The Case of PCOS: Evaluating the difference between ovarian and adrenal hormones

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Objectives

- Understand the typical presentation
- Review how to diagnose true PCOS
- Discuss insulin’s role
- Review the androgens
- Understand what other labs you might run
- Case review
- Understand different treatments
PCOS: polycystic ovarian syndrome

It seems to fall on a spectrum
sometimes it involves insulin
sometimes it’s really an adrenal problem
How the usual story goes...

- 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
  - The nipple area, top lip, chin area → put on Spironolactone and/or Accutane
- Started gaining weight around the middle despite trying a “good diet” and regular exercise
- By the twenties and thirties hair started thinning/falling out

Why is she seeing you?
She wants to get pregnant so she stopped the pill and never got her period back
What is the typical presentation?

**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: 2 out of 3

1. Androgen excess (labs and symptoms)
2. Ovulatory dysfunction
3. Polycystic Ovarian Morphology
Is obesity part of the diagnosis?
Is obesity part of the diagnosis?

Not always → 30%-75% are obese
Insulin is the big culprit!
Insulin Resistance $\rightarrow$ Hyper-Insulinemia

- Obesity
- ↓ SHBG
- Theca cells enlarge in the ovary
- ↑ Testosterone
- Anovulation
- ↓ Progesterone

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Remember: 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

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“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 Schoenfeld, MPH, RD - www.chriskresser.com
What you’re telling me is... maybe it’s the adrenal glands?
What should you consider testing?

- Fasting glucose/Fasting insulin (Hemoglobin A1c, 2hr glucose insulin tolerance test)
- Thyroid panel with antibodies and rT3
- Prolactin
- FSH/LH
- Cardiovascular testing
- Leptin?
- 17, hydroxyprogesterone
- Anti-mullerian hormone
- *Consider a pelvic u/s
- Hormone testing
Hormone testing: what is DUTCH?

- It’s an acronym!

- Dried
- Urine
- Test for
- Comprehensive
- Hormones
What do you get in a DUTCH test?

1. Androgen Metabolism
2. Estrogen Metabolism
3. Progesterone Metabolites
4. Metabolized Cortisol/Cortisone
5. Free Cortisol/Cortisone
6. The Diurnal Pattern (Can include the CAR)
7. DUTCH Extras: includes OATs, Melatonin and 8-OHdG
Those who are new to spot urine testing and use saliva:

Urinary Free Cortisol

Salivary Free Cortisol

Dried versus Liquid Urine

Dried vs. Liquid Urine (n=300)

\[ y = 0.9606x + 0.637 \]
\[ R^2 = 0.9987 \]
24-Hour Correlation

4-Spot vs 24Hr Collection: Testosterone

```
y = 2.1335x + 0.4393
R^2 = 0.97
```

4-Spot vs 24Hr Collection: Estradiol

```
y = 1.7811x + 0.3235
R^2 = 0.9214
```

4-Spot vs 24Hr Collection: b-Pregnanediol

```
y = 1.8711x + 56.556
R^2 = 0.9977
```
Dried urine versus Serum

- Precision Analytical has shown statistical equivalence between dried urine results and serum results drawn on the same day – Publication pending (stay tuned!)
DUTCH Complete Test Collection
The Flagship dried urine only test

4 urine samples done throughout the day and dried
1. First thing on waking
2. 2 hours later
3. Around dinner
4. Before bed
   ▪ Optional 5th strip if wake and urinate in the middle of the night
5 **Saliva** collections
   - Waking, +30 min, +60 min, 5pm, Bedtime
   - Easier collections using cotton swabs

4 **Dried urine** collections

- #1: Upon Waking
- #2: 30 Min After Waking
- #3: 60 Min After Waking
- #4: 2-3 Hrs After Waking
- #5: 4pm to 5pm
- #6: 10pm to Midnight
When should you test hormones?

- Still cycling regularly? Days 19, 20 or 21 of a typical 28 day cycle
- Long or short cycles but regular? Shift up or down accordingly
- Irregular cycles? Do ovulation predictor kits or track ovulation signs until positive then test 5-7 days after that
- No ovulation and irregular? Call the office for help.
Why testing in the luteal phase is important
Case Study: 33yo female presents with

- Recent (!) irregular cycles the last 6 months
- Noticing more acne and hair growth on her face
- Her primary doctor diagnosed PCOS = suggested the pill

- High stress (married mother of 2, in a PhD program)
- Gut infection – recently diagnosed with SIBO, has symptoms
- Normal weight, glucose/insulin wnl, Thyroid wnl, prolactin wnl
Summary:
- Progesterone = low
- Estrogen = high
- Phase 1 and 2 detox = problems

Not ovulating = low progesterone
Estrogen dominant
Unhealthy Phase 1 detox – favors the 4OH and 16OH
Sluggish phase 2 detox (COMT?)
Quick review of estrogen detox phase 1:

- Estrogen dominant
- Unhealthy Phase 1 detox – favors the 4OH and 16OH
Quick review of estrogen detox phase 1:

Estrogen dominant

Unhealthy Phase 1 detox – favors the 4OH and 16OH compared to the 2OH
Quick review of estrogen detox phase 2:

The ability to move from 2-OH to 2-Methoxy
Androgens:
Do you go down the pathway that causes hair loss, acne, and facial hair growth in unwanted places?
Lower DHEA-S = inflammation

Elevated DHEA metabolites

5α Reductase dominant
What is 5a-Reductase?

- Converts testosterone into more potent DHT/alpha metabolites.
- **Symptoms:** acne, hirsutism, hair loss on head, anger/irritation.
- **Increased via:** genetics, inflammation, insulin, obesity.
What did her adrenals look like?

She's making a ton of cortisol – it’s all red!
What do her DUTCH Extras/Organic Acids look like?

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Result</th>
<th>Units</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DUTCH Extras</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin (<em>measured as 6-OH-Melatonin-Sulfate</em>) - (Urine)</td>
<td>Melatonin* (Waking)</td>
<td>Within range</td>
<td>ng/mg</td>
<td>10 - 85</td>
</tr>
<tr>
<td>Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)</td>
<td>8-OHdG (Waking)</td>
<td>Within range</td>
<td>ng/mg</td>
<td>0 - 5.2</td>
</tr>
<tr>
<td><strong>Nutritional Organic Acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 Marker (may be deficient if high) - (Urine)</td>
<td>Methylnalont (MMA)</td>
<td>Within range</td>
<td>ug/mg</td>
<td>0 - 2.8</td>
</tr>
<tr>
<td>Vitamin B6 Marker (may be deficient if high) - (Urine)</td>
<td>Xanthrenate</td>
<td>High end of range</td>
<td>ug/mg</td>
<td>0 - 1.6</td>
</tr>
<tr>
<td>Glutathione Marker (may be deficient if low or high) - (Urine)</td>
<td>Pyroglutamate</td>
<td>Below range</td>
<td>ug/mg</td>
<td>37 - 70</td>
</tr>
<tr>
<td><strong>Neurotransmitter Metabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dopamine Metabolite - (Urine)</td>
<td>Homovanillate (HVA)</td>
<td>Low end of range</td>
<td>ug/mg</td>
<td>4.5 - 13</td>
</tr>
<tr>
<td>Norepinephrine/Epinephrine Metabolite - (Urine)</td>
<td>Vanilmandelate (VMA)</td>
<td>Below range</td>
<td>ug/mg</td>
<td>2.7 - 6.4</td>
</tr>
<tr>
<td>Serotonin Metabolite - (Urine)</td>
<td>5-Hydroxyindoleacetaete (5HIAA)</td>
<td>Below range</td>
<td>ug/mg</td>
<td>3 - 7.5</td>
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Let’s focus in...

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Low HVA and VMA: Maybe COMT?
Low 5HIAA? Maybe high estrogen/cortisol/gut
Tryptophan can choose 2 pathways

Excess estrogen, cortisol, inflammation and LPS push →
What do you do?
Where do you start?
Is it really PCOS?
Health Goals:

- Address the cause!
- Focus on diet and lifestyle
- Improve cortisol levels!
- Address blood sugar and insulin
- Restore ovulation, improve estrogen balance
- Reduce androgenic symptoms
First, address the cause

In the case study, high stress and gut inflammation is likely upregulating the HPA axis resulting in high cortisol (weight gain, irregular cycles), and elevated androgens (acne and hirsutism)
Second: address diet/insulin/lifestyle factors

- Berberine – 500mg TID with meals
- Inositol – 1000-2000mg/day (some use inositol as cheaper than D-pinitol)
- D-pinitol – 1000-2000mg/day
- Chromium – 500-1000mcg/day
- Fish oil – average dose is 1000-3000mg/day
- Cinnamon – consider using as a spice routinely
- N-acetyl-Cysteine – 500mg-1000mg/day
- Zinc – depends on needs and if deficient. 10-100mg/day (be aware of copper)
- Alpha lipoic acid – 500-1000mg/day
- Green tea (EGCG) – 500-1000mg/day, drinking several cups/day helps too
- Gymnema – 250-500mg/day
- Medication: Metformin (Glucophage)
- Weight training and resistance training
Third: address the stress/cortisol

- Address the cause, meditation, acupuncture, journaling, counseling, finding joy/happiness, proper sleep hygiene
- Adaptogens
- Calming support examples:
  - Phosphatidyl Serine – 100-400mg
  - Ocimum sanctum (Holy Basil) – 500-1500mg/day in divided doses
  - Magnolia bark – 250-500mg at night
  - Scutellaria lateriflora (Skullcap) – 200-500mg/day often at night
  - L-theanine – 200-1000mg/day divided doses
Fourth: Improve ovulation/progesterone

- Vitex agnus-castus (Chaste Tree berry) – 250mg-500mg daily
- Vitamin B6 (P5P) – 25-100mg P5P
- Maca (be aware this could also raise androgens and estrogen) – 1000-2000mg/day
- Cordyceps – 500-1000mg/day
- Evening primrose oil – 500mg-1000mg/day
- Homeopathics
- Seed cycling
- Improve melatonin release from the pineal gland
- Bio-identical Progesterone
  - Topical, oral, sublingual, vaginal
  - Often done in the luteal phase only if the luteal phase is known
- Acupuncture
Lastly: reduce androgen/5a symptoms

- Address the insulin and/or cortisol causes
- Spearmint tea is anti-androgenic
- 5a-Reductase “blockers”:
  - Serenoa repens (Saw palmetto) – 250-1000mg/day
  - Zinc – depends on needs and if deficient, 10-100mg/day (watch copper)
  - Urtica dioica (Stinging Nettles root) – 500-1000mg/day
  - Pygeum africanum (bark) – 500mg/day
  - Reishi mushroom- 500-1500mg/day
  - EGCG from green tea – 250-500mg/day
  - Spironolactone - medication
What did I do for her?

- Sleep hygiene
- Morning routine/ask for help/stress reduction
- Regular eating patterns/be prepared
- Address her SIBO/gut symptoms first for a month
  - Then added:
    - Adrenal adaptogen
    - Chaste tree berry every morning
    - B-Complex with P5P
5 month follow-up

- Husband and her mom were helping more with the kids
- Her digestion was significantly improved
- She worked hard to NOT skip meals
- She worked hard to NOT be on her computer at night (school)
- She had more energy, was in a better mood!
- Her last 2 cycles were perfectly normal
- Her skin had improved – breakout sometimes with PMS
- The hair growth was still there but not worse
- Repeating DUTCH Test and will go from there (ie. Estrogen detox)
Having the most comprehensive, easy to collect adrenal and hormone test (now with DUTCH extras) available allows you to make a greater impact on your patients at a deeper level.
References:

4. Arentz S, Abbott JA, Smith CA and Bensoussan A. Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. BMC Complement Altern Med. 2014;18(14)511.
19. la Marca A, Morgante G, Palumbo M, Cianci A, Petraglia F, and De Leo V. Insulin lowering treatment reduces aromatase activity in response to follicle stimulating hormone in women with polycystic ovary syndrome. Fertility and Sterility. 2002;78(6):1234-1239.
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