Polycystic Ovarian Syndrome (PCOS)

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PCOS: Looking back at history… 1935

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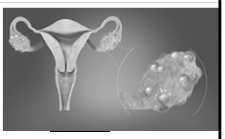
AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES*

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

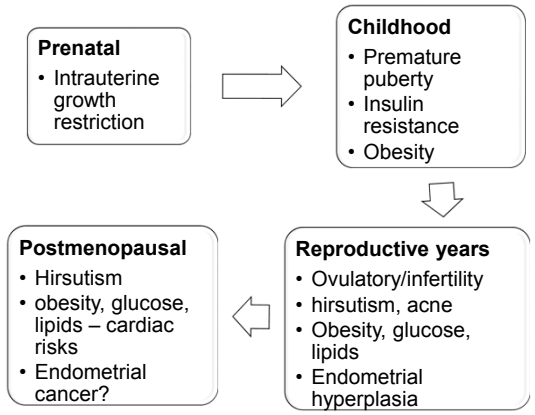
- PCOS affects 5-15%* of women of childbearing age.
- PCOS is the most common endocrine disorder.
- PCOS is a *syndrome* and not a disease.
- PCOS describes a heterogeneous group of women, making one consistent diagnosis a challenge.
- Definition has evolved over time.

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**

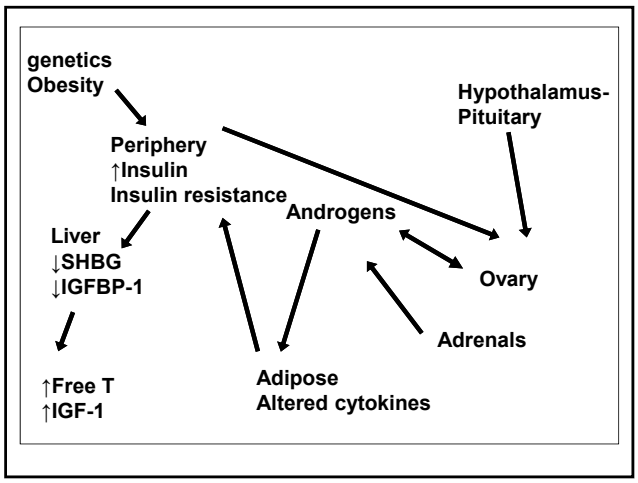
Pathology

- **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?**

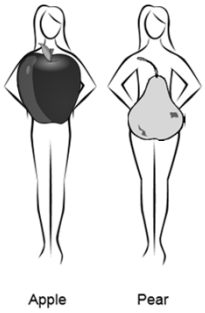
→ Multiple levels of dysfunction with interactions between them

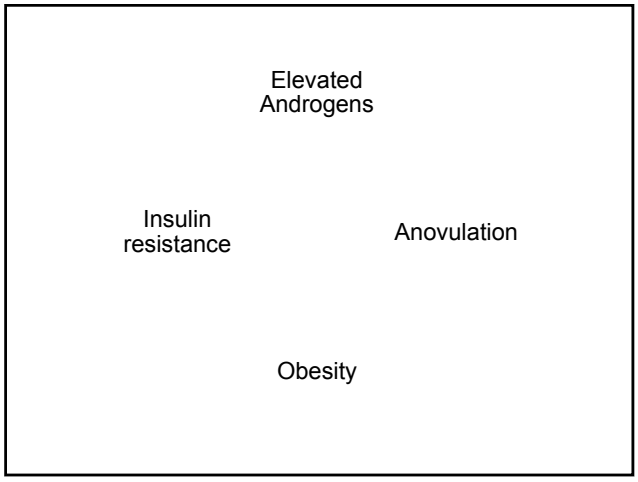


Pathology

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

	NIH 1990	Rotterdam 2003 (2 out of 3)	AES-PCOS 2009/2013
Oligomenorrehea	+	+/ -	+/ -
Hyperandrogenism	+	+/ -	+
Polycystic ovaries by ultrasound	+/ -	+/ -	+/ -

****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
- Hyperprolactinomia
- 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

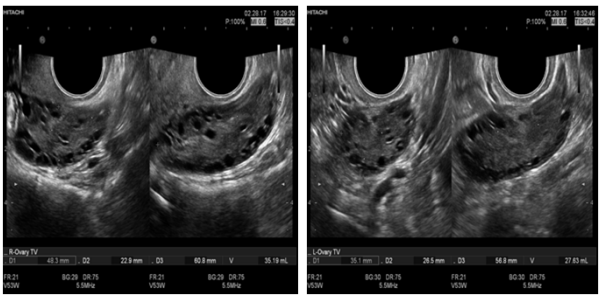
3.Polycystic ovarian morphology by ultrasound

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

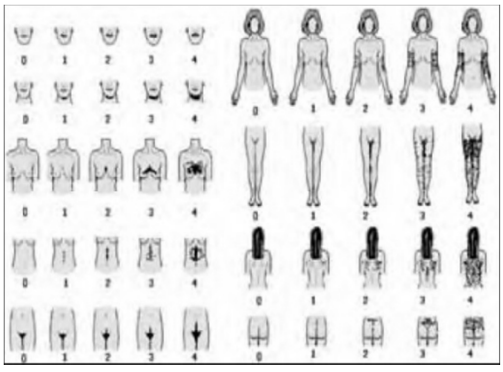


Images courtesy of Dr. Michael Blumenfeld

PCOS Hyperandrogenic symptoms

- **<u>Hirsutism:</u>**
- **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

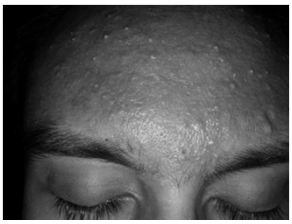


PCOS Hyperandrogenic symptoms

- **Male pattern hair loss**

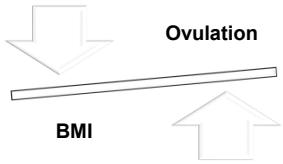
PCOS Hyperandrogenic symptoms

- 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/m^2 or higher.
- Weight reduction can restore regular menstrual cycles in these women.



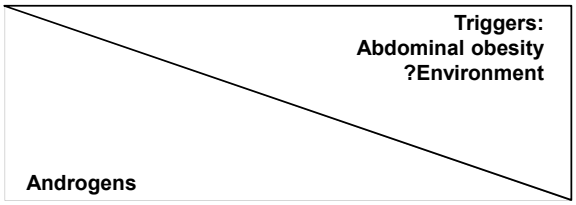
Not all obese women have PCOS

- 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



Evaluation

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

Evaluation

History
Pubertal age/sexual development
Menstrual history (menarche, menstrual pattern)
Reproductive history
Obesity (onset, progression)
Androgen related symptoms (acne, hirsutism, virilization)
Family history
OSA screening

Evaluation

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

Evaluation

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

Disorder	Test
Pregnancy	Serum or urine hCG
Thyroid disease	TSH
Prolactin excess	Serum prolactin
Congenital adrenal hyperplasia	Serum 17-OHP
Hypothalamic amenorrhea	LH, FSH, estradiol

2013 Endocrine Society
Excluding other pathology

Disorder	Test
Primary ovarian insufficiency	FSH, estradiol
Androgen secreting tumor	Testosterone, DHEA-s (ultrasound, MRI adrenals)
Cushing's syndrome	24 hr urine cortisol, late night salivary cortisol, dex suppression
Acromegaly	IGF-1

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,m edium 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

Treatment	Menstrual regularity	Androgen level	Insulin sensitivity	Hirsutism improved
TLC	↑	↓	↑	No
OCPs	↑	↓	---	Yes
Insulin sensitizers	↑*	↓	↑	No
Androgen blockers	↑*	↓	---	Yes

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.**