30-year-old Female with Oligomenorrhea

1/31/13
Jess Hwang
Oligomenorrhea/Infertility HPI

- For the last year, irregular menstrual cycles (she has only had 3-4 in the last 12 months)
- Prior to this, never irregular
- 1 week prior to seeing us she was started on an OCP and was currently having spotting
- Had seen REI doctor in the last month → Pelvic US/HSP normal
- Patient and husband would like to conceive as soon as possible
HPI

• In 2011 she lost 25 lb for her wedding by dieting/exercising over the course of 3-4 months. Has gained back 15 lb.
• Headaches over the past year, never prior
• +Fatigue, +easy bruising
• No vision complaints, no galactorrhea, no hirsuitism
• No depression, anxiety. No stress.
• No history of past steroid use.
PMH
- Oligomenorrhea
- Collar bone fracture

SHx
- Never smoker
- 3 glasses wine/wk
- Married

Fam Hx
- Mother: hypothyroidism
- MGF: lymphoma
- PGF: lung cancer

Meds
- OCPs x 1 week
Physical Exam

Vitals: 128/91, 89, 5’6”, 133lb, BMI 21.5
Gen: no apparent distress
HEENT: no pharyngeal erythema. No facial hair.
Neck: subcm thyroid nodule L lobe
CV: RRR, no murmurs
GI: soft, non-tender, non-distended. No rebound or guarding. Normal bowel sounds. No striae.
Skin: no acanthosis nigricans. No bruising.
Neuro: alert and oriented.
Psych: normal mood.
July of 2011-148 lbs

December 2011-125 lbs
Pre-clinic labs 7/2012

- hCG < 2 mIU/ml
- FSH 3.2
- LH < 0.2
- Estradiol 33 pg/ml (RR < 31 = post-menopausal)
- Prolactin 6.1 ng/ml (RR 3-30)
- TSH 1.12, FT4 1.2
- A1c 5.1
- BMP/LFTs normal
MRI pituitary 7/2012

- 7 x 7 mm focal area of nonenhancement in the L side which could be consistent with a pituitary microadenoma
- Visual fields: B non-specific mild defect
Post-clinic Labs 10/2012

After no OCPs and no exercise for 6 weeks

- **IGF-1** 293 (53-331)
- **ACTH** 96 pg/ml (RR 6-50)
- **Plasma cortisol** 25 (RR 4-22)
- **FSH** 7.1, **LH** 2.0, estradiol 44 pg/ml
- **Total testosterone** 27 (RR 2-45), free testosterone 3.9 (RR 0.1-6.4)
Clinical suspicion of Cushing’s syndrome

Consider 2 of the following:
- 24-hour urinary cortisol level
- Midnight salivary cortisol level
- Low-dose DST

Normal

Cushing’s syndrome ruled out

Elevated

Cushing’s syndrome

ACTH level and high-dose DST

Elevated cortisol on HDDST and ACTH-independent Cushing’s syndrome: consider other sources

Suppressed cortisol on high-dose DST with ACTH-dependent Cushing’s syndrome

MRI pituitary + SPGR sequences

Adenoma identified

Cushing’s Disease

24h Urine Free Cortisol

- 87.5 mcg (RR 4-50), 2.5L

Low Dose Dexamethasone Suppression Test

- ACTH 84 pg/ml (RR 6-50)
- 8AM cortisol 18.5 mcg/dl (4-33)
- 24h UFC 30.8 (RR 4-50), 2.2L
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Cushing’s Disease

High Dose Dexamethasone Suppression Test

• ACTH 20 pg/ml (RR 6-50)
• 8AM cortisol 1.7 mcg/dl (RR 4-22)
• 24h UFC 4.7 mcg (RR 4-50), 2.7L
Clinical suspicion of Cushing’s syndrome

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Adenoma identified
Cushing’s Disease

MRI Pituitary wwo

Relatively well-circumscribed, ovoid shaped hypoenhancing lesion in the L paramedian pituitary gland. Current measurement is 0.9 cm x 0.6 cm x 0.7 cm
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Normal pituitary tissue

http://pathology.mc.duke.edu/research/Histo_course/antpituitary.jpg
Prolactin

Pathology: negative for prolactin, GH (LH, FSH, TSH as well)
Pathology: positive for ACTH.
Surgical Course

- HC 40 mg/20 mg → HC 15 mg/5 mg
- Triple dose x 3-4 days if she gets sick
- No evidence of DI

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<thead>
<tr>
<th></th>
<th>POD#0</th>
<th>POD#1</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>102</td>
<td>17.5</td>
</tr>
<tr>
<td>Cortisol</td>
<td>18.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Post-hospital course

• She started ovulating and has had her first menstrual cycle since surgery
• Has seen ENT twice and septum has healed
• Due to see neurosurgery next week
• Due to see endocrinology end of the month
Clinical Concepts

- Differentiating Pseudo-Cushings vs Cushings
- Pathophysiology of infertility in Cushings
- Infertility in Cushings vs PCOS
- Ovarian morphology in Cushings
Pseudo-Cushings vs Cushings

- JCEM 2007, Gatta B.
- 14 Pseudo-Cushings, 17 Cushings Disease
  - Matched for 24h UFC
- Aim: DST-CRH vs DST
- Conclusion: DST-CRH not superior to DST
- Midnight plasma cortisol (256 nmol/L=9.27 mcg/dL) was 100% Sn and 96% Sp
Pseudo-Cushings vs Cushings
LDDST

Our patient
510 nmol/L = 18.5 mcg/dL

55 nmol/L = 1.99 mcg/dL
94% Sn, 86% Sp

Gatta B et al. JCEM 2007;92(11):4290-4293
Menstrual irregularity in Cushing’s

- 45 patients with new diagnosis of CD.
- Subdivided into 4 groups according to duration of their menstrual cycles
  - BL labs and LH/FSH response to GnRH
- Results: 80% of patients with CD had menstrual irregularity and this was most closely related to serum cortisol. 95-100% LH/FSH response to GnRH.
Menstrual irregularity in Cushing’s

<table>
<thead>
<tr>
<th></th>
<th>Normal cycles</th>
<th>Oligomenorrhea</th>
<th>Amenorrhea</th>
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<tbody>
<tr>
<td>LH (IU/L; NR, 1–13)</td>
<td>5.6 (2.6–12.6)</td>
<td>4.8 (1.4–15.2)</td>
<td>2.5 (0.8–14.5)</td>
</tr>
<tr>
<td>FSH (IU/L; NR, 0.3–10)</td>
<td>3.8 (0.8–5)</td>
<td>3.2 (1.1–6.6)</td>
<td>2.6 (0.3–7.2)</td>
</tr>
<tr>
<td>PRL (mIU/L; NR, up to 360)</td>
<td>309.5 (193–768)</td>
<td>246.5 (107–649)</td>
<td>231 (118–440)</td>
</tr>
<tr>
<td>Testosterone (nmol/L; NR, 0.5–3)</td>
<td>2.5 (1.6–3.1)</td>
<td>2.3 (0.6–3.4)</td>
<td>2.1 (1.3–4.6)</td>
</tr>
<tr>
<td>Androstenedione (nmol/L; NR, 3–8)</td>
<td>11.9 (6.1–21)</td>
<td>14.4 (2.7–23)</td>
<td>13 (7.6–17.5)</td>
</tr>
<tr>
<td>DHEAS (μmol/L; NR, 1.9–9.4)</td>
<td>8.9 (1.8–14.4)</td>
<td>4.8 (2.3–28)</td>
<td>10 (1.7–20)</td>
</tr>
<tr>
<td>SHBG [nmol/L; NR females, 38–103]</td>
<td>24 (15–43.3)</td>
<td>18.5 (10–40)</td>
<td>13.25$^a$ (10–31)</td>
</tr>
<tr>
<td>FAI [(T/SBHG) x 100]</td>
<td>11.5 (4.2–18)</td>
<td>14.5 (2–31)</td>
<td>14 (6–46)</td>
</tr>
<tr>
<td>Estradiol (pmol/L; NR, 200–1000)</td>
<td>279 (99–444)</td>
<td>225 (117–500)</td>
<td><strong>110$^b$ (39–290)</strong></td>
</tr>
<tr>
<td>Cortisol, 0900 h (nmol/L; NR, 200–700)</td>
<td>580 (390–930)</td>
<td>602 (183–1100)</td>
<td><strong>800$^b$ (439–1258)</strong></td>
</tr>
<tr>
<td>Cortisol, 1800 h (nmol/L; NR, 100–300)</td>
<td>523.5 (275–830)</td>
<td>557.5 (110–1060)</td>
<td><strong>816$^b$ (503–1600)</strong></td>
</tr>
<tr>
<td>Cortisol, 0000 h (nmol/L; NR, &lt;50)</td>
<td>320.5 (250–711)</td>
<td>453 (292–1060)</td>
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</tr>
<tr>
<td>Mean cortisol (nmol/L)</td>
<td>459 (313–780)</td>
<td>491.1 (212–1073)</td>
<td>753$^b$ (393–1367)</td>
</tr>
</tbody>
</table>

Cortisol inversely correlated with estradiol
No significant difference between groups with androgens.

PCOS vs Cushing's: infertility

- Clin Endo 2000, Kaltsas GA et al.
- 13 premenopausal women w/Cushing’s Syndrome (median age 32 yo)
  - 100% had at least symptoms of hyperandrogenism (hirsuitism, male-pattern baldness, acne)
  - 70% with menstrual disturbance
- All androgen levels, DHEA-S were normal
  - 6 of 13 (46%) had ovarian morphology to suggest polycystic ovaries
Ovaries in Cushing’s Syndrome

- Iannaccone. NEJM 1959
- Post-mortem exam: 10 patients w/CS (6 were between 30-37 yo)
- Imaging of 6 additional patients w/CS
- Observations: reduction in all phases of follicular activity
  - Failure of normal gonadotropic stimulation
Take Home Points

• LDDST is not inferior to DST-CRH test in differentiating between PCS, CD
• Menstrual irregularity in Cushings is from cortisol’s effect on the hypothalamus.
• As in PCOS, ovarian morphology is variable in Cushings Syndrome
References

• Lado-Abeal J et al. Menstrual Abnormalities in Women with Cushing’s Disease are Correlated w/Hypercortisolemia rather than Raised Circulating Androgen Levels. JCEM 1998;83:3083-3088.
• Iannaccone A et al. The Ovaries in Cushing’s Syndrome. NEJM 1959;261:775-780.
• Zada G. Diagnosis and Multimodality Management of Cushing’s Disease: A Practical Review. Volume 2013 (2013), Article ID 893781, 7 pages.
• Gatta B et al. Re-eval of the Combined DST-CRH Test for Differentiation of Mild CD from PCS. JCEM 2007;92(11):4290-4293.