The Nuts and Bolts of Polycystic Ovary Syndrome

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Learning Objectives

• Identify the diagnostic criteria for PCOS
• Identify risk factors that place PCOS women at high risk for cardiometabolic disturbances
• Select the best diagnostic test to document anovulatory bleeding in females with clinical findings suggestive of PCOS
• Highlight the key investigations of both reproductive & cardiometabolic features of PCOS
• Discuss management of menstrual, cutaneous & metabolic abnormalities in PCOS
Background

• Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, affecting approximately 6% - 15% of adult women\textsuperscript{1,2}

\textsuperscript{1}Knochenhauer et al JCEM 1998
\textsuperscript{2}Azziz et al JCEM 2004
\textsuperscript{3}Dumesic DA et al. Endocr Rev 2015
Characterized clinically by **oligomenorrhea** and **hyperandrogenism**

- **Three** different **diagnostic criteria** for PCOS, which presents up to 10 possible PCOS phenotypes:

<table>
<thead>
<tr>
<th>NIH consensus criteria, 1990 (all required)</th>
<th>Rotterdam criteria, 2003 (two out of three required)*</th>
<th>AES definition, 2008 (all required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and/or biochemical signs of hyperandrogenism</td>
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</tr>
<tr>
<td>Menstrual irregularity due to oligo- or anovulation</td>
<td>Oligo- or anovulation</td>
<td>Ovarian dysfunction – oligo- anovulation and/or polycystic ovaries on ultrasound</td>
</tr>
<tr>
<td>Exclusion of other disorders: NCCAH, androgen-secreting tumors</td>
<td>Polycystic ovaries (by ultrasound)</td>
<td>Exclusion of other androgen excess or ovulatory disorders</td>
</tr>
</tbody>
</table>

* Rotterdam criteria based upon a 2003 consensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine consensus workshop group).
Background

- PCOS is associated with obesity (30-75%), problems with glucose regulation, dyslipidemia, hypertension, sleep apnea and cardiac dysfunction

- Hyperinsulinemia/insulin resistance with or without obesity is an integral component of PCOS with heightened risk of type 2 diabetes

- Controversy continues whether or not cardiovascular disease (CVD) is increased in PCOS
Origins of PCOS
The “Two Hit” Hypothesis

• Genetic or epigenetic factors reset reproductive and metabolic trajectories in early life, while

• Factors later in life influence the severity of the adult PCOS phenotype
  ▫ Nutrition
  ▫ Ethnicity/race
  ▫ Other environmental influences

¹Dumesic et al Rev Endocr Metab Disord 2007
The First Hit
Genetic or Epigenetic Factors

- Heritability
  - Twin studies show a strong genetic contribution to PCOS\(^1\)
  - Several genes implicated with PCOS, each contributing a moderate effect\(^2,3\)
  - Increased prevalence of PCOS in mothers (8-24%) and sisters (16-32%) of PCOS probands\(^4-6\)

South Asians and Caribbean-Hispanic women with PCOS are more insulin resistant than affected women in other ethnic groups.
Impact of Lifestyle

- **Obesity** influences PCOS phenotype by unmasking or amplifying symptoms of hyperinsulinemia and hyperandrogenism.

- \(\downarrow FSH \quad \downarrow \text{follicle maturation} \quad \rightarrow \text{anovulation}\)

- \(\uparrow LH \quad \rightarrow \uparrow \text{P450c17} \quad \rightarrow \uparrow \text{androgens (ov/adrenal)}\)

- \(\uparrow \text{Insulin} \quad \rightarrow \downarrow \text{SHBG} \quad \rightarrow \uparrow \text{Free T}\)

- **Signs of androgen excess**

- \(\uparrow \text{DHT}\)
PCOS Pathogenesis

Key:
- SHBG: Sex-hormone binding globulin
- LH: Luteinizing hormone
- FSH: Follicle stimulating hormone
- ACTH: Adrenal corticotrophic hormone
- GnRH: Gonadotropin releasing hormone
- DHEAS: Dehydroepiandrosterone sulphate

- Virilization
- Anovulation
- Acne
- Hirsutism
- Infertility
Environmental

• Bisphenol A
  ▫ Widely used estrogenic industrial plasticizer
  ▫ Excreted in urine & detectable in 92% of American’s urine specimens
  ▫ Elevated in PCOS women
  ▫ Displaces androgen from testosterone’s binding protein (SHBG) to increase androgen availability
  ▫ Enhances ovarian androgen production
PCOS Characteristics

- **Endocrine Disturbances**
  - Oligo- or amenorrhea / oligo- or anovulation
  - Hyperandrogenism
    - Hirsutism
    - Acne
    - Alopecia
  - PCO morphology
  - ↓ fertility

- **Metabolic Disturbances**
  - Obesity
  - Insulin resistance
    - Impaired glucose tolerance (IGT)
    - Type 2 diabetes mellitus
  - Dyslipidemia
  - Hypertension
  - Obstructive sleep apnea
  - ?CVD
Endocrine Disturbances

- Oligo- or amenorrhea
  - Menstrual cycle frequency < 8 cycles/year

- Hyperandrogenism
  - Hirsutism in a male pattern
  - Acne
  - Alopecia in a male pattern
PCO Morphology

- Presence of >10-12 follicles/cysts and 2-8 mm in diameter that are peripherally arranged in a “string of pearls” appearance

and/or

- Increased ovarian volume (>10mL or cm³)

- Does not apply to females taking OCPs
Ferriman-Gallwey Scoring of Hirsutism

- Hirsutism = excessive growth of facial or body hair, specifically terminal hair (long, coarse and pigmented), in an androgen-dependent/male pattern in women

- F-G score ≥ 6-8 defines hirsutism

Yildiz Nat Clin Prac Endo & Metab 2008
Differential and Work-up for PCOS

- ✓ TSH
- ✓ Prolactin (PRL)

✓ Total and free Testosterone (T) and DHEA-S

Evaluate for Hypothyroidism (↑TSH) and Hyperprolactinemia

Evaluate for PCOS

- ↑ Total/free T and DHEA-S or
- Hirsutism and/or significant acne and
- Normal TSH, PRL, 17-OHP
- Consider pelvic ultrasound if labs are normal and there is a history of primary amenorrhea

History of primary amenorrhea without significant clinical hyperandrogenemia?

✓ LH and FSH; if normal & prior labs are normal, consider pelvic ultrasound

Evaluate for gonadal failure (↑LH and FSH)

Define internal anatomy or structural abnormality:

- Ovarian size (>10cm³ c/w PCO)
- Uterine length (>3.5-7 cm is pubertal, 7-8 cm is adult)
- Presence of peripheral cysts/multiple follicles
- Endometrial stripe thickness
## Work-up of PCOS

<table>
<thead>
<tr>
<th>Clinical signs of virilization?</th>
<th>Clinical signs of Cushing’s syndrome?</th>
<th>History of irregular menses and early pubic hair development?</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Total/free T and DHEA-S</td>
<td>✓ 24-hour urine for free cortisol (UFC) and correct for patient’s BSA</td>
<td>✓17-OH Progesterone (17-OHP)</td>
</tr>
</tbody>
</table>

### Evaluate for virilizing tumor
- If above hormones are ~2x normal, consider CT/MRI of adrenals +/- pelvic US

### Evaluate for Cushing’s syndrome
- If UFC is elevated, refer to Endo for dexamethasone depression test

### Evaluate for Non-Classical CAH (NC-CAH)
- If 17-OHP elevated, refer to Endo for ACTH stimulation test
Steps in PCOS Work-up

- Evaluate for clinical/hormonal criteria for PCOS
- R/o other causes of hyperandrogenism & oligomenorrhea
- Next, consider documenting anovulatory bleeding (if oligomenorrhea)
  - Measure fasting morning progesterone level 3 weeks after her LMP
  - If low (<10 ng/mL), ovulation has not likely occurred
Association With Metabolic Syndrome (MetS)

• Various definitions or criteria exist but generally include:
  ▫ Increased waist circumference
  ▫ Elevated glucose (fasting or post-prandial)
  ▫ Elevated triglycerides and/or low HDL
  ▫ Elevated blood pressure

• MetS is 2.5-4x more common in women with PCOS than in general population¹

• The odds of adolescent girls with PCOS having MetS is 4.5-6x higher than that of girls in the normal population¹ (after adjusting for BMI)

¹Behboudi-Gandevani S et al Clin Endocrinol 2017
Metabolic and CV Disease Risk

• **High risk** in all PCOS patients with:
  ▫ MetS
  ▫ Type 2 diabetes mellitus
  ▫ Known CV or kidney disease

• **At risk** in PCOS patients with:
  ▫ Obesity
  ▫ Smoking
  ▫ Dyslipidemia
  ▫ HTN
  ▫ Impaired glucose tolerance
Key Risk Factors to Assess

- BMI
- Blood pressure
- Baseline fasting lipid profile, especially if +FHx of hyperlipidemia
- If BMI >27 kg/m², 75 g oral glucose tolerance test (OGTT)
- Mood disturbances: depression, abnormal eating patterns and reduced QOL
Long-Term Treatment Goals For Patients With PCOS

• Suppress androgen production and action

• Regular menstrual shedding of the endometrium in women not desiring pregnancy, to decrease the risk of developing endometrial hyperplasia

• Promote fertility/ovulation in those desiring pregnancy
Long-Term Treatment of PCOS Patients With Metabolic Syndrome

• **Lifestyle modification** (diet + exercise +/- behavioral therapy) is the first-line therapy

• 3-6 months in a formal exercise program resulted in:
  - Reductions in BMI, waist circumference, BP\(^1\), HDL and TGs\(^2,4\)
  - Increased insulin sensitivity\(^3,4\)
  - Improved menses, ovulation, pregnancy rate\(^5\)
  - Improved VO\(_{2\text{max}}\)^2 and aerobic fitness\(^3\)

Long-Term Treatment of Patients With PCOS and Metabolic Syndrome

- Add-on medication often includes **metformin** if there is mild/moderate obesity with:
  - impaired fasting glucose or impaired glucose tolerance
  - signs of insulin resistance such as skin tags or acanthosis nigricans
  - marked hyperlipidemia
  - contraindication to OCP use
Metformin

- Improves the effectiveness of insulin produced by the body
- Beneficial for metabolic/glycemic abnormalities and for improving menstrual irregularities
- SEs: nausea, abdominal pain, diarrhea; lactic acidosis (rare)
- It has limited benefit in treating hirsutism, acne, or infertility
Exercise + Diet + Metformin

48 week intervention → Ovulation and androgen concentrations
A) Metformin 850 mg BID
B) Lifestyle modification + Metformin
C) Lifestyle modification + placebo
D) Placebo only

Results
- ↓ circulating androgens only in the combo (B) group
- No difference in ovulation rates among groups but was strongly associated with weight loss

Hoeger K et al Fertility and Sterility 2004
Exercise + Diet + Metformin

6 months of 150 min/wk exercise combined with low-calorie diet plus:
A) Metformin 500-2000 mg per day
B) Placebo only

Results
- ↓ circulating testosterone at 4 months with no group differences
- No difference in ovulation rates
- Weight decreased at all points in both groups, no group differences
- Metformin + lifestyle added little reproductive or glycemic benefit

Ladson G et al Fertility and Sterility 2011
Long-Term Treatment of Patients With PCOS and Acne/Hirsutism

- **OCPs** are the 1st line tx of hirsutism & acne in women with PCOS, 6 month trial recommended.

- Effect can be potentiated when combined with **spironolactone**, a peripheral androgen receptor blocker (50-100 mg BID)
  - SE: hyperkalemia, risk of feminizing a male fetus if used in pregnancy, menstrual dysfunction
  - Because of the latter two reasons, it is recommended that an OCP be used in combo

Alpañés M et al Eur J Endocrinol 2017
Actions of OCPs

**Progestin**
- Inhibits ovulation by **suppressing LH** from the pituitary
- Androgenic potential, especially 1\textsuperscript{st} and 2\textsuperscript{nd} generation progestins
- Creates thick cervical mucus that slows sperm transport

**Estrogen**
- Inhibits ovulation by suppressing FSH which inhibits follicle development and **suppresses LH surge**
- Increases SHBG levels
- Accelerates ovum transport which decreases fertilization time
Actions of OCPs in PCOS Treatment

Key:
- SHBG: Sex-hormone binding globulin
- LH: Luteinizing hormone
- FSH: Follicle stimulating hormone
- ACTH: Adrenal corticotrophic hormone
- GnRH: Gonadotropin releasing hormone
- DHEAS: Dehydroepiandrosterone sulphate

- Virilization
- Anovulation
- Acne
- Hirsutism
- Infertility
Impact of OCPs

Side effects:
- Abnormal menstrual bleeding, nausea, breast tenderness, headache, mood changes
- No association with weight gain

Absolute contraindications:
- Smoker > age 35
- HTN (SBP ≥ 160 mmHg, DBP ≥ 100 mmHg)
- History of or current VTE
- Migraine with focal neurological symptoms
- Known thrombogenic mutations (ex. Factor V Leiden, etc)
- History of stroke, ischemic heart disease, complicated valvular heart disease

\(^1\)Gallo MF et al 2011 Cochrane Review
OCP Use and Related Health Concerns

- **Glucose metabolism**
  - Some studies indicate impairment of glucose tolerance during OCP use
  - Meta analysis revealed not enough data to make conclusions about risk

- **Lipid metabolism**
  - Increase in HDL and triglycerides

- **Thromboembolism**
  - No conclusive data in women with PCOS
  - General OCP users have 3-4x risk for VTE
  - Risk is estrogen dose-dependent and risk decreases after 1 yr of use

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Preferred OCPs for PCOS

- **3rd generation OCPs**
  - Desogestrel: Kariva, Ortho-Cept/Desogen
  - Norgestimate: Ortho-Cyclen, Sprintec

- **4th generation OCPs**
  - Drospirenone: Yaz (Gianvi, Loryna), Yasmin (Ocella, Syeda, Zarah), Beyaz and Safyral

  - Caution given two studies reporting 2-3x greater risk of VTE than levonorgestrel-containing pills (2nd generation)
Acne In PCOS

• In general, OCPs are shown to be effective treatment for acne

• Two studies compared OCP vs. placebo for 6 cycles\textsuperscript{1,2}
  • Total, inflammatory and non-inflammatory lesions improved with OCP

• One study compared OCP vs. metformin x 12 months\textsuperscript{3}
  ▫ Both treatments were equally effective

\textsuperscript{1}\textit{Maloyney et al 2008}, \textsuperscript{2}\textit{Koltun et al 2008}, \textsuperscript{3}\textit{Harborne et al JCEM 2003}
**Hirsutism In PCOS**

- **Vaniqa 13.9% cream** (eflornithine)- inhibition of topical hair growth by inhibiting the enzyme needed for hair growth (treat BID x 8 weeks)
  - SEs: rash, stinging, redness, acne

- Temporary cosmetic strategies (bleaching, shaving, waxing, etc)
  - SEs: painful, erythema, scarring

- Mechanical methods of hair removal (laser, electrolysis)
  - SEs: expensive but efficient, scarring, dyspigmentation
Other Metabolic and Mood Co-Morbidities

- Dyslipidemia
- Glucose abnormalities
- Hypertension
- Mood disturbances including depression and anxiety
Dyslipidemia in Obesity & PCOS

- Combined dyslipidemia pattern:
  - **Mild elevation in LDL**
    - Increased intake of simple carbs drives hepatic production of VLDL, which can cause increased LDL in some
  - **Moderate-severe elevation in TG**
    - More FFAs delivered to liver from expanded adipose tissue
  - **Low HDL**
    - Reduced lipolysis
  - **Mild elevation in Total Cholesterol**
Dyslipidemia Risk factors

- +FHx
  - MI, angina, CABG or PCI, sudden cardiac death
  - Parent, grandparent, aunt, uncle
  - <55 yo for males, <65 yo for females
- HTN that requires drug therapy
- Smoking
- BMI ≥ 25 kg/m²
- Presence of high-risk condition (such as T1DM/T2DM)
**Statins**

- HMG-CoA reductase inhibitors
  - Inhibits cholesterol synthesis in hepatic cells
- Lowers LDL, some decrease in TGs, modest increase in HDL
- FDA approved for ages 10-18
  - Postmenarcheal
  - Pravastatin approved ≥ age 8
- Magnitude of effect is specific to dose
- SEs: elevated liver enzymes, myopathy, rhabdomyolysis
Statins

• Short-term safety and efficacy data is positive

• Risk during pregnancy
  ▫ Cholesterol is critical for embryonic cell signaling & production of steroid hormones
  ▫ 2004 review of FDA reports of statin exposure during pregnancy
    • 214 pregnancies
    • 70 were evaluable
    • 31 had adverse outcomes
      • 22 structural defects – severe midline CNS, limb, VACTERL
      • 4 IUGR
      • 5 IUFD
Hypertriglycerideridemia

- **>500-1000 mg/dL** = risk for pancreatitis
  - Limit dietary fats
  - Start fish oil, max 4g/day; fibrates or niacin are additional options with greater side effects

- **150-499 mg/dL**
  - May be a role for fish oil here
  - Reduce simple sugar intake (sweetened beverages, cereals, baked goods)
Initial Treatment of Hypertriglyceridemia

- 25-30% calories from fat, ≤ 7% from saturated fat
- Cholesterol<200 mg/d
- **Decrease sugar intake**
  - Replace simple sugar with complex carbs
  - No sugar-sweetened beverages
- **Increase dietary fish to increase omega-3 fatty acids**; supplements:
  - 1000 mg of DHA and EPA
  - Side effects = indigestion, gas
  - Mechanism not well-understood
PCOS Management Goals

• Provide expectations of various therapies, risks/benefits and side effects

• Arrange follow-up visit in 4-6 months to review lifestyle and symptom progress, assess side effects and advise further management

• Set realistic goals to permit an individualized strategy

Dumesic Patient-Centered Management of Hirsutism 2011
Thank You!