Polycystic Ovarian Syndrome (PCOS)

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PCOS: Looking back at history…
1935

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIESS*

Irving F. Stein, M.D., and Michael L. Leventhal, M.D..
Chicago, Ill.

(From Michael Reese Hospital and Northwestern University Medical School)
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**

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<tr>
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<tbody>
<tr>
<td><strong>Oligomenorrhea</strong></td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td><strong>Hyperandrogenism</strong></td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Polycystic ovaries by ultrasound</strong></td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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**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 w/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.
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

Androgens

Triggers:
Abdominal obesity
?Environment
Evaluation

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

<table>
<thead>
<tr>
<th>History</th>
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<tr>
<td>Pubertal age/sexual development</td>
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<tr>
<td>Menstrual history (menarche, menstrual pattern)</td>
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<tr>
<td>Reproductive history</td>
</tr>
<tr>
<td>Obesity (onset, progression)</td>
</tr>
<tr>
<td>Androgen related symptoms (acne, hirsutism, virilization)</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>OSA screening</td>
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</table>
## Evaluation

### Physical
- Vitals (BP, BMI, waist circumference)
- Cutaneous manifestations (acne, hirsutism, acanthosis, skin tags)
- General exam
- May require pelvic exam (GYN)

### Laboratory
- Pregnancy test
- Gonadotropins (high LH or LH:FSH ratio >2-2.5)*
- Prolactin, Thyroid (TSH)
- Androgens (Testosterone**, DHEA-s)
- Adrenal steroids (excess cortisol, 17-OHP)
- AMH***
- Glycemic evaluation: fasting glucose, Hemoglobin A1c, 2-hr glucose tolerance
- Fasting lipids
- Hepatic function (fatty liver)
- Renal function (for treatment)
### 2013 Endocrine Society

Excluding other pathology

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
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</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Serum or urine hCG</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>TSH</td>
</tr>
<tr>
<td>Prolactin excess</td>
<td>Serum prolactin</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Serum 17-OHP</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
<td>LH, FSH, estradiol</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
</tr>
</thead>
<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
- Pioglitzaone 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.

Medications

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
**Medications**

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?

**Medications**

- 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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<tr>
<td>TLC</td>
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<td>↓</td>
<td>↑</td>
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<tr>
<td>OCPs</td>
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<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>
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<td>Yes</td>
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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.
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<tbody>
<tr>
<td>• There are varied symptoms based on timing of presentation and spectrum of severity.</td>
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<td>• Evaluate each women closely with focused history, physical and lab assessment.</td>
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<td>• Treatment options for comprehensive management should be explored.</td>
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<td>• Fulfilling care for the patient and provider involves a multidisciplinary approach.</td>
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