Polycystic Ovarian Syndrome

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Disclosure

Alison McAllister, ND, is employed by ZRT Lab.

Professional Education Services Group staff have no financial interest or relationships to disclose.

Disclosure

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Learning Objectives

• At the conclusion of this activity, the participant will be able to:
  – Discuss new groupings and 2 commonly seen variants of PCOS.
  – Review common signs and symptoms of PCOS.
  – Discuss conventional medications, adrenal support, and surgical options used to treat PCOS.

PCOS is extremely common

• 4-10% of all women – many who are undiagnosed
• Treatable, but not curable
• Cause not known, but getting closer
  – 3 SNPs identified w/insulin receptor
  – SORCS1 polymorphism (rs1358030, rs1416406 and rs11192966)
  – Abnormal Heat Shock protein 90B1
  – Mitochondrial SNPs positive (ND5 T12338C and tRNAser C7492T)
  – Abnormal AntiMullerian Hormone secretion

PCOS Diagnostic Requirement

Symptoms of high androgens
High Androgens on testing

There are multiple phenotypes
No cysts need to be seen on ultrasound, although usually are seen
New Groupings of PCOS

- **Traditional PCOS** -- anovulatory, increased androgens, no insulin resistance
- **Endocrine syndrome X** -- anovulatory, increased androgens, insulin resistance or type 2 diabetes
- **Non-traditional PCOS** -- anovulatory, normal androgens, obese, insulin resistant or type 2 diabetes
- **Non-traditional PCOS** -- ovulatory, increased androgens, mild insulin resistance
- **Idiopathic hirsutism** -- ovulatory, increased androgens, no insulin resistance

http://www.wdxyber.com/dxinf001.htm

2 Commonly Seen Variants

<table>
<thead>
<tr>
<th>Ovarian only</th>
<th>Ovarian &amp; Adrenal</th>
</tr>
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<tbody>
<tr>
<td>Leaner</td>
<td>Obesity</td>
</tr>
<tr>
<td>Less hyperinsulinemic</td>
<td>Hyperinsulinemic</td>
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<tr>
<td>Difficult infertility</td>
<td>Oligomenorrhea or regular cycles</td>
</tr>
<tr>
<td>High Testosterone, but normal DHEAS</td>
<td>High DHEAS &amp; Testosterone</td>
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</table>

Common signs and symptoms

- Overweight/Obese
- Acne
- Increase facial/body hair
- Oligomenorrhea
- Amenorrhea
- Infertility
- Family history
- Acanthosis
- Type 2 Diabetes
- Endometrial hyperplasia
- Menorrhagia
- Hypertension
- Reactive hypoglycemia
Remember it’s not only the ovary!

Acanthosis nigracans

Hirsutism

Remember that PCOS is a syndrome

Best Scenario
- Depigmentation
- Bowel function
- Easy weight gain
- Amenorrhea

Worst Scenario
- Obesity
- Gestational diabetes
- Hypertension
- Hypothyroidism
- Amenorrhea that results in hot flushes
The Ovary

PCOS Ovaries are Abnormal

- Increased testosterone producing stromal tissue
- Pearly, thick coated ovaries
- Enlarged ovaries

The Polycystic Ovary
Ovarian Component

- LH
- Theca cell
- Granulosa cell
- Testosterone
  - 5 alpha reductase
  - DHT
  - Aromatase
  - Estradiol

Bringing in the Adrenal Glands

- ACTH
- LH
- P450c17α
- DHEA(S)
- 11 beta HSD1
- Cortisol
  - 5 alpha reductase
  - Cortisone
  - Testosterone
  - DHT
  - aromatase
  - Estradiol
Anti-Mullerian Hormone

- AMH is expressed by Granulosa cells
- Starts around gestational 25th week – until menopause
- Expressed all steps of folliculogenesis
- Initiated in recruitment to preantral follicles
- Not expressed during FSH follicular growth
- Functions to inhibit FSH induced pre-antral follicle growth
- Regulates FSH sensitivity

Anti-Mullerian Hormone

- Higher serum AMH – intrinsic dysregulation of the granulosa cells
- Over expression of AMH receptors
- Androgens – due to thecal cells defects
- FSH stimulate AMH in small follicles but in larger follicles – increasing E2 production – FSH would inhibit AMH through negative feedback of E2
- AMH decreases FSH receptor expression but also ovarian aromatase expression – leads to the defect in ovulation when elevated
- LH stimulates AMH production
- LH reduces AMH Receptor II expression in normal ovaries; lack in PCOS ovaries
- AMH > 4.9 ng/mL
Prevention of PCOS

Pediatric Adrenal Gland → Adrenal Gland at Adrenarche → Adult Adrenal Gland

INSULIN

McCartney et al., 2007

Neurotransmitters and PCOS
Norepinephrine

- Higher levels found in PCOS marker or increases sympathetic nervous system activity
- PCOS patients have higher muscle sympathetic nerve activity, altered heart rate variability and heart rate after exercise.
- Tx: weight loss, low-freq electroacupuncture, Obstructive sleep apnea, renal denervation
• Expression of neurotransmitter receptors – 5HT1A, GABA-B1, D2R, and alpha1A receptors decreased; NMDA receptors increased.
• Alterations may change GnRH pulsatility

Free Fatty Acids Cause Altered Lipolysis

- Interfere with insulin signaling
- HPA axis disruption
- Sympathetic activation disturbed
- Insulin resistance
- Lower SHBG

HYPERINSULINEMIA
Hyperinsulinemia – Not high glucose

Labs to run on women with suspected PCOS

- E2
- Pg
- T
- DHEAS
- Cortisol
- Thyroid panel & TPO
- Fasting Insulin/glucose; 2 hour postprandial
- 17a-hydroxyprogesterone
- CBC/Chem screen
- Prolactin
- LH/FSH – day 3 of cycles
- CRP
Goals of Treatment

- Lower Androgens – testosterone and DHEAS
- Increase Sex Hormone Binding Globulin (SHBG)
- Normalize insulin resistance and hyperinsulinemia
- Optimize hormone balance overall
- Reduce inflammatory state

Conventional Medications

- Oral Contraceptives
- Spironolactone
- Metformin HCl
- Clomiphene
- Letrozole

Oral Contraceptives

- Choose: estrogenic, high progestogenic, low androgenic
- Oral contraceptives increase SHBG \(\rightarrow\) Free testosterone
- Benefits include
  - Changes in SHBG lasts unknown time after discontinuation of OBCP
  - Dec. skin/hair issues
  - Regulate cycles
- Risks
  - May worsen insulin sensitivity (not thought to be significant)
Best Choice

- Ethinyl Estradiol & Drospirenone
  - Drospirenone – spironolactone analogue with antimineralcorticoid. No estrogen, progesterone, testosterone or glucocorticoid-like activity.
  - Caution for adrenal insufficiency patients

- Other Top contenders: Tricyclics – Norgestimate and ethinyl estradiol

Spironolactone

- Blocks 5 alpha reductase
  - ↓ SHTP
  - Decrease ovarian and adrenal androgens
  - Has progestational effects
  - May cause high potassium & many drug interactions.
  - Dosage: 50-200mg po days 4-21; or 50mg BID po days 4-21.
  - 40% improvement in 6 months

Metformin

- ↓ carbohydrate absorption
- ↓ gluconeogenesis
- ↑ insulin sensitivity of skeletal muscle
- Reduces Ovarian P450c17alpha (CYP17)
- Benefit for lean and obese hyperinsulinemic, normal glucose women
- May improve weight loss success
- Reduce miscarriage; improve lactation
- Lower SHBG predicts benefits
- Dosage 500-1000 mg BID po. Some physicians are using it topically with great success
**Clomiphene citrate**

- May have up to 30\% up to 70\% success
- Estrogen antagonist \( \rightarrow \) stimulates \( \uparrow \) FSH \( \rightarrow \) \( \uparrow \) estradiol
- Maybe mixed agonist and antagonist
- Women are at increased risk for hyperstimulation of the ovaries (20\% multiples with gonadotropin injections)

**Glucocorticoid - Cortisol**

- Cortisol suppresses adrenal androgen production
- Decrease ACTH stimulation
- Dr Thatcher’s dosing
  - 0.25mg Prednisone (5mg hydrocortisone) nightly for up to 6 months.
  - 5mg Prednisone (15mg Hydrocortisone) days 2/3 to day 12/14 (Protocol with Clomid days 5-9).

**Natural Products to consider**

- Progesterone
- Chromium
- Gymnema sylvestre
- GABA
- Licorice
- Green Tea
- Flax seeds
- D-Chiro-Inositol/D-Pinitol/myo-inositol
- Vitamin D
- Calcium/Magnesium
- NAC
- Saw Palmetto
Insulin Sensitizing

- Chromium 200mcg – 500mcg QD-TID cc
- Gymnema sylvestre
- Berberine
- Inositol

Berberine

- Has been studied in type 2 DM
- Similar effect to metformin
- Decreases insulin and glucose and HgbA1c – Activates AMPK (regulating metabolism)
- Anti-inflammatory, antibiotic and androgen inhibition
- Dosage: 500 QD-BID

D-Chiro-Inositol

- Deficiency may be cause of PCOS
  - D-chiro-inositol allows the cell to appropriately process glucose.
- From lecithin, fruits and vegetables
- Dec. insulin resistance, lipids, HTN
- 86% ovulated
- Dosage 1200mg po QD
- Limited availability – Varying dosages
D-Pinitol

- 3-O-methyl-D-chiro-inositol
- Converted to d-chiro-inositol in the body
- 1-2 capsules BIDcc – 600mg/capsul

Myo-Inositol

- Myo-inositol levels in follicular fluid is associated with good oocyte quality.
- 2000mg (2g) myo-inositol + 400ug BID x 3 months vs 400 ug BID control
- Follicles > 15mm; visible, retrieved were significantly higher, average number of embryos and transfer quality. Reduced immature oocytes as well.

Myo-inositol vs Metformin

- Women with PCOS – alone and in combo with r-FSH).
- 120 women – metformin 1500mg/day or 4gms myo-inositol.
- Metformin – 50% spontaneous ovulation; 18% of these became pregnant. An additional 11 women received pregnancy with rFSH. Total pregnancy rate 36.6%
- Myo-inositol – 65% spontaneous ovulation; 30% pregnancy. 38 women also given rFSH – additional 11 women became pregnancy. Total pregnancy rate 48.4%.
Myo-inositol on PCOS

• 12 weeks of MYO – LH, prolactin, testosterone, insulin and LH/FSH are all reduced.
• Glucose-insulin ratio and HOMA reduced
• Menstrual cycle restoration

Myo-inositol

• Italian Study
• Phase IV clinical trial – comparing DCI vs MI for IVF.
• DCI 1.2mgs vs 4gm/days MI

• Italy – inofolic and inofolic plus – Myo-inositol + folic acid + melatonin. 4gms/day MI; 3mg melatonin.
• Study with 46 women who had failed IVF.
• Number of eggs the same; but quality of embryos and total embryos were statistically available.
• 13 pregnancy – 9 maintained.
Myo-inositol vs D-chiro-inositol in intracytoplasmic sperm injection
• PCOS patients – euglycemic.
• 84 women doing ICSI – 2 groups – 2gms BID vs 0.6 gms BID.
• Number of eggs same.
• Mature oocytes significantly higher in MI
• Less immature oocytes w/ MI
• MI – higher top quality embryos and number of pregnancies.
• MI was better than DCI

Myo-inositol
• Other studies
  – Irregular periods
  – Irregular menstruation
  – Gestational diabetes
  – Moods swings associated with PCOS
  – Post-menopausal women with metabolic syndrome
  – Decreasing neural tube defects

• Saw Palmetto – 350mg per day
  – 5 alpha reductase inhibition – dec. DHT
  – Inhibits DHT receptor binding
  – Promotes DHT metabolism
  – (nettles/green tea

• N-acetyl Cysteine
  – 1.8 gms per day po (start low and work up)
  – Improved peripheral insulin sensitivity
  – Only helped hyperinsulinemic patients
  – May improve clomid success
Adrenal Support

- Improve Cortisol – dec ACTH
- Licorice
  - Inhibits 11 beta-hydroxysteroid dehydrogenase thus maintaining cortisol ½ life
  - Reduces ACTH feedback
  - Reduces adrenal hyperandrogenism

Progesterone

- Inhibits 11 beta-hydroxysteroid dehydrogenase
- Regulate menstrual cycles
- Aromatase inhibition
- Oppose estrogen dominance

Maitake Mushroom

- Induces insulin sensitivity
- 79% ovulation with Maitake vs 93% Clomiphene. (80 women)
- Only 1 woman who failed either treatment did not ovulate with a combination treatment
  - Chen et al. 2010
Calcium and Vitamin D

– Needed for healthy follicular development
– Vitamin D – improve insulin resistance and secretion
– Dosage – as appropriate to correct deficiency
  • Minimum 1200 IU (1 TBSP Cod liver oil)

– Thys-Jacobs et al. 1999 found 2/13 women became pregnant; 7/13 regular periods were established; 2/13 had normalization of DUB within 2 months.

• Increase SHBG
  – Flax Seeds
  – Green Tea
    • Also lipolytic
    • Inhibit 5 alpha reductase
    • Study showed that weight loss was increased

Surgical Options

• Ovarian Wedge Resection
• Ovarian Drilling – preferred option
  – Maintains more ovarian tissue
  – Ovary remains responsive to stimulation
  – Ovulation success is 53-92% (Sanzel, 1989; Gjonnaess, 1984)
  – 37-86% pregnancy success
Common Conventional Treatments

- Ovarian Drilling
  - 4-20 holes are inserted into both ovaries
  - Goal is to remove the testosterone producing stroma tissue
  - 53-92% ovulation
  - 37-86% pregnancy

Clinical Case #1

- 25 year old woman presenting with acne
- Hx
  - acne with weight gain (age 15) despite exercise
  - irregular periods ~ about 3 per year
  - Wants to get pregnant, but also get healthier
  - Fatigue 9/10
- PE – patient overweight 5’5”, 200lbs. Moderate hirsutism on face, periareolar, lower abdomen, and thighs. BP 165/85
- Oily skin, cystic acne, abdominal weight distribution, 2+ pitting edema.

- Labs –
  - E2 2.2
  - Pfg 9 L
  - T 86 VH
  - DHEAS 25 VH
  - C1 2.3 L
  - C2 1.0 L
  - C3 0.9 H
  - C4 1.0 HN
  - T4 0.9 L
  - T3 1.6 L
  - TSH 4.5 H
  - TPO 378 H

Saliva test results
Adrenal + Ovarian PCOS with Adrenal dysfunction
Sub-clinical hypothyroidism and Hashimotos
### Treatment
- Zone diet – Barry Sears; eat 1 tbsp ground flax QD
- T4 100mcg QD; T3 5mcg QD
- Adrenal support formula 2 caps TID
  - B vit, licorice, ginseng, ashwagandha, astragalus, vitamin C
- Chromium 200 mcg BID-TID depending on meals
- Serenoa repens 750mg BID
- Inositol 4 gms in divided dosages
- Progesterone 20mg QD topically days 15-26
- Selenium 400mcg QD

### Acne improved
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<table>
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<tr>
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<tbody>
<tr>
<td>E2</td>
<td>2.1 N</td>
</tr>
<tr>
<td>Pg</td>
<td>500 N</td>
</tr>
<tr>
<td>T</td>
<td>55 HN (previous level 86)</td>
</tr>
<tr>
<td>D</td>
<td>14 H (previous level 25)</td>
</tr>
<tr>
<td>C</td>
<td>6.0</td>
</tr>
<tr>
<td>C2</td>
<td>3.2</td>
</tr>
<tr>
<td>C3</td>
<td>0.8</td>
</tr>
<tr>
<td>C4</td>
<td>0.2</td>
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Normalization of the circadian rhythm

### Alison’s Absolutes
- Lifestyle – low carb; higher protein diet
- SLEEP
- Inositol
- Berberine OR Metformin
- Adrenal support including licorice (HTN caution)
Resources

• The Natural Diet Solution for PCOS and Infertility by Nancy Dunne, ND
• PCOS the Hidden Epidemic by Samuel Thatcher, MD, PhD.

Thank you
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