</th>
<th>Ht SDS</th>
<th>Ht SDS BA</th>
<th>Tanner stage</th>
<th>Stop E₂</th>
<th>CA (years)</th>
<th>FHt/NFHt (cm)</th>
<th>PFHt (cm)</th>
<th>PFHt-FHt (cm)</th>
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<td>Mean (SD)</td>
<td>10.0 (2.1)</td>
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<td>155.0 (9.8)</td>
<td>2.6 (0.8)</td>
<td>1.04 (0.7)</td>
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<td>15.3 (0.8)</td>
<td>174.3 (2.6)</td>
<td>178.6 (3.8)</td>
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<td>Group B: Untreated</td>
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<td>Mean (SD)</td>
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<td>3.0 (1.4)</td>
<td>1.8 (0.9)</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pretreatment/Equivalent age</th>
<th>Post- or during treatment/Equivalent age</th>
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<tr>
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<td>2</td>
<td>12.3</td>
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<tr>
<td>3</td>
<td>9.0</td>
<td>33</td>
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<tr>
<td>4</td>
<td>8.0</td>
<td>25</td>
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<tr>
<td>Group B: Untreated</td>
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<tr>
<td>5</td>
<td>11.9</td>
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<td>8(\textsuperscript{a})</td>
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<td>0.2</td>
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</table>
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?
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.
## Affect of ARB on Linear Growth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-ARB</th>
<th>Post-ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean(±SD)</td>
</tr>
<tr>
<td>Change in Body Mass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg/yr)</td>
<td>3.4</td>
<td>3.62(1.59)</td>
</tr>
<tr>
<td>Weight Z-score/yr</td>
<td>+0.3</td>
<td>+0.61(2.54)</td>
</tr>
<tr>
<td>BMI (kg/m²/yr)</td>
<td>0.3</td>
<td>0.48(1.10)</td>
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<tr>
<td>BMI Z-score/yr</td>
<td>+0.1</td>
<td>+0.21(0.53)</td>
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<tr>
<td>Change in Linear Growth</td>
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<tr>
<td>Height (cm/yr)</td>
<td>9.0</td>
<td>9.63(7.47)</td>
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<tr>
<td>Height Z-score/yr</td>
<td>-0.1</td>
<td>+0.14(0.61)</td>
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<tr>
<td>Height Velocity Z-score</td>
<td>+0.7</td>
<td>+0.98(1.64)</td>
</tr>
</tbody>
</table>

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


