Polycystic Ovarian Syndrome (PCOS)

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PCOS: Looking back at history…
1935

*American Journal of Obstetrics and Gynecology*

*Stein Leventhal Syndrome*

- 7 cases of women with:
  - amenorrhea
  - fertility issues

→ completed ovarian wedge resections after failed medical therapy
  1) Resumption of monthly cycles in all cases.
  2) One pregnancy after surgery.

→ Proposed that the ovarian changes occurred due to hormonal stimulation.

What is PCOS?

- Described initially with focus on the ovary and phenotypic characteristics seen in these cohorts – hair growth, masculine features, obesity – but endocrine disruption was thought to cause the manifestations of the condition.
**PCOS...AKA**

- Stein Leventhal Syndrome
- Polycystic Ovary Syndrome
- Syndrome “O” (Ovarian Confusion and over nourishment)
- Syndrome XX
- Metabolic Reproductive Syndrome

**Background**

- PCOS affects 5-15%* of women of childbearing age.
- PCOS is the most common endocrine disorder.
- PCOS is a syndrome and not a disease.
- PCOS describes a heterogeneous group of women, making one consistent diagnosis a challenge.
- Definition has evolved over time.

**Background**

- Genetic and environmental factors contribute to the pathophysiology and clinical manifestations.
- PCOS is not cured but instead requires management of symptoms, risk factors, and comorbidities.
- There may be different symptoms through a woman’s lifetime, adding to the difficulty in diagnosis and management.
- There is much still to be learned about PCOS, adding to treatment challenges.

**Background**

- Based on the NIH 2012 workshop report:
  - PCOS affects about 5 million reproductive-aged females in the United States.
  - Cost to the healthcare system for diagnosing and treating PCOS was approximate $4 billion annually not including the cost of serious comorbidities.
Group effort

- PCOS may be managed by many different medical specialties
  - Pediatricians/Internists/Family practice
  - Dermatologists
  - OB/GYN, reproductive endocrinologists
  - Endocrinologists
  - Psychologists, Psychiatrists
  - Nutritionist, Weight management centers

Pathology

- The pathogenesis of PCOS is not fully understood.
- There is some evidence of a polygenic component.
- Insulin resistance is an important element in the development of PCOS but there are complex interactions involving many systems.

Pathology

- Disordered gonadotropin secretion?
- Primary ovarian/adrenal hyperandrogenism?
- Disordered insulin sensitivity?

→ Multiple levels of dysfunction with interactions between them
Pathology

Androgen exposure
- Change in distribution of adipose tissue?
- Larger adipose cells?

Diagnosis

- Diagnostic criteria has changed and evolved over time
- Many different professional medical groups have offered guidelines
### Diagnostic Criteria

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Polycystic ovaries by ultrasound</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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</table>

**Exclusion of other pathology**

### Differential Dx in PCOS

- Congenital adrenal hyperplasia
- Androgen secreting tumor (ovary, adrenal)
- Idiopathic Hyperandrogenism
- Idiopathic Hirsutism
- Syndromes of Severe Insulin Resistance
- Hyperprolactinemia
- Thyroid Abnormalities
- Cushing’s Syndrome
- Androgenic Anabolic Steroid Usage
- Other Medications Usage: Danazol, Phenothiazines, Corticotropin or ACTH analogues, Valproate

### International PCOS Network Guidelines 2018

**Rotterdam Criteria**

1. Irregular cycles/ovulatory dysfunction
2. Biochemical hyperandrogenism or clinical hyperandrogenism
3. Polycystic ovarian morphology by ultrasound

### PCO Morphology

**Ultrasound:**

- Subjective with reader variability and requires an experienced ultrasonographer and radiologist.
- Not specific: Polycystic ovaries may be present in up to 25% of unaffected women.
PCO Morphology

Images courtesy of Dr. Michael Blumenfeld

PCOS Hyperandrogenic symptoms

• Hirsutism:
  • Excessive growth of androgen-dependent terminal hair typically appearing in a male growth pattern in females
  - Hypertrichosis: any excess hair growth (vellus or terminal) that can occur all over the body (hereditary or medication side effect).

Ferriman–Gallwey score

PCOS Hyperandrogenic symptoms

• Male pattern hair loss
**PCOS Hyperandrogenic symptoms**

- Acne – persistent into adulthood, different parts of the body, oily skin

**PCOS and obesity**

- Reproductive disturbances more common in obese women regardless of the diagnosis of PCOS.
- Risk of anovulatory infertility increases at a BMI > 24 kg/m² or higher.
- Weight reduction can restore regular menstrual cycles in these women.

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**Not all obese women have PCOS**

- Majority of obese women do not develop hyperandrogenism and do not have PCOS.
- Non PCOS obese may have increased androgen production (esp w/upper-body obesity) but clearance is also increased = no net change
- In PCOS, bioavailable androgen levels are increased

**Obesity is not a diagnostic criteria for PCOS**

**PCOS Heterogeneity Spectrum of severity**

Lean ------------------------------------------ Obese

Triggers:
- Abdominal obesity
- Environment

Androgens

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BMI

Ovulation
### Evaluation

- History and exam
- Metabolic parameters
- Appropriate screening and counseling

<table>
<thead>
<tr>
<th>Physical</th>
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<tbody>
<tr>
<td>Vitals (BP, BMI, waist circumference)</td>
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<tr>
<td>Cutaneous manifestations (acne, hirsutism, acanthosis, skin tags)</td>
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<tr>
<td>General exam</td>
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<tr>
<td>May require pelvic exam (GYN)</td>
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</table>

### Laboratory

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<thead>
<tr>
<th>Laboratory</th>
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<tbody>
<tr>
<td>Pregnancy test</td>
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<tr>
<td>Gonadotropins (high LH or LH:FSH ratio &gt;2-2.5)*</td>
</tr>
<tr>
<td>Prolactin, Thyroid (TSH)</td>
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<tr>
<td>Androgens (Testosterone**, DHEA-s)</td>
</tr>
<tr>
<td>Adrenal steroids (excess cortisol, 17-OHP)</td>
</tr>
<tr>
<td>AMH***</td>
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<tr>
<td>Glycemic evaluation: fasting glucose, Hemoglobin A1c, 2-hr glucose tolerance</td>
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<tr>
<td>Fasting lipids</td>
</tr>
<tr>
<td>Hepatic function (fatty liver)</td>
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<tr>
<td>Renal function (for treatment)</td>
</tr>
<tr>
<td>Disorder</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Prolactin excess</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
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<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
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<tbody>
<tr>
<td>Primary ovarian insufficiency</td>
<td>FSH, estradiol</td>
</tr>
<tr>
<td>Androgen secreting tumor</td>
<td>Testosterone, DHEA-s (ultrasound, MRI adrenals)</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>24 hr urine cortisol, late night salivary cortisol, dex suppression</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>IGF-1</td>
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**Treatment**

**MY PCOS**

- Metabolic
- cYcle control
- Psychosocial
- Cosmetic
- Ovulation
- Sleep apnea

**Metabolic treatment**
PCOS and exercise

**Suggestions**

- Moderate intensity aerobic activity for 30 mins x 5 days/week (brisk walking)
- Vigorous intensity aerobic activity for 20 mins x 3 days/week (jogging)
- Resistance training on 2 nonconsecutive days/week

Lifestyle

**Nutrition**

- Irrespective of caloric restriction, overall there is no uniform evidence that any unique type of diet optimizes weight loss or reproductive or metabolic changes in women with PCOS.
- In obese women with PCOS any type of tolerable hypocaloric diet which can be maintained long-term should be used.
- Meta-analyses of studies with exercise show additional benefits to body composition, hyperandrogenism, and insulin resistance.

Lifestyle support

- Nutrition/dietary counseling
- Exercise program or wellness centers, personal trainers
- Technology – online weight loss programs or smart phone applications with food logging and support groups.

Medications

**Metformin**

- Most popular, cheap (free), safe
- Decreased hepatic glucose production and intestinal glucose absorption, improved peripheral glucose uptake
- 1.5-2.5 grams per day, 1-2 g/day if XR; divided doses with meals
- Dose response present
- SE: Nausea, diarrhea
- Pregnancy: Increased live births, reduced GDM, not teratogenic
- Not used with reduce creatinine clearance
- Reduced androgens and some studies show improved menstrual cycling
- Medium weight loss benefit
- Vs OCPs: Blunting of BMI gains; pro-fibrinolytic (anti-thrombotic)
### Medications

**Thiazolidinedione**
- PPAR-gamma agonist to reduce insulin resistance
- Pioglitazone 15-45mg.
- Contraindicated: Pregnancy, CHF, peripheral edema
- SE: weight gain, edema (rare: bladder cancer, fracture)
- Reduces insulin levels but weight gain and lack of impact on hyperandrogen related symptoms makes this less optimal of a choice.
- Small cohorts with reduced DHEA-s and increased SHBG, improved menstrual regularity.

**Liraglutide**
- GLP-1 receptor agonist (stimulates insulin secretion, central appetite suppression, reduces glucagon secretion, slows intestinal glucose absorption)
- 1.2-1.8 mcg/day (3.0 mg/day) subcutaneous injection; dose responsive.
- Contraindicated: pregnancy, MTC, MEN2, pancreatitis, gastroparesis
- SE: Nausea, vomiting, headache (rare is intractable N/V)
- Greatest weight loss potential of drugs used with PCOS

**Liraglutide (continued)**
- Reduced visceral adiposity, reduced serum testosterone
- Pre-conception therapy – some data for improved IVF pregnancy rates (even without weight difference in MET vs LIRA groups)
- Unknown genetic variability in the GLP-1 receptor likely affects response
- Cost may be barrier
- Other drugs: exenatide, class effect with the weekly formulations?

**Orlistat**
- Blocks fat absorption, 120mg TID with fat restriction, GI side effects, medium weight loss benefit

**Acarbose**
- Delayed glucose absorption, 50-100mg TID with food, GI side effects, medium weight loss benefit

**Phentermine or Phentermine/topiramate**
- Used in obesity practices, unclear if any difference in PCOS population. Short term use only.

**Sibutramine**
- Weight loss, improved insulin resistance, lowered triglycerides and free testosterone but increased BP and HR.
Surgery

- Bariatric surgery has been shown to be effective as with all cases of obesity.
- Option in those without success from long term diet strategies
- BMI > 40 or BMI > 35 with obesity related condition

Cardiovascular risk reduction

- Cholesterol lowering drugs
  - LDL > 160 (non-HDL > 190)
  - LDL > 130 with 2 risk factors
  - Aggressive LDL reduction (<70-100) if high risk (MBS, T2DM, overt vascular/renal disease)

- Only statins studied in PCOS patients
  - ↓ LDL, IR, inflammation, Testosterone
  - Contraception needed

Cardiovascular risk reduction

- Antihypertensives
  - Recommended if BP >140/90
  - Ideally BP < 120/80

- Optimal regimen not clear

- ACE/ARB, diuretics, b-blockers all require contraception

Cycle regulation

- Cycle control
- Endometrial hyperplasia risk assessment
- Hormonal therapies
  - Combined estrogen-progestin therapy
  - Cyclic progestin therapy (1-3 months)
Hormonal therapy

- Oral Contraceptives
  - Recommended if menstrual cycle > 3 months to avoid endometrial hyperplasia and cancer
  - Suppression of ovarian androgen production and increasing SHBG.
- Results: regulation of menstrual cycles, improved androgenic symptoms.
  - Effective in improving hirsutism (60-100% of patients).

Hormonal therapy

- Oral contraceptives recommended due to more data
- Combination therapy with estrogen and progestin compounds.
- Limited data investigating the efficacy of different formulations, but there currently is no consensus on preferred agents.

Psychosocial

Supportive care
  - Acknowledge psychosocial impact
  - Screening for depression, anxiety or other mood or eating disorders
  - Referral for psychology or psychiatric consultation

Cosmetic

- Hirsutism: shaving, tweezing, waxing, chemical removal, bleaching
- Medications: OCPs, Antiandrogens, topical.
  - Antiandrogen after 6 months
  - minoxidil (OTC) for androgenetic alopecia
- Dermatologic: laser therapy, electrolysis
Ovulation

- Ovulation
  - Fertility/pregnancy goals – immediate and long term
  - Encourage TLC
  - Metformin – data mixed but improves regularity
  - Reproductive endocrinology referral if indicated

- Emphasize that pregnancy is not impossible and may still occur spontaneously

Sleep

- Sleep apnea
  - Screening tools (STOP-BANG, Epworth Sleepiness scale)
  - Refer for sleep study

- Sleep quality

Medications in PCOS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Menstrual regularity</th>
<th>Androgen level</th>
<th>Insulin sensitivity</th>
<th>Hirsutism improved</th>
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<tbody>
<tr>
<td>TLC</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>OCPs</td>
<td>↑</td>
<td>↓</td>
<td>---</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin sensitizers</td>
<td>↑↑</td>
<td>↓</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td>Androgen blockers</td>
<td>↑↑</td>
<td>↓</td>
<td>---</td>
<td>Yes</td>
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</table>

Summary

- PCOS is a common syndrome and managed by many different specialists.
- Diagnostic criteria are slightly varied but focus on ovulatory dysfunction and hyperandrogenism.
- Pathology is not clearly understood but is thought to include insulin resistance, enzymatic defects in steroidogenesis favoring androgen excess and GnRH dysregulation affecting the HPG axis.
- Depth of evaluation may be patient dependent but exclusion of other common endocrine disorders is warranted.
Summary

- There are varied symptoms based on timing of presentation and spectrum of severity.
- Evaluate each women closely with focused history, physical and lab assessment.
- Treatment options for comprehensive management should be explored.
- Fulfilling care for the patient and provider involves a multidisciplinary approach.