

Everything You Ever Wanted to Know About Polycystic Ovary Syndrome

Jan Shepherd, MD, FACOG

Disclosure

- Speakers Bureau - Merck
- I have no financial disclosures regarding this material
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Objectives

- Discuss the current theory on the pathophysiology of PCOS.
- Identify management options for the gynecologic consequences of PCOS.
- Identify management options for the metabolic effects of PCOS.

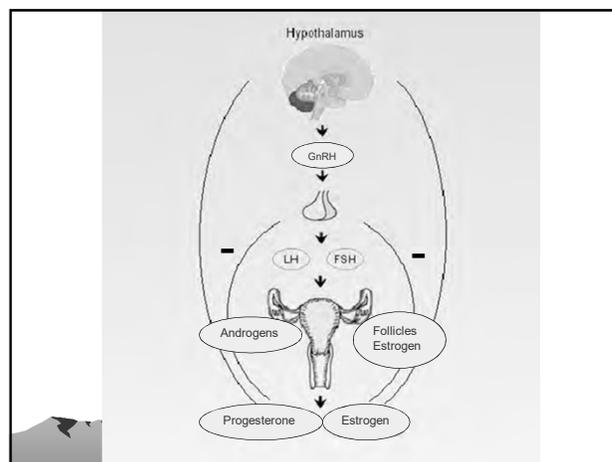
Polycystic Ovary Syndrome (PCOS)

- Most common endocrine abnormality in reproductive-aged women
 - Affects 8-13%
- 35% of adult-onset anovulation
- Most common cause of hyperandrogenism



Genetic Susceptibility

- Apparent autosomal dominant pattern
 - 70% concordance in identical twins, 5-7X increased risk in siblings
- BUT
- Many genes and environment interact
 - 20-40% penetrance
 - Variable presentation in females
 - Males hyperandrogenic and insulin resistant
 - Entire family needs increased surveillance



Proposed Pathophysiology

Genetic susceptibility (+ risk factors)
↓
Abnormal setting of hypothalamus
↓
Abnormal pulsatility of GnRH
↓
↓ FSH and ↑ LH production
↓
↓ FSH → arrested ovarian follicles → cysts, anovulation
↑ LH → ↑ ovarian androgens

Excess in ovarian androgens →→

- Excess terminal hair production, also acne and sometimes alopecia
AND
- Increased peripheral conversion of androstenedione to estrone
– Occurs in fat tissue

↑ Estrone Production →→

- Further inhibits FSH production, which further arrests follicle development and maturation
AND
- Proliferates the endometrium unopposed, which increases the risk of endometrial hyperplasia and cancer (3-6x)

In Addition...

- Various diabetes susceptibility genes appear to be linked to genes affecting GnRH sensitivity →→
- 50-75% of PCOS patients are insulin-resistant, which can lead to:
 - Impaired glucose tolerance (30-40%)
 - T2 diabetes mellitus (7.5-10%)
 - Acanthosis nigricans
 - Central obesity (~60%)
 - Metabolic syndrome (43-46%)
 - Nonalcoholic fatty liver disease

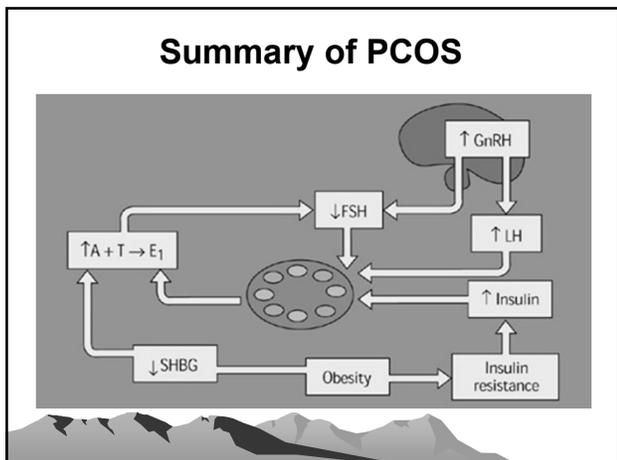
Associated Clinical Features

- Hypertension
- Hyperlipidemia (70%)
↑ total cholesterol, ↑ LDL, ↓ HDL, ↑ TG
- Atherosclerosis
↑ intimal thickness
↑ coronary artery calcification
↑ CVA

Can occur without obesity but are ↑ with obesity

And...

- Both the ovary and adrenal gland contain insulin receptors
- LH is augmented by insulin
- Further increase in androgen synthesis



Psychological Issues

- Increased prevalence of psychological difficulties documented in PCOS patients
 - Depression, anxiety
 - Eating disorders
 - Sexual and/or relationship dysfunction
- ? Related to the hormonal imbalance itself or to its manifestations
- Consider depression screen for all patients
- Be alert - refer for counseling/intervention

Fertil Steril 2018;109:888-99.

Criteria for Diagnosis

Stein-Leventhal (1935)	1990 NIH Conference	2003 Rotterdam Consensus Workshop*
Amenorrhea	Oligo-ovulation	2 out of 3 Oligo-ovulation
Hirsutism	Clinical or biochemical hyperandrogenism	Clinical or biochemical hyperandrogenism
Polycystic ovaries	Exclusion of other endocrinopathies	Polycystic ovaries (≥12 follicles, 2-9mm)
Incidental finding: ~ 60% obese		Plus Exclusion of other endocrinopathies

*Reaffirmed by the Endocrine Society December 2013

J Clin Endocrinol Metab 2013;98(12):4565-4592.

How Important Are Cysts?

- Ovaries in women with PCOS are usually 2-5 times larger than normal
- Usually have a thickened cortex with multiple cysts

BUT

- Only 50-75% of women with clinical PCOS have polycystic ovaries
- 75% of anovulatory women from any cause have polycystic-appearing ovaries
- 8-25% of endocrinologically normal women have polycystic-appearing ovaries
- Change the name of the syndrome!*

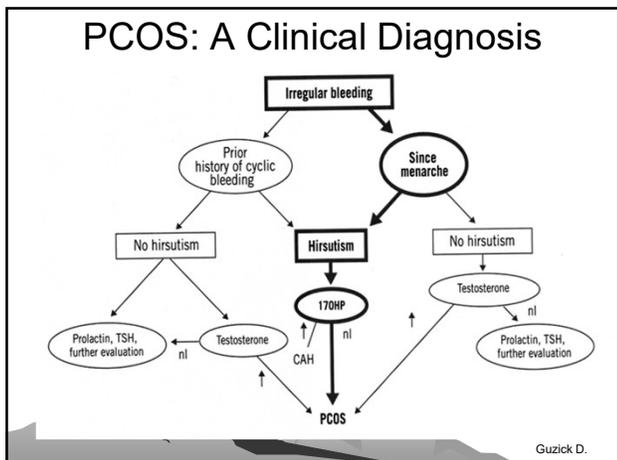
J Clin Endocrinol Metab 2013;98(12):4565-4592.

PCOS: A Practical Evaluation

- History
 - Age at onset of oligomenorrhea, hyperandrogenism
 - Rate of progression
 - Rule out symptoms of related endocrinopathies
 - Galactorrhea
 - Hyper/Hypothyroidism
 - Cushing's syndrome
- Physical Exam
 - Signs of hyperandrogenism
 - Acanthosis nigricans
 - Signs of related endocrinopathies

Case

A 22-year-old Caucasian female g0 presents with irregular (q 3-4 months) heavy menses. She states her periods have never been regular and she's had a long-standing problem with facial hair. On PE, you note evidence that she has shaved her chin and upper lip and a male escutcheon on her lower abdomen. What tests are needed to make your diagnosis?



17-OH Progesterone Rules Out Nonclassic Congenital Adrenal Hyperplasia

STERIOD	ENZYME	CLINICAL CONSEQUENCES OF ENZYME DEFICIENCY
Cholesterol		
↓		
Pregnenolone	20-22-Hydroxylase 20-22-Desmolase	Feminization in males, salt loss
↓		
Progesterone	Δ^5 - Δ^4 -Isomerase	Feminization in males, masculinization in females
↓		
17-Hydroxyprogesterone	17-Hydroxylase	Feminization in males, absent puberty, hypertension
↓		
11-Deoxycortisol	21-Hydroxylase	Virilization in females, salt loss
↓		
Cortisol	11-Hydroxylase	Virilization in females, hypertension

Most prevalent in Ashkenazi Jews, Hispanics, Italians, Yugoslavs, and Inuits

Case

- A 23-year-old Chinese-American g0 presents with irregular (q 3-4 months) heavy menses since menarche at age 11. She denies hirsutism and you see no evidence of it on PE. She denies galactorrhea and any symptoms of thyroid dysfunction. What tests are needed to make your diagnosis?

Case

- A 30-year-old AA female g2p2 presents with increasingly irregular and heavy menses for the past year. She has also begun to notice facial hair during this time and states the problem is getting worse. On exam you notice a male escutcheon and mild clitoromegaly. What tests are needed to make your diagnosis?

Additional Supporting Tests

- TSH, prolactin (normal)
- LH, FSH
 - LH/FSH > 2 is consistent with PCOS
- Pelvic ultrasound
- Rarely
 - DHEAS (> 700 = adrenal pathology)
 - 24-hour urine free cortisol (r/o Cushing's)

Polycystic Ovary on Ultrasound

- Hyperechogenic stroma, volume ≥ 10 ml
- ≥ 12 small (2-9mm) subcapsular cysts in one or both ovaries
- "String of pearls" effect

Consider measurement of endometrial thickness

Essential Medical Evaluation

- Weight → BMI, waist circumference
- Blood pressure
- Fasting lipid profile
- 2-hour GTT
 - Insulin Resistance: FBS \geq 110, 2 hr. \geq 140
 - Type II Diabetes: FBS \geq 126, 2 hr. \geq 200

Management of PCOS: A Practical Approach

- Control weight with diet and exercise to reduce health risks and improve ovulation
- Utilize hormones, antiandrogens, and local treatments to reduce hirsutism
- Assure adequate progestin to reduce risk of endometrial hyperplasia
- Individualize endocrine treatment based on presentation and time in life cycle
 - Need for contraception
 - Infertility
- Employ insulin-sensitizing agents as indicated

Management will span all of a woman's lifetime

Case

- A 22-year-old Caucasian female g0 presents with irregular (q 3-4 months) heavy menses. She states her periods have never been regular and she's had a long-standing problem with facial hair. On PE, you note evidence that she has shaved her chin and upper lip and a male escutcheon on her lower abdomen. How will you manage her PCOS?

Management of Hirsutism

- Local treatments
- Oral contraceptives
- Anti-androgens
- Insulin-lowering agents

Local Treatments

- Temporary
- Permanent
 - Electrolysis
 - Photoepilation (laser) – quicker and less painful, but more expensive
- Eflornithine
 - Blocks enzyme required for hair growth
 - Applied bid, works in 6-8 weeks
 - Effect stops when discontinued, expensive

Oral Contraceptives (OCPs)

- Highly effective
 - \downarrow LH \rightarrow \downarrow ovarian androgen production
 - \uparrow estrogen \rightarrow \uparrow SHBG \rightarrow \downarrow free testosterone (dose-related)
- BUT
 - Ethinyl estradiol can \downarrow insulin sensitivity (dose-related)
 - Some progestins are androgenic and these can also \downarrow insulin sensitivity
 - Low androgenic OCPs \downarrow LDL, \uparrow HDL, but \uparrow triglycerides
 - OCPs \uparrow risk of VTE, especially with obesity

OCPs = First-Line Treatment

- Overall, OCP use does not ↑ metabolic risk¹
- Benefits outweigh risks for most patients²
- Choose 20-30 µg pill with minimally androgenic (norgestimate, desogestrel, norethindrone) or anti-androgenic (drospirenone) progestin
- Add metformin if insulin resistant
- Add statin if abnormal lipid profile
- Individualize!

1. Cochrane Review 2007. 2. J Clin Endocrinol Metab 2013;98(12):4565-4592.

Alternatives to OCPs

- Women with PCOS more likely to have absolute contraindications to OCPs than unaffected women
- If OCP contraindicated
 - Consider metformin, if appropriate
 - Systemic progestin-only contraception will ↓ LH and may help alleviate hirsutism

Anti-Androgens

- Androgen receptor blockers
 - Spironolactone - 50-100 mg bid
 - Flutamide - 250 mg bid
 - 5 α-reductase inhibitor
 - Finasteride - 5.0-7.5 mg/day
- BUT**
- Can feminize a male fetus!
 - Use only if not sexually active or in combination with highly effective contraception

Cochrane Review
Br J Dermatol 2016;175:45-61.

Optimal Management of Hirsutism: Combination Therapy

- 200 PCOS patients with documented hirsutism treated with OCP alone, spironolactone alone, or combination
- Best results with combination
- Response peaked at 6 months, optimal when combined with electrolysis

J Women Health 2018;27:892-902.

Prevention of Endometrial Hyperplasia

- With regulation of menstrual cycle
 - Oral contraceptives, if not contraindicated
 - Cyclic progestins
- Endometrial protection only
 - Progestin-only contraceptives
 - Levonorgestrel IUS (no effect on hirsutism)

Infertility

- Clomiphene leads to increased FSH → enhanced follicular development
 - 70-80% of PCO patients ovulate¹
- Metformin corrects insulin, androgen, and LH imbalances
 - 70-80% of PCO patients ovulate²

1. J Clin Endocrinol Metab 1998;83:2361-65.
2. J Clin Endocrinol Metab 2000;85:139-146.

Metformin +/- Clomiphene (CC)

	% Live births	% Multiple Pregnancy	% SAB
Metformin/Placebo	7*	0	21
CC/Placebo	23	6	8
Metformin/CC	27	3	9

*p<0.001

Reproductive Medicine Network
N Engl J Med 2007;356:551-66.

Clomiphene vs Letrozole (Aromatase Inhibitor)¹

	*Ovulation	*Conception	[†] Live births	SAB
Clomiphene	288 (76.6%)	103/376 (27.4%)	72/376 (19.1%)	49/154 (31.8%)
Letrozole	331 (88.5%)	154/374 (41.2%)	103/374 (27.5%)	30/103 (29.1%)

*p<0.001

[†]p=.007

Effect greatest in obese women

Use of letrozole also supported by Cochrane Review²

1. Reproductive Medicine Network. N Engl J Med 2014;371:119-129.
2. Fertil Steril 2015;103:353-5.

Letrozole (Femara®) for Induction*

- 2.5 mg days 3-7, stepwise ↑ up to 7.5 mg per cycle if anovulatory
- Aromatase inhibitor vs SERM
 - ↓ effect on endometrium and cervical mucus
 - ↓ multiple birth in some studies (NS in RMN)
 - ↓ hyperstimulation syndrome in some studies
- Congenital anomalies
 - Letrozole 4 vs clomiphene 1 (NS)
- Fewer hot flashes than clomiphene

*Off-label use

*Obstet Gynecol Clin North Am 2009;36:333-46.
Cochrane Database 2011, #7.

Clomiphene/Letrozole Resistant?

- Pretreat with OCP
- If DHEAS ≥ 200, add dexamethasone .5 mg cycle days 3-12
- Add metformin, especially if obese
- BUT weight loss alone effective
 - 5-10% reduction enough to resume ovulation*

Effect of Weight Loss

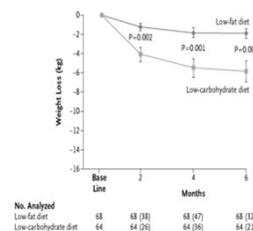
- Increased physical activity, caloric restriction, and weight loss medication (sibutramine or orlistat) for 4 months before ovulation induction*

	Experimental	Control
Weight loss	- 6.2%	-1%
Ovulation	60%	42%
Live birth rate	26%	12%

*J Clin Endocrinol Metab 2015;100:4048-58.

Weight Loss

- Exercise!
- Low-carbohydrate diet may be superior to low-fat diet in obese women with metabolic syndrome
- Bariatric surgery
 - For BMI >40 or >35 with other risk factors
 - Balance risks vs. benefits for pregnancy
 - Wait 1 year before attempting pregnancy



N Engl J Med 2003;348:2074-81.

Vitamin D for Infertility in PCOS

Appears to play a role in insulin resistance, dyslipidemia, obesity, inflammation and infertility

Vitamin D level	OR (95% CI) of Live Birth with Ovulation Induction
< 30 ng/ml	0.58 (0.53-0.92)
≥ 38 ng/ml	1.42 (1.08-1.80)
≥ 40 ng/ml	1.51 (1.05-2.17)
≥ 45 ng/ml	4.46 (1.27-15.72)

J Clin Endocrinol Metab 2016;101:3027-35.

Medical Management

- Routine assessment
 - Weight → BMI, waist circumference
 - Blood pressure
 - 2-hour glucose tolerance (q 2-3 yrs.)
 - If known insulin insensitivity, can monitor HbA1c annually
 - Lipid profile (q 2-3 yrs. and every year after age 40)
- Routine guidance re weight control
- Insulin-sensitizing agents (2-hr. glucose 140-199)
 - Metformin
 - ? Thiazolidinediones (rosiglitazone, pioglitazone)

Benefits of Metformin

- Improves insulin sensitivity
- ↓ Insulin levels → ↓ Testosterone levels
 - Can restore menses, ovulation
- ↓ Total cholesterol, LDL, triglycerides Lp(a), homocysteine, small ↑ HDL
- Small ↓ blood pressure
- 2-4% weight reduction
- Pregnancy Category B
- **PLUS** – Antiproliferative effect on endometrium*

* Gynecol Endocrinol 2013;29:119-24.

Risks of Metformin

- Side effects – nausea, diarrhea, abdominal cramps
 - Start gradually
- Folate/B12 deficiency
 - Need supplemental B complex
- Lactic acidosis
 - Avoid dehydration
 - Discontinue if NPO
- Contraindicated with renal (cc < 30) or hepatic disease
 - Obtain baseline profiles and monitor regularly
 - Rule out high ETOH use

Use of Metformin

- PCOS patients with insulin resistance
- Target dose 1500-2500 mg/day
- Start 500 mg qd and dose 500 mg/week
- Consider extended-release form:
750 mg with dinner, ↑ to 1500 as tolerated

Role of Thiazolidinediones

- Improve insulin resistance
 - May prevent or delay diabetes
 - Reduce androgen levels
- BUT
 - Less evidence than metformin
 - Associated with weight gain and edema
 - Possible hepatotoxicity → monitor ALT levels
 - ? Long-term cardiovascular safety, bladder cancer
 - Pregnancy Category C

Safety concerns → Use only if metformin not tolerated

J Clin Endocrinol Metab 2013;98(12):4565-4592.

Role of Incretin Mimetics

- Improve glycemic control in Type 2 DM
- Not associated with weight gain
- One study of exenatide showed ↓ T, ↑ cyclicality¹

BUT

- Exenatide is a subq injection
 - Side effects, risk of pancreatitis
 - Pregnancy Category C
- Many more studies needed

Endocrine society advises against use²

1. J Clin Endocrinol Metab 2008;93:2670-8.
2. J Clin Endocrinol Metab 2013;98(12):4565-4592.

Role of Statins

- Simvastatin with OCPS¹
 - Further reduction in total cholesterol and LDL
 - Prevents ↑ triglycerides
 - Further reduction in total and free testosterone
 - 45% ↓ in C-reactive protein
- Similar effects with atorvastatin and simvastatin alone

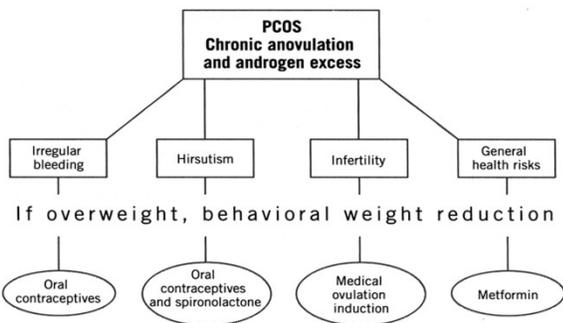
BUT

- Can ↓ insulin sensitivity
- Long-term effects in young women unknown
- Pregnancy Category X!

→ Use only in women who need treatment for hyperlipidemia²

1. J Clin Endocrinol Metab 2007;92:456-61.
2. J Clin Endocrinol Metab 2013;98(12):4565-4592.

Summary: Management of PCOS



Guzick D.