62 y.o. female with hirsutism
HPI

- 62 y.o. female who has been following in the clinic for postsurgical hypothyroidism, pituitary microadenoma on routine f/u visit noted with significant hirsutism
HPI

- Noted new facial hair growth 1-2 years ago accelerated over last 3-6 months
- Now requiring weekly waxing
- Denies significant worsening hair growth in other areas (thighs, pubic, arms, breast/chest etc.), maybe some over lower legs and perineal area
- Deepening of the voice noted years ago (after thyroidectomy 2014) and was investigated, no change since
- Denies thinning of scalp hair
- More oily skin, + acne
- Clitoral enlargement noted ~2 years ago when became sexually active again
- No changes in sex drive
Other pertinent history

- Menstrual periods regular, however heavy
- Last MP 12/1997
- Hysterectomy 3/1998 due to excessive bleeding
- G1P0 (abortion) did not try more
- In her 30s was told she has ovarian cysts at 2 different occasions
Past medical history:

- **Hypothyroidism**: diagnosed with multinodular goiter in 2005. She is s/p total thyroidectomy with Dr. Angelos on 4/1/14. Benign pathology. LT4 was tapered down from 137 mcg post op to 88 mcg recently after presentation with thyrotoxicosis.

- **Pituitary microadenoma**: initially noted at 6 mm in 2005 with no significant changes until 2015 when it was measured at 3 mm.

- repeat MRI 2017: punctate T2 hyperintensity within the left aspect of the anterior pituitary gland, measuring 3 x 3 mm. also possible relative hypoenhancement along the inferior aspect of the right lateral anterior gland measuring 2-3. there is a slightly heterogeneous enhancement pattern of the gland.

  she had normal ACTH stimulation test, normal FSH, IGF-1, and prolactin. normal visual field testing in November 2013. Her prolactin was mildly elevated in 2005. She was never treated with a dopamine agonist.
PMHx

Migraine HA
Secondary hyperparathyroidism
?RA on steroids/methotrexate/Plaquinil at some point
Depression/anxiety
Rosacea/acne vulgaris
CKD III
Family history

- Mother with Hx of migraine, depression, DM II, pancreatic cancer metastasized to Ovaries
- Father: prostate CA, asthma
- PGM: pancreatic Ca
- Breast Ca in multiple fam members maternal side
ROS

- Constitutional: no fever/chills, night sweats, denies weight loss, + fatigue, + anxiety
- HEENT: no blurred or double vision, no dysphagia, + hoarseness
- RESP: no dyspnea, no cough or increased WOB
- CV: denies CP/palpitations, LE edema
- GI: no abdominal pain/N/V/diarrhea, no constipation
- GU: no urinary symptoms, + vaginal dryness (Tx with estrogen pills)
- MSK: + joint pain (chronic OA)
- Neuro: + HAs, no paresthesia’s, no weakness
- Endo: no cold/heat intolerance, + oily skin, no hair loss
- Psych: + anxiety/depression, not suicidal
Physical exam

- Vital signs: Blood pressure 132/84, pulse 91, height 177.8 cm (5' 10''), weight 89.6 kg (197 lb 9.6 oz), BMI 28.4
- Const: NAD
- Generally: a well-appearing female in no acute distress.
- Neck - thyroidectomy scar
- Pulm - CTAB
- CV - no LEE
- Neuro - non focal, Axox3
- MuscSkelet - nl ROM
- GI - soft abdomen, not distended
- Skin - coarse hair chin and sideburns, acne
medications

- albuterol, mometasone, singulair, Flonase
- azelaic acid (AZELEX) 20 % Top cream
- cetirizine HCl, fexofenadine HCl
- chlorthalidone (HYGROTON) 25 mg Oral tablet
- clindamycin (CLEOCIN-T) 1 % Top topical gel, topical metronidazole, econazole, sulfacetamide Na-sulf
- clonazepam 0.5 mg Oral tablet
- cyclobenzaprine (FLEXERIL) 10 mg Oral tablet.
- escitalopram oxalate (LEXAPRO) 20 mg Oral
- estradiol 10 mcg VAGINAL tablet
- levothyroxine 88 mcg Oral tablet
- omeprazole (PRILOSEC), Zantac
- tramadol (ULTRAM) 50 mg Oral tablet
Thoughts on d/d and workup?
### ENDOCRINOLOGY

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
<th>Ref Range &amp; Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHCG, Plasma, Quant</td>
<td>1.4 *</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>5.9 *</td>
<td></td>
</tr>
<tr>
<td>Estradiol (Endo Lab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>48.0 *</td>
<td>35 - 201 ng/mL</td>
</tr>
<tr>
<td>LH</td>
<td>43.6 *</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>22.70</td>
<td></td>
</tr>
<tr>
<td>SMC/IGF1 Stim Panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Binding Globulin</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Calculated Free Te...</td>
<td>34 *</td>
<td></td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>Test Information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DIABETIC SCREENING...

| Glucose, Non-Fasting       | 5.7 * | 4.8 * |
| HbA1C                      |       |       |

**FSH 42.2 (20-135)**
Imaging

- CT UPPER ABD AND PELVIS W 9/23/2019
- ADRENAL GLANDS: No significant abnormality noted.
- LYMPH NODES: No significant abnormality noted.
- PELVIS: Exam suboptimal due to beam hardening artifact from right hip prosthesis.
- UTERUS, ADNEXA: Status post hysterectomy.
- IMPRESSION: Unremarkable study.
Non tumorous (functional) hyperandrogenism

- Polycystic ovary syndrome
- Congenital adrenal hyperplasia
- Ovarian hyperthecosis
- Obesity
- States of insulin resistance
- Endocrinopathies

- Iatrogenic

Cushing's syndrome
Acromegaly
Testosterone/DHEA supplementation
Antiepileptics (valproic acid and oxcarbazepine)
Danazol

Tumorous hyperandrogenism

- Adrenal tumors
  - Androgen-secreting carcinomas
  - Androgen-secreting adenomas
  - Sertoli–Leydig cell tumors (androblastomas)
  - Hilus cell tumors
  - Granulosa theca cell tumors
  - Metastatic neuroendocrine/gastrointestinal tumors
  - Cystadenomas

- Ovarian tumors
Is it physiologic/functional?

The postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and estrogens, many years after menopause [10]. Estrogen levels drop abruptly after menopause whereas androgen secretion gradually declines during the reproductive years. Subsequently, an imbalance among estrogens and androgens during menopause, amplified by a decrease in SHBG concentrations and may result in hyperandrogenic symptoms.

May be more pronounced in women with prior Dx of PCOS and CAH.
Is it exogenous?

- Exogenous testosterone
- Supplements
- Medications
Cushing's syndrome (CS) may also be diagnosed after menopause and cause symptoms or signs of androgen excess. Hirsutism can be found in approximately 50% of patients with CS mainly attributed to adrenal androgen excess; endogenous hypercortisolism also correlates positively with free androgen levels probably due to SHBG reduction. In contrast to CS secondary to adrenal carcinomas, signs of hyperandrogenism are usually mild in women with the adrenocorticotropic hormone- (ACTH-) dependent CD and are virtually absent in women with adrenal adenomas.
Androgen secreting adrenal tumors

- Incidence - 1-2 cases/million population per year, usually malignant
- Adrenal androgen-secreting neoplasms are usually large and aggressive carcinomas that present also with Cushing’s syndrome (25%) and have a very rapid progression and almost invariably a fatal outcome
- The differentiation between adrenal adenomas and carcinomas depends not on histology but on the benign or malignant clinical outcome after successful surgery.
- Adrenal tumors frequently present with increased DHEAS levels, however testosterone was shown to be the most consistently elevated androgen
- Probability of adrenal incidentaloma in patients over 70 yr of age reaches 7%
Is it ovarian?

**Hyperthecosis ovary**

- Hyperthecosis is a severe form of PCOS and results from an overproduction of androgens in the ovarian stromal cells. Typically presents with slowly progressive acne and likely to be virilized.
- Exact etiology is unclear thought to be related to elevated postmenopausal gonadotropin levels.
- Patients with hyperthecosis typically have normal serum dehydroepiandrosterone sulfate (DHEA sulfate) concentrations, testosterone >150 ng/dL and elevated gonadotropin levels.
- Ultrasonography in women with hyperthecosis usually shows a bilateral increase in ovarian stroma and the ovaries appear more solid.
- Characteristics of hyperthecosis include severe hyperandrogenism, insulin resistance (hyperinsulinism that further increase androgen production by binding to IGF1 receptors), hirsutism, and virilization.
- Dx - histologic examination.

**FIG. 2.** Histological examination of the ovaries showing the nests of luteinized theca cells (black arrows) scattered throughout a hyperplastic ovarian stroma characteristic of ovarian hyperthecosis.
Is it ovarian?

- Sertoli-Leydig cell tumors (androblastoma) <1%, large at the time of presentation, ¼ presents at menopause
- granulosa-theca cell tumors (> estradiol, ~10% androgen secreting)
- hilus-cell tumors (more freq. in postmenopausal, small at the time of Dx, highly elevated testosterone levels);
- estradiol and testosterone, inhibin and anti-Müllerian hormone can be used as specific tumor markers
- majority of ovarian androgen-secreting tumors is of relatively large size, ranging between 3 and 12 cm at diagnosis, and only a small minority may elude detection with current imaging modalities.
- Besides sex cord-derived tumors, androgen secretion may be the result of ovarian metastases from neuroendocrine tumors, other malignancies, and serous cystadenomas that are not known to be steroidogenic. In such cases, ectopic secretion of b-hCG has been speculated to stimulate the steroidogenic cells through a paracrine mechanism
Gonadotroph cell tumor

Most hormonally silent tumors (NFPA), usually express gonadotropin subunits detectable by immunohistochemistry but not sufficient to elevate blood levels.

Most macro adenoma

Usually discovered because of space occupying defects, loss of vision, hypopit, hyperprolactinemia

Extremely rare

MANAGEMENT: surgery If threaten vision or macroadenoma. Although GnRH antagonists and somatostatin analogues modestly shrink tumor in some patients they are not sufficiently effective to be recommended as a therapy
Acromegaly is a rare cause of hyperandrogenism in women, although hirsutism and less commonly acne can be found in up to 50% of the patients. Growth hormone (GH) hypersecretion induces a state of ovarian hyperandrogenism that along with the increased insulin-like growth factor 1 levels and concomitant hyperinsulinemia stimulate ovarian testosterone production. In addition, GH levels correlate negatively with SHBG levels, contributing to elevated free androgen levels.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (percent)</th>
<th>Age of onset years</th>
<th>Time of onset to presentation</th>
<th>Menstrual disturbance</th>
<th>Virilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS and related disorders</td>
<td>&gt;95</td>
<td>15 to 25</td>
<td>Years</td>
<td>+/-</td>
<td>Rare</td>
</tr>
<tr>
<td>CAH</td>
<td>1 to 2</td>
<td>Congenital</td>
<td>Birth/adolescence/adulthood</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>&lt;1</td>
<td>Any time</td>
<td>Weeks-months</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ovarian tumor</td>
<td>&lt;1</td>
<td>Any time</td>
<td>Weeks-months</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>&lt;1</td>
<td>Any time</td>
<td>Months-years</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperthecosis ovary</td>
<td>&lt;1</td>
<td>Pre- to post-menopause</td>
<td>Months-years</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

PCOS: polycystic ovary syndrome; CAH: congenital adrenal hyperplasia; (+): present; (-): absent; (+/-): present or absent.

Lab evaluation

- Pit. axis eval (LH, FSH, alpha-subunit, PRL, T4, T3, TSH, cortisol, IGF1, DHEA and DHEAS)
- Cosyntropin stim (with venous sampling)
- Low dose dexamethasone suppression: sensitivity of 100% and a specificity of 88%
- GnRH suppression

TRH stimulation (most NFTs are capable of synthesizing gonadotropin hormones and subunits (beta-FSH, beta-LH). Most patients in our study responded by either FSH, LH or alpha-SU secretion after TRH, independent of basal hormone levels. Furthermore, recent studies show that by measurement of TRH stimulated beta-FSH and beta-LH one might further improve the diagnostic tools. Gonadotropin response and possibly alpha-SU to TRH are also found in some patients with acromegaly. This could be a marker of a plurihormonal pituitary tumor)
imaging

- CT/MRI adrenal
- US ovaries (transvaginal)
- If no tumor detected imaging of ovaries and adrenals after IV radiolabeled iodomethylnorcholesterol (NP-59) (detects active steroid producing tumors)

**Selective ovarian or adrenal vein catheterization and sampling** may be considered before surgical exploration, but simultaneous catheterization of all adrenal and ovarian veins is difficult, with success rates as low as 26 - 45%. Procedure consists of introducing a femoral catheter to reach both the adrenal and ovarian veins. Adrenal and ovarian venous sampling with peripheral vein control is performed simultaneously, androgen concentrations (usually testosterone) are measured, and the adrenal or ovarian/peripheral gradient is calculated. In the adrenal sample, cortisol is also measured to ensure that the catheter is properly placed. Unilateral adrenal and ovarian lesions are associated with an ipsilateral gradient and different threshold values have been proposed to discriminate tumoral from non-tumoral causes. Gradients >4.51 nmol/L have a reported sensitivity and specificity of 94% and 78%, respectively. Venous sampling has also been reported to predict the correct localization of the lesion in 66% of cases. The limitations of lesion localization using venous sampling include the technical difficulty associated with the accurate catheterization of 4 veins, with a 4 vein catheterization success rate of 27 to 45%.

- WBPET (9)
## Treatment options

<table>
<thead>
<tr>
<th>Non tumorous etiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional hyperandrogenism (PCOS, NCAH, and obesity)</td>
<td>Cyproterone acetate, Spironolactone/flutamide, Insulin sensitizers (metformin), Local therapies (hirsutism), Diet and exercise, Surgical resection/GNRH analogs, Discontinuation of drugs/supplements</td>
</tr>
<tr>
<td>Ovarian hyperthecosis iatrogenic</td>
<td>Surgical resection/adrenolytics, Surgical resection/Somatostatin analogs/pegvisomant</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Surgical resection (stage I/II), Adjuvant therapy – mitotane (stage III/IV), Oophorectomy, GNRH analogs</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Tumorous etiology</th>
<th>Treatment</th>
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<td>Adrenal tumors</td>
<td></td>
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<tr>
<td>Ovarian tumors</td>
<td></td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome; NCAH, non-classic adrenal hyperplasia.
Long-term GnRH agonist treatment is an acceptable choice for treatment of postmenopausal hyperandrogenism in patients where ovarian origin of androgen excess is ascertained, and especially in those patients who have an increased risk for surgery due to comorbidities or who are unwilling to undergo bilateral oophorectomy.
Back to our patient

Right Ovary
Visualized. Outline: smooth. Size 18 mm x 15 mm x 10 mm. Vol. 1.5 cm³

Left Ovary
Visualized. Size 17 mm x 13 mm x 13 mm. Vol 1.5 cm³

Cyst(s)
Size 12 mm x 10 mm x 13 mm. Mean 11.7 mm. Vol 0.817 cm³. Unilocular cyst, smooth internal wall, cystic contents with 'ground glass' appearance, acoustic shadows not present, color score 2 (minimal color). Presumed endometrioma vs. unknown pathology

Cul de Sac
Visualized. No free fluid visualized

Impression
Ms. DUPREE is referred for an ultrasound at the Center for Advanced Care for high serum testosterone, hirsutism. History of hysterectomy in 1998. Patient states history of left ovarian cyst.

Multiple transabdominal and transvaginal images were taken to evaluate the pelvis. Transvaginal ultrasound imaging is limited due to ovarian mass, therefore, transabdominal images were obtained to better visualize the entire pelvis.

Uterus is surgically absent.
Vaginal cuff appears unremarkable.
Right ovary appears within normal limits.
Left ovary is seen with a 12 x 10 x 13 mm unilocular cyst as described above.
No free fluid is visualized in the cul-de-sac.
Previous ultrasound on 12/10/2007.
Take home points

- Careful history taking is important
- Laboratory investigation can guide in a right direction, but none are 100% reliable
- Positive imaging findings must always be interpreted carefully while taking into account the clinical context of the patient
- After menopause, ovarian causes of hirsutism and virilization are more frequent compared with adrenal disorders and include androgen secreting neoplasms and benign disorders such as ovarian stromal hyperplasia and hyperthecosis
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3 Thyroid. 1998 The effect of thyrotropin-releasing hormone on gonadotropin and free alpha-subunit secretion in patients with acromegaly and functionless pituitary tumors, Popovic V, Damjanovic S.

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5 J Clin Endocrinol Metab. August 2012, Management of Postmenopausal Virilization, Macarena Alpan3, Jose M. Gonzalez-Casbas, Juan Sanchez, Hector Pian, and Hector F. Escobar-Marriale

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7 Hyperandrogenism in Postmenopausal Women, Solved After “White” Oophorectomy Guadalin, Sonsoles MD; Vazquez, Tamara MD; Jodar, Esteban MD, PhD; Fernandez, Sofia MD., The Endocrinologist: November/December 2009

8 J Clin Endocrinol Metab. 2011 Gonadotropin-releasing hormone agonist treatment in postmenopausal women with hyperandrogenism of ovarian origin. Vollaad ES1, van Beek AP, Verburg FA, Roos A, Land JA.

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13 Neurosurgery. 2016 functional Gonadotroph Adenomas: Case Series and Report of Literature, David J. Cote, BS, 1 Timothy R. Smith, MD, PhD, MPH, 1 Courtney N. Sandler, MD, MPH, 2 Tina Gupta, MD, 2 Tejas A. Bait, MD, 3 Wenyia Linda Bi, MD, PhD, 1 Ian F. Dunn, MD, 1 Umberto De Girolami, MD, 3 Whitney W. Woodmansee, MD, 2 Ursula B. Kaiser, MD, 2 and Edward R. Laws, Jr, MD


Small relatively echogenic appearing soft tissue foci in the thyroid bed bilaterally, suspected to be residual thyroid tissue. Correlation with nuclear medicine study and surgical history recommended.

NM THYROID IMG SNG/MLT UPTKS QNT MSRMNTS, 4/17/2018: no functioning thyroid tissue
Postmenopausal hyperandrogenism

- a state of relative or absolute androgen excess originating from either the adrenals and/or the ovaries, clinically manifested as the appearance and/or increase in terminal hair growth or the development of symptoms/signs of virilization