8yo F with sexual precocity
Chief Complaint

- 8 3/12yo F with h/o sexual precocity presents for a 3rd opinion
HPI

- First seen at 5 1/12 yrs for evaluation of pubic hair and body odor
Review of Systems

- No headaches, visual disturbances, or weakness
- Mild acne. No other skin lesions
- No hair changes, temperature intolerance, weight change
- No noted breasts
- No height acceleration
- No vaginal discharge
- No known exposure to hormone containing products
Past Medical History

- Full-term, AGA for weight and length
- Uncomplicated pregnancy and delivery
- Normal development
- Allergic rhinitis
- Lactose intolerance
- PE tubes @ 18 mos of age
- Meds: none
- Allergies: NKDA
Social and Family History

- Lives with parents and 2 healthy brothers.
- Father’s ht: 5’10.5”. Normal timing of puberty.
- Mother’s ht: 5’7.5”. Normal timing of puberty, menarche at 14 yrs.
- No family history of early puberty, childhood deaths, fertility problems, diabetes or other metabolic disorders
PE

- Vitals: within nL, Wt 70th%, Ht 60th%, BMI 20 (93rd%)
- General: well-nourished, NAD
- Neck: No thyromegaly
- CV/Resp/Chest: RRR, no murmur, CTAB, Tanner 1 breasts, no axillary hair
- GU: nL external F genitalia, Tanner 2 pubic hair
- Neuro: alert, no focal deficits
- Skin: warm, dry, nL pigmentation, no rash
- Psychiatric: nL mood, affect and behavior
Differential Diagnosis?
DDx for Premature Pubarche

- Idiopathic premature pubarche
- Premature adrenarche
- Late-onset congenital adrenal hyperplasia
- Androgen-secreting tumor
- Exogenous hormones
- True precocious puberty
Evaluation for Premature Pubarche

- Idiopathic premature pubarche
- Premature adrenarche
- Late-onset congenital adrenal hyperplasia
- Androgen-secreting tumor
- Exogenous hormones
- True precocious puberty
- Bone age
- DHEAS
- 17-OH progesterone, consider ACTH stim
- AD, DHEAS, testosterone
- LH, FSH, E2, consideration of Lupron stim test
- TSH, FT4
Results of Evaluation

- Bone age: NL by report
- Adrenal U/S: NL
- DHEA 337 (< 377)
- DHEAS 164 (< 34)
- Androstendione 69 (6-115)
- Total testosterone 4 (< 8)
- Free testosterone 8.3 (4.5-12.5)
- TSH 2.20
- T4 8.3

ASSESSMENT?
Assessment/Plan

- Results consistent with premature adrenarche
- Observation advised
HPI cont’d

- Seen for a 2\textsuperscript{nd} endocrine opinion at 5 11/12 yrs
- Increased pubic hair, continued body odor, no noted breast development

- PE: NL vitals (BP 92/60), Wt (60\textsuperscript{th}%), Ht (70\textsuperscript{th}%)
- Prominent thyroid
- “Some breast tissue but no breast buds” $\rightarrow$ lipomastia?
- Tanner 1 axillary hair, Tanner 2 pubic hair
- NL neuro exam
Impression and Plan

- DDx: Premature adrenarche vs precocious puberty
- Plan: Labs, Bone age and possible Lupron stimulation test
Evaluation at 6 1/12yrs

- Bone age repeated: read as 6 10/12yrs by radiology but 8 3/12yrs by endo
  - Predicted height = 60”
- Pelvic U/S: prepubertal configuration
- MRI: possible L-sided microadenoma, no additional abnormalities

Labs:
- ACTH 35
- Cortisol 21.3
- Prolactin 19.3 (<12)
- TSH 2.07, FT4 1.2
- Anti-TG/TPO Ab negative
- LH 0.038 (0.02-0.3)
- FSH 0.516 (1.0-4.2)
- Estradiol <1
- Total testosterone 16 (<10)
- DHEA 575 (19-592)
## Lupron Stim Test at 6 3/12yrs

<table>
<thead>
<tr>
<th></th>
<th>Time 0</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
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</thead>
<tbody>
<tr>
<td>FSH</td>
<td>0.424</td>
<td>5.1</td>
<td>8.0</td>
<td>9.8</td>
</tr>
<tr>
<td>LH</td>
<td>0.017</td>
<td>0.743</td>
<td>0.965</td>
<td>0.976</td>
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<tr>
<td>Estradiol</td>
<td>2.2</td>
<td></td>
<td>&lt;1.0</td>
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<tr>
<td>Testosterone</td>
<td>13</td>
<td></td>
<td>11</td>
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</table>

No 24-hr estradiol
### Lupron Stimulation Test at 6 3/12yrs

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<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSH</strong></td>
<td>0.424 (0.5-2.9)</td>
<td>5.1 (5.7-18)</td>
<td>8.0</td>
<td>9.8 (9.3-37)*</td>
</tr>
<tr>
<td><strong>LH</strong></td>
<td>0.017 (0.1-0.3)</td>
<td>0.743 (0.9-4.1)</td>
<td>0.965 (0.2-2.9)</td>
<td>0.976</td>
</tr>
<tr>
<td><strong>Estradiol</strong></td>
<td>2.2 (5-8)</td>
<td>&lt;1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Testosterone</strong></td>
<td>13 (&lt;10)</td>
<td></td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

**Prepubertal normal values**

*at 4-hrs

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HPI cont’d

- Pubertal axis interpreted to be “activated”
- Plan for repeat bone age and Lupron suppression if bone age advanced

- Bone age at 6 4/12yrs = 8 4/12yrs
  - Predicted height = 61.5” (previously 60” at 8 3/12yrs)

- Question of breast tissue at this time by mother
- Supprelin implant placed at 6 5/12yrs
HPI cont’d

Follow-up at 6 9/12yrs
› Testosterone 12 (<10), DHEA 588 (19-592), BA 8 10/12yrs (61.2”)
› Tx: Started Metformin 250mg QD

Follow-up at 7 3/12yrs
› Testosterone 13, DHEA 558, BA 9yrs (63”)
› Tx: Increased Metformin to 250mg BID
› Plan: 17OHP, AD and possible cosyntropin stim test at next visit

Follow-up at 7 11/12yrs
› Testosterone 16, DHEA 853, 17OHP 82(< 91), AD 79 (<10-17)
› LH 0.22, FSH 0.8, estradiol 1.3, BA 10 6/12yrs (60.7”)
› Assessment: Likely 3BHSD deficiency
› Plan: Metformin 500mg BID, started Arimidex, replaced Supprelin
U of C: 3rd opinion at 8 3/12yrs

- Cont’d pubic hair growth, body odor, and possible breast development
- ROS as per HPI and otherwise unremarkable
- On Metformin, Arimidex, and Supprelin

Physical exam

- Wt 35.8 kg (92\textsuperscript{nd}%), Ht 134.1 cm (80\textsuperscript{th}%), BMI 20 (93rd%)
- +Adiposity, no breast tissue
- Tanner 3 pubic hair
Assessment

- Most likely premature adrenarche with bone age advancement
- Need to further assess for late-onset CAH
- Impossible to comment on current pubertal status, but no definitive evidence of puberty prior to Supprelin implant
Labs 09:11 a.m.

- ACTH 30
- Cortisol 14
- 17OHP 76 (< 90)
- 17OH preg 328 (< 72)
- DHEA 553 (19-592)
- DHEAS 211 (< 92)
- AD 79 (6-115)
- Total Testosterone 16 (<36)
- Free Testosterone 1.1 (0.2-5.0)
## Cosyntropin Stimulation Test

<table>
<thead>
<tr>
<th></th>
<th>Time 0</th>
<th>30 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>81.5</td>
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<tr>
<td>17OHPreg</td>
<td>1280</td>
<td>1570</td>
<td>1560</td>
</tr>
<tr>
<td>17OHP</td>
<td>283</td>
<td>271</td>
<td>258</td>
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<tr>
<td>DHEA</td>
<td>9.7</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>AD</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>28.5</td>
<td>34.9</td>
<td>37.8</td>
</tr>
</tbody>
</table>
## Cosyntropin Stimulation Test

### 3BHSD deficiency

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<td>ACTH</td>
<td>81.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17OHpreg</td>
<td>1280 (335-4100)*</td>
<td>1570</td>
<td>1560 (1763-2391)</td>
</tr>
<tr>
<td>17OHP</td>
<td>283</td>
<td>271</td>
<td>258</td>
</tr>
<tr>
<td>DHEA</td>
<td>9.7</td>
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<td>Cortisol</td>
<td>28.5</td>
<td>34.9</td>
<td>37.8</td>
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</tbody>
</table>

precursor:product ratios (>10)

DHEA:AD = 0.09

17-OHpreg:17-OHP = 4.5

17OHpreg:F ratios

Baseline = 44.9 (>1700)

Stimulated = 41.3 (>1930)
Summary

Impression: 8 3/12yo F with premature adrenarche
  - No clear signs of puberty but now on Supprelin

Plan: Remove Supprelin after 1-yr (from placement)
  - Discontinue Arimidex
  - Continue Metformin
Clinical Questions

- What is the role of Metformin in the tx of premature pubarche?
Early vs. Late Metformin tx

- 38 LBW females with precocious puberty
- Followed from age 8-15yrs
- Divided into 2 groups: early vs late Metformin tx

Outcomes in LBW-PP Females

<table>
<thead>
<tr>
<th></th>
<th>Early metformin (0–4 yr)</th>
<th>Late metformin (5–6 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>2386 ± 107</td>
<td>2471 ± 116</td>
</tr>
<tr>
<td>Birth weight Z-score</td>
<td>-1.8 ± 0.1</td>
<td>-1.7 ± 0.1</td>
</tr>
<tr>
<td>Age at PP (yr)</td>
<td>5.4 ± 0.3</td>
<td>6.1 ± 0.3</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>12.5 ± 0.2</td>
<td>11.4 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Distance to target height (cm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.0 ± 1.9</td>
<td>33.6 ± 1.3</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>1.4 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Ferriman-Gallwey score</td>
<td>6.9 ± 0.4</td>
<td>10.1 ± 0.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>197 ± 11</td>
<td>215 ± 10</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>8.6 ± 0.9</td>
<td>8.2 ± 0.6</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.9 ± 0.2</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>53 ± 5</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>104 ± 10</td>
<td>113 ± 8.9</td>
</tr>
<tr>
<td>Androstenedione (ng/dl)</td>
<td>98 ± 7</td>
<td>91 ± 10</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>32 ± 3</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>107 ± 7</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>74 ± 10</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>White blood cell count (10&lt;sup&gt;3&lt;/sup&gt;/µl)</td>
<td>7.9 ± 0.4</td>
<td>7.6 ± 0.3</td>
</tr>
<tr>
<td>Neutrophil count (10&lt;sup&gt;3&lt;/sup&gt;/µl)</td>
<td>4.2 ± 0.3</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0.4 ± 0.1</td>
<td>1.6 ± 0.5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>—</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>BMD (g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.75 ± 0.02</td>
<td>1.16 ± 0.02</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>19.7 ± 0.7</td>
<td>34.5 ± 0.9</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>10.8 ± 0.7</td>
<td>27.1 ± 1.8</td>
</tr>
<tr>
<td>Abdominal fat (kg)</td>
<td>3.0 ± 0.4</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>Abd fat (% abd soft tissue mass)</td>
<td>19.7 ± 2.2</td>
<td>19.3 ± 1.7</td>
</tr>
<tr>
<td>Abd sc fat (cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>15 ± 18</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>Abd visceral fat (cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>32 ± 2</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Visceral to sc fat</td>
<td>0.25 ± 0.02</td>
<td>0.33 ± 0.03&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intrahepatic lipid content (%)</td>
<td>115 ± 1.3</td>
<td>16.6 ± 1.5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Early vs Late Metformin Tx

Early vs Late Metformin Tx


<table>
<thead>
<tr>
<th>Androgen excess</th>
<th>Early metformin (n = 19)</th>
<th>Late metformin (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferriman Gallwey score &gt;8</td>
<td>2 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12 63</td>
</tr>
<tr>
<td>Serum testosterone above +2 sd (≥48 ng/dl)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 63</td>
</tr>
<tr>
<td>Total (clinical and/or biochemical)</td>
<td>6 32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13 68</td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea (no menses for &gt;3 months)</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Oligomenorrhea (cycles &gt;45 d)</td>
<td>1&lt;sup&gt;d&lt;/sup&gt; 5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7&lt;sup&gt;d&lt;/sup&gt; 37</td>
</tr>
<tr>
<td>Total (amenorrhea or oligomenorrhea)</td>
<td>1&lt;sup&gt;d&lt;/sup&gt; 5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7&lt;sup&gt;d&lt;/sup&gt; 37</td>
</tr>
<tr>
<td>Polycystic ovaries (by ultrasound)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ovarian volume ≥10.0 ml ≥12 cysts (2–9 mm) in one or both ovaries</td>
<td>3 16</td>
<td>3 16</td>
</tr>
<tr>
<td>Total (by volume and/or cyst number)</td>
<td>3 16</td>
<td>4 21</td>
</tr>
<tr>
<td>PCOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH definition</td>
<td>1&lt;sup&gt;d&lt;/sup&gt; 5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7&lt;sup&gt;d&lt;/sup&gt; 37</td>
</tr>
<tr>
<td>AES definition</td>
<td>1&lt;sup&gt;d&lt;/sup&gt; 5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>8&lt;sup&gt;d&lt;/sup&gt; 42</td>
</tr>
</tbody>
</table>

Change in Abdominal Fat (% of Abd Soft Tissue Mass)

- PCOS at age 15 yr
- No PCOS at age 15 yr

Change in Androstenedione (ng/dl)

- PCOS at age 15 yr
- No PCOS at age 15 yr
Summary

- Early Metformin showed reduction in PCOS in high-risk females (LBW-PP)
- These results are possibly attributed to reduction in adiposity
References