The Case of PCOS: The Assessment, Treatment, and Clinical Pearls of a Complicated Hormone Condition

Presented by: Carrie Jones, ND, MPH
DISCLAIMER: THIS PRESENTATION DOES NOT PROVIDE MEDICAL ADVICE

The information, including but not limited to, text, graphics, images and other material contained on this presentation are for informational purposes only. The purpose of this conference is to promote broad consumer understanding and knowledge of various health topics. It is not intended to be a substitute for professional medical advice, diagnosis or treatment. Always seek the advice of your physician or other qualified health care provider with any questions you may have regarding a medical condition or treatment and before undertaking a new health care regimen, and never disregard professional medical advice or delay in seeking it because of something you have encountered in this presentation.

SHEI does not recommend or endorse any specific tests, physicians, products, procedures, opinions or other information that may be mentioned in this presentation. Reliance on any information appearing in this presentation is solely at your own risk.
Disclaimer:

• Medical Director, Precision Analytical, Inc.
• I have no financial ties to any medication or supplement company
Objectives:

Upon completion of this general case, participants will be able to:

1. Understand the basics of PCOS including diagnosis
2. Properly work-up and evaluate for suspected PCOS
3. Identify common hormone irregularities
4. Incorporate genetic snp results into the treatment
5. Identify and address common lifestyle triggers for PCOS
Typical symptom picture

**Androgen Excess**
1. Hirsutism
2. Male pattern hair loss
3. Acne/cystic acne
4. Anger/irritation/mood swings

**Ovulatory issues**
1. Anovulation
2. Irregular cycles/oligomenorrhea
3. Fertility challenges

Polycystic Ovary Morphology (PCOM)
Diagnostic criteria is 2 out of 3:

1. Confirmed androgen excess on labs and androgen excess symptoms
2. Ovulatory dysfunction
3. Multiple cysts on ovaries (PCOM) diagnosed via imaging
Is obesity part of the diagnosis?
Is obesity part of the diagnosis?

Not always → 30%-75% are obese
Commonly heard story

Menarche began later in teen years if at all or began ‘on time’ and then was very irregular ever since.

→ put on the birth control pill as a result

Cystic acne started to develop as did hair growth in places she didn’t want like the nipple area, top lip, chin area

→ put on spironolactone and/or Accutane as a result

Started gaining weight around the middle despite trying a “good diet” and regular exercise

By the twenties and thirties hair started thinning/falling out

Wants to get pregnant so stopped the pill and never got her period back
Pathophysiology of PCOS

↑ leptin
↓ FSH

↑ in stim. of granulosa cells

↑ leptin
↓ Test.

↑ insulín

↑ obesity

↑ risk BrCA

↑ risk endometrial cancer

↑ risk estrogen

↑ 11βHSD1 = ↑ Free Cortisol
↑ Metabolized cortisol

↑ aromatization (T→E)

↑ 5a-reductase

↑ obesity

↑ Aromatization (T→E)

↑ SHBG

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells

↑ obesity

↑ aromatization (T→E)

↑ leptin

↑ in stim. of granulosa cells
Keep in mind it’s not just an ovarian problem…

The Ovaries produce roughly:
- 25% of the Testosterone
- 50% of the Androstenedione
- 20% of the DHEA (not DHEA-s)

The Adrenals produce roughly:
- 25% of the Testosterone
- 50% of the Androstenedione
- 80% of the DHEA
- 100% of the DHEA-s

The other 50% of Testosterone is made in adipose tissue via androstenedione conversion
“While insulin resistance and elevated insulin often drive the ovarian production of testosterone, it is the hypothalamus-pituitary-adrenal (HPA) axis that stimulates the production of DHEA/DHEA-S and androstenedione. These hormones can be converted to testosterone by peripheral tissues in the body. This process can occur independently from the ovaries and any involvement with insulin.

This means that a woman with PCOS symptoms could have normally functioning ovaries with no cysts and no insulin resistance, yet still fit the symptomatic profile of the syndrome.”

-Laura Shoenfeld, MPH, RD - www.chriskresser.com
Common labs:

1. Fasting glucose/Fasting insulin (Hemoglobin A1c, 2hr glucose insulin tolerance test *(C-peptide: often low/N with LADA and high with type II DM)

2. Thyroid panel with antibodies

3. Prolactin (ideal <20ng/ml)

4. FSH/LH

5. Cardiac markers: lipids, homocysteine, fibrinogen, CRPhs

6. 17, hydroxyprogesterone
   (>80 ng/dL in follicular phase or >285 ng/dL in luteal phase = suspect CAH, cortisol will be low too)

7. Anti-mullerian hormone (>4ng/ml suspect PCOS)

*Consider a pelvic u/s
Inflammation ↓ DHEA-s

↓ ovulation = no or low progesterone

5a preference (androgenic)

Poor phase 1 = prefers 4 and 16OH

Poor phase 2

↑ Estrogens
↑ Metabolized (total) cortisol = inflammation, infection, insulin issues, obesity, long term stress

Free cortisol okay (too high through the night though)

↑ 11bHSD1 = more cortisol systemically (think inflammation and obesity)
Primary hormones (i.e., CAPS) are made by organs by taking up cholesterol and converting it locally, for example, progesterone. Much less is made from circulating precursors like pregnenolone. For example, taking DHEA can create testosterone and estrogen, but far less is made by the ovaries or ovaries respectively.

**Steroid Pathways**

- **DHEA (Sulfate)**
  - Spironolactone, Congenital adrenal hyperplasia (CAH), Luteinizing hormone (LH)
  - Spironolactone, aging, chronic exposure, licorice

- **17α-Hydroxylase**
  - High insulin, POIS, hyperglycemia, stress, alcohol

- **Androstenedione**
  - Progesterone, testosterone, androstenedione, heavy alcohol use, POIS, high insulin, food, male

- **Androgens**
  - Inflammation, stress, obesity, DHEA, food, alcohol

- **Estrogens**
  - Inflammation, stress, obesity, DHEA, food, alcohol

- **Progesterone**
  - Inflammation, stress, obesity, DHEA, food, alcohol

**Other factors affecting the production of primary reproductive and adrenal hormones:**
- Increased Cortisol: Stress, inflammation, Cushing's disease, obesity
- Decreased Cortisol: Glucocorticoid use, opioid use, Addison's disease, Accutane, chronic marijuana use
- Increased DHEA: POIS, scurvy, hypothyroidism, Alzheimers (AD) (ADD), male
- Decreased DHEA: Aging, high blood levels, Varietalma, Menopause, opioid, glucocorticoids, hormonal birth control, anabolic steroids, diabetes mellitus
- Increased Testosterone: POIS, HCG, HGH, D-Depo, Clomiphene Citrate (CC)
- Decreased Testosterone: Obesity, opioids, hormonal birth control, aceta diseae, aging, high insulin, stress, use
- Increased Estrogens: POIS, inflammation, pregnancy, DHEA/Triiodothyronine
- Decreased Estrogens: Hormonal birth control, ovulation failure, anovulation, obesity, underweight

**Additional factors:**
- Increased Progesterone: Pregnancy, progesterone supplementation
- Increased Estrogens: Hormonal birth control, stress, high insulin, opioids, HADD and age > 30 years

**Metabolism of OHE1:**
- OHE1 is metabolized to OHE2, which is further metabolized to E2.

**Effects of OHE1 and OHE2:**
- Effects like mood, cognitive function, sexual function are seen.

**References and Further Reading:**
- Information on this chart is for educational purposes only and is not a substitute for consultation with any of the cited references. For more information, please consult a qualified healthcare professional.
Let's evaluate some problem genetics...

**Estrogen Phase 1**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1048943</td>
<td>CYP1A1*2C A4889G</td>
<td>C</td>
<td>TT</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1799814</td>
<td>CYP1A1*4 C2453A</td>
<td>T</td>
<td>GG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2472304</td>
<td>CYP1A2*1F</td>
<td>A</td>
<td>AG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs762551</td>
<td>CYP1A2*1F C164A</td>
<td>G</td>
<td>AC</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2069526</td>
<td>CYP1A2*1K -739T&gt;G</td>
<td>G</td>
<td>TT</td>
<td>+/-</td>
</tr>
<tr>
<td>rs56276455</td>
<td>CYP1A2*3 D348N</td>
<td>A</td>
<td>GG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2839942</td>
<td>CYP1A2*6 R431W</td>
<td>T</td>
<td>CC</td>
<td>+/-</td>
</tr>
<tr>
<td>rs28936700</td>
<td>CYP1B1 10233C&gt;T</td>
<td>T</td>
<td>CC</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1056827</td>
<td>CYP1B1 A119S</td>
<td>A</td>
<td>AC</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1056836</td>
<td>CYP1B1 L432V</td>
<td>C</td>
<td>GG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1800440</td>
<td>CYP1B1 N453S</td>
<td>T</td>
<td>CT</td>
<td>+/-</td>
</tr>
<tr>
<td>rs10012</td>
<td>CYP1B1 R48G</td>
<td>G</td>
<td>CG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs9282671</td>
<td>CYP1B1 T241A</td>
<td>A</td>
<td>AA</td>
<td>+/-</td>
</tr>
<tr>
<td>rs4644637</td>
<td>CYP3A4 C202T</td>
<td>A</td>
<td>GG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2246709</td>
<td>CYP3A4 T258C</td>
<td>G</td>
<td>AG</td>
<td>+/-</td>
</tr>
<tr>
<td>rs12721627</td>
<td>CYP3A4*16 T185S</td>
<td>G</td>
<td>GG</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Glutathione S-Transferase: inactivates catechol estrogen quinones

<table>
<thead>
<tr>
<th>RS#</th>
<th>Call</th>
<th>Risk Allele</th>
<th>Gene</th>
<th>Variation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1056806</td>
<td>G</td>
<td>T</td>
<td>GSTM1</td>
<td>7730C&gt;T</td>
<td>+/-</td>
</tr>
<tr>
<td>rs7483</td>
<td>G</td>
<td>T</td>
<td>GSTM3</td>
<td>V224I</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1138272</td>
<td>A</td>
<td>T</td>
<td>GSTP1</td>
<td>A114V</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1695</td>
<td>G</td>
<td>G</td>
<td>GSTP1</td>
<td>I105V</td>
<td>+/-</td>
</tr>
</tbody>
</table>

GST saves the day

Depurinating adducts on DNA → mutations → Cancer

Methylation — MTHFR, MTR & MTRR

<table>
<thead>
<tr>
<th>RS#</th>
<th>Call</th>
<th>Risk Allele</th>
<th>Gene</th>
<th>Variation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1801131</td>
<td>GT</td>
<td>G</td>
<td>MTHFR</td>
<td>A1298C</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1801133</td>
<td>AG</td>
<td>A</td>
<td>MTHFR</td>
<td>C677T</td>
<td>+/-</td>
</tr>
<tr>
<td>rs17865704</td>
<td>AG</td>
<td>G</td>
<td>MTHFR</td>
<td>A1572G</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2054470</td>
<td>AG</td>
<td>A</td>
<td>MTHFR</td>
<td>83P</td>
<td>+/-</td>
</tr>
<tr>
<td>rs2274976</td>
<td>CT</td>
<td>T</td>
<td>MTHFR</td>
<td>G1793A(R5940)</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1805087</td>
<td>AA</td>
<td>G</td>
<td>MTR</td>
<td>A2756G</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1801394</td>
<td>GG</td>
<td>G</td>
<td>MTRR</td>
<td>A666G</td>
<td>+/-</td>
</tr>
<tr>
<td>rs162036</td>
<td>AA</td>
<td>G</td>
<td>MTRR</td>
<td>K350A</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1802059</td>
<td>GG</td>
<td>A</td>
<td>MTRR-1</td>
<td>A666A</td>
<td>+/-</td>
</tr>
<tr>
<td>rs1532968</td>
<td>CC</td>
<td>T</td>
<td>MTRR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3776467</td>
<td>AA</td>
<td>G</td>
<td>MTRR</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>rs932</td>
<td>GG</td>
<td>A</td>
<td>MTRR</td>
<td></td>
<td>+/-</td>
</tr>
</tbody>
</table>
SULT2A1 adds the "s" to DHEA

<table>
<thead>
<tr>
<th>rs</th>
<th>SULT2A1 SNP</th>
<th>Alleles</th>
<th>Genotypes</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs296366</td>
<td>SULT2A1 A20117G</td>
<td>T</td>
<td>TT</td>
<td>+/-</td>
</tr>
<tr>
<td>rs11083907</td>
<td>SULT2A1 C90C</td>
<td>A</td>
<td>GG</td>
<td>-/-</td>
</tr>
<tr>
<td>rs4149452</td>
<td>SULT2A1 G17136A</td>
<td>T</td>
<td>CC</td>
<td>-/-</td>
</tr>
<tr>
<td>rs11569679</td>
<td>SULT2A1 G781A</td>
<td>T</td>
<td>CC</td>
<td>-/-</td>
</tr>
<tr>
<td>rs2547231</td>
<td>SULT2A1 G9598T</td>
<td>C</td>
<td>AC</td>
<td>+/-</td>
</tr>
<tr>
<td>rs4149449</td>
<td>SULT2A1 G9696A</td>
<td>T</td>
<td>CT</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Catecholamines

* There are preformed concentrations of NE and Epi that release immediately via Ach in fight/flight

* Increased cortisol will increase the NE $\rightarrow$ Epi conversion in the adrenal gland

* NE and Epi degradation via COMT and MAO
GAD:

* decarboxylation of Glutamate to GABA (and CO2) via GAD

→ progesterone turns into allopregnaneolone which acts as an agonist to GABA-a receptor

* GAD is a target for antibodies = type 1DM or LADA

* also plays a role in schizophrenia, Parkinson’s and cerebellar disorders

+ low progesterone = really anxious/sleep issues
Where do you start?

(with the basics of course!)
PCOS is...

A metabolic disorder wreaking havoc on the Hypothalamic-Pituitary-Ovary Axis (HPO) combined with an Hypothalamic-Pituitary Axis (HPA) disorder complicated by some cranky genetics.

(per Dr. Carrie Jones)
Suggested Treatments:

1. Start with the diet/blood sugar/insulin and the Gut → reduce inflammation (Berberine, Inositol, D-Pinitol, Tumeric, Curcumin, Fish oil…etc)

2. Get her stress down and focus on quality sleep (no phones before bed)

3. Reduce 11bHSD1 (Magnolia, Skullcap, zizyphus, Polymethoxylated Flavones)

4. Consider Adrenal support as needed (adaptogens, glandulars, phos. Serine)

5. Get her MOVING → HIIT, weight lifting, resistance = Anabolic

5. Get her cycle back/ovulating : Chaste tree/Vitex, B6 (P5P), Evening Primrose Oil, glandulars, homeopathics, Progesterone

6. Address her Estrogen (DIM, appropriate methylation and COMT support, glutathione, NAC)

7. Slow the 5a: Saw Palmetto, Zinc, Pygeum, Reishi mushroom

8. Lower her Testosterone: White peony, Licorice (if warranted), Green tea (EGCG)

9. Remember the big picture – look at the SNPs and see what fits (L-theanine? 4-amino-3-butyric-acid?)
Thank you for listening!

Carrie Jones, ND, MPH
drcarriejones@gmail.com
References


- la Marca A, Morgante G, Palumbo M, Cianci A, Petraglia F, and De Leo V. Insulin lowering treatment reduces aromatase activity in reponse to follicle stimulating hormone in women with polycystic ovary syndrome. Fertility and Sterility. 2002;78(6):1234-1239.


- Rudnicka E, and Radowicki S. Androgen and 17-hydroxyprogesterone concentrations in blood serum versus menstrual patterns in women with polycystic ovary syndrome (PCOS). Ginekol Pol. 2010;81(10):745-9


