Polycystic Ovary Syndrome

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Objectives

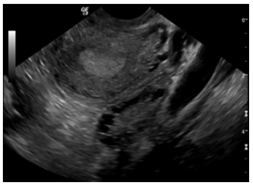
- Background – epidemiology, definition, and diagnosis
- Evaluation – history and physical, laboratory, imaging
- Gynecology and endocrinology workup and management
- Case studies to illustrate:
  - Clinical manifestations
  - Evaluation, workup
  - Treatment, management

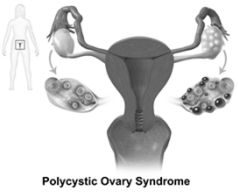
PCOS Background

- Most common endocrine disorder among reproductive age women
- Different PCOS phenotypes and variations
- Patients may present to different specialists based on symptoms
- Recognition and diagnosis may be variable and take time
- Inconsistent approach and care, frustration for patient and physician
- Improvement is needed! reproductive, metabolic, psychological health

PCOS Definition

- A disorder characterized by hyperandrogenism, ovulatory dysfunction, polycystic ovaries
- No universally accepted definition or criteria.





Polycystic Ovary Syndrome

Diagnosis

NIH 1990	Rotterdam 2003	AE-PCOS Society 2006
- Chronic anovulation - Hyperandrogenism	- Oligo and/or anovulation - Hyperandrogenism - Polycystic ovaries	- Hyperandrogenism - Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology)
* Both criteria needed	* 2/3 criteria needed	* Both criteria needed

Exclude other causes.

Differential diagnosis: gynecology

- secondary amenorrhea
  - pregnancy
  - hypothalamic amenorrhea
  - primary ovarian insufficiency
- physiologic adolescent anovulation
- ovarian androgen secreting tumor
- anovulatory bleeding, obesity

Case 1: LS

32yo G0 presented with secondary amenorrhea, increase in facial hair, acne, weight gain.

- PMHx: none
- PSHx: none
- Family Hx: DM, hypertension, heart disease, lipid disorder

Clinical Manifestations

- Reproductive abnormalities:
  - Menstrual disorders
  - Infertility
  - Pregnancy complications
  - Polycystic ovaries
- Hyperandrogenism:
  - Hirsuitism
  - Acne
  - Male pattern balding

Clinical Manifestations

- Metabolic issues
  - Obesity
  - Insulin resistance, DM
  - Nonalcoholic fatty liver disease
  - Metabolic syndrome
  - Dyslipidemia
  - Sleep apnea
  - Cardiovascular disease
- Psychiatric disorders
  - Depression
  - Anxiety
  - Eating disorders

PCOS Evaluation: History

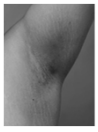
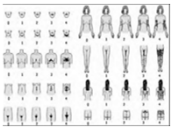
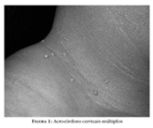
- Menstrual history: menarche, cycle length, bleeding pattern
- Pregnancy history, or infertility history and treatments
- Hyperandrogenism: onset of symptoms, duration, changes
- Medications
- Family history
- Lifestyle factors: nutrition, physical activity, sleep

LS: Evaluation

- Physical exam:
  - BP 120/76, weight 161lb, BMI 27.6
  - acanthosis nigricans
  - mild hirsutism, scars from acne
  - normal pelvic exam
- Labs
- Pelvic ultrasound

PCOS Evaluation Physical Exam

- Physical Exam:
  - Assess for hyperandrogenism: acne, balding, facial and body hair
  - Pelvic exam: evaluate for clitoromegaly, enlarged ovaries
  - Signs of insulin resistance: acanthosis nigricans, skin tags
  - Signs of Cushing syndrome

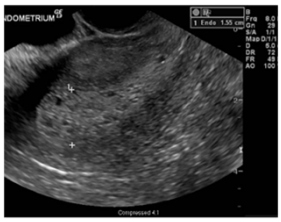




PCOS Evaluation: Labs

- Evaluate oligo/amenorrhea:
  - Pregnancy test! TSH, prolactin,
  - FSH/LH, estradiol
- Serum androgens
  - Total testosterone or free (depending on lab assay, or calculated from total and SHBG)
  - DHEA-S
- Exclude other endocrine pathology

LS: Results

TSH	2.4 (wnl)
PROLACTIN	6.4 (wnl)
DHEA-SULFATE	302 (wnl)
ESTRADIOL, ENHANCED	39.8
FSH	4.3
LH	14
TESTOSTERONE, FREE	**0.85 (H)**
TESTOSTERONE	**58 (H)**
BETA HCG (QUAL), SERUM	Negative



- Mildly enlarged ovaries bilaterally with multiple small peripheral follicles bilaterally.
- Diffuse thickening of the endometrial stripe without focal endometrial lesion identified. Appearance is most consistent with endometrial hyperplasia.

LS: Pelvic Ultrasound

LS: Workup after diagnosis

- Lipid panel: **Cholesterol 220 (H), TG 164 (H), LDL 140 (H)**
- DM screening: A1C 5.2; 2h GTT: 94, 87, 111
- OSA screen: neg
- Depression screening: neg
- **Endometrial biopsy:**
  - **complex hyperplasia without atypia**

After PCOS Diagnosis

- Cardiometabolic risk assessment:
  - BP, weight, BMI
  - Fasting lipids, Diabetes screening: 2h GTT (repeat Q1-2y)
- Check ovulatory status if patient desires fertility
  - Menstrual history, luteal phase progesterone, AMH (TBD)
- Screen for depression and anxiety
- Screen for sleep apnea

LS: Management

- Lifestyle changes: healthy eating, exercise
- Provera challenge
- Hysteroscopy D&C, polypectomy
  - Pathology complex hyperplasia with focal atypia
- Treatment with Megace
- Repeat pelvic ultrasound, endometrial biopsy

Cycle management

- Goals: Menstrual regulation, endometrial protection
- Lifestyle changes -- 5-10% weight loss can help
- Combined oral contraceptives first line
  - progesterone: Norgestimate, norethindrone, drospirinone
- Progesterone
  - Cyclic provera: 5-10mg daily x 10-14 days, Q1-2 months
  - IUD, depo, nexplanon, POPs, high dose progesterone

Lifestyle changes

- Exercise: 150 min exercise/week
- Strength training 2-3x/week
- increase daily activity and steps
- Nutrition consult
- Sleep hygiene, OSA treatment if needed
- Treatment for depression, anxiety

Hyperandrogenism Management

- Acne, hirsutism, hair loss
- First line: combined oral contraceptives
- After 6 months, can add antiandrogen
  - Spironolactone: 50-100mg twice daily.
- Eflornithine (Vaniqa)
- Minoxidil (Rogaine)
- Dermatology referral
- Mechanical removal

Fertility

- Preconception counseling:
  - nutrition, exercise, weight reduction, smoking cessation
- Infertility: likely due to anovulation
  - Basic evaluation: Semen analysis with morphology, +/- HSG
  - Assess ovulation
  - Ovulation induction: letrozole is first line
  - Second line treatment with gonadotropins (REI)

LS: Outcomes

- Weight loss! 8lb, regular exercise with trainer, diet changes
- Lipids improving:
  - Cholesterol 187 (wnl)
  - HDL 38 (L)
  - TG 96 (wnl)
  - LDL 130 (H, previously 140)
- Repeat endometrial biopsy benign, normal ultrasound

Pregnancy outcomes

Risks in Pregnancy

- Miscarriage
- Gestational diabetes
- Pre-eclampsia
- Pre-term birth
- Multiple gestation
- C-section
- depression

Postpartum Risks

- Thrombotic disease
- Pre-eclampsia
- Heart failure, cardiomyopathy
- depression

For the future…

AMH levels

- Anti Mullerian Hormone
- secreted by granulosa cells
- correlates with ovarian reserve and ovulation potential
- Significantly higher in PCOS
- alternative to ultrasound?
- No international standard

Inositol

- dietary supplement
- alternative to metformin
- Myo- and D-chiro
- insulin sensitizer
- improvement in ovulation
- pregnancy, GDM prevention

Polycystic Ovary Syndrome

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Diagnosis: Recall

NIH 1990	Rotterdam 2003	AE-PCOS Society 2006
- Chronic anovulation - Hyperandrogenism * Both criteria needed	- Oligo and/or anovulation - Hyperandrogenism - Polycystic ovaries * 2/3 criteria needed	- Hyperandrogenism - Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology) * Both criteria needed

Exclude other causes.

Other endocrine disorders that may mimic PCOS presentation.

2013 Endocrine Society Guidelines

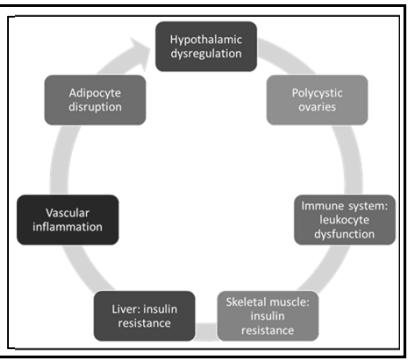
Exclusion of other disorders:

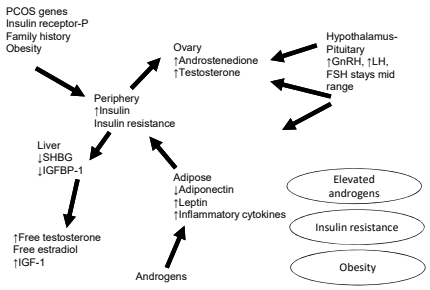
Disorder	Test
Pregnancy	Serum or urine hCG
Thyroid disease	TSH
Prolactin excess	Serum prolactin
Congenital adrenal hyperplasia	Serum 17-OHP
Hypothalamic amenorrhea	LH, FSH, estradiol
Primary ovarian insufficiency	FSH, estradiol
Androgen secreting tumor	Testosterone, DHEA-s (ultrasound, MRI adrenals)
Cushing's syndrome	24 hr urine cortisol, late night salivary cortisol, dex suppression
Acromegaly	IGF-1

2018 Endocrine Society Guidelines

DIFFERENTIAL DIAGNOSIS OF HIRSUTISM/HYPERANDROGENISM			Distinguishing Features	
Condition	Hyperandro-genic	Irreg Menses	Clinical	Hormonal
Nonclassic 21-hydroxylaseCAH	Yes	Not typically	+FHx infertility, hirsutism; Eastern Europe Jewish (Ashkenazi)	High basal or ACTH stimulated 17-OHProg
Cushing's Syndrome	Yes	Yes	HTN, striae, easy bruising	Incr. 24hr urinary free cortisol
↑ Prolactin	No/Mild	Yes	Galactorrhea	Elevated prolactin level
Primary Hypothyroidism	No/Mild	May be present	Goiter, etc.	Elevated TSH, low T_4/FT_4
Acromegaly	No/Mild	Often	Acral enlargement, coarse features, prognathism	Increased IGF1
Primary Ovarian Insufficiency	No	Yes	Other autoimmune disorder, recurrent miscarriage	Increased FSH Low E2 Low AMH
Simple Obesity	Often	Variable	Dx of Exclusion	None
Virilizing Neoplasms	Yes, extreme	Yes	Clitoromegaly, extreme hirsutism, pattern alopecia	Extreme elevation of androgen levels
Medications	Variable	Variable	History	Variable

Metabolic Reproductive Syndrome





Insulin resistance in PCOS

- PCOS women are more insulin resistant than weight matched control women
  - Peripheral insulin sensitivity reduced in all PCOS women.
  - Insulin mediated glucose disposal is decreased by 35-40% in PCOS (compared to same weight controls).
  - Defect is worsened by obesity
  - Hepatic insulin resistance is demonstrated in obese women with PCOS.
- Insulin impacts androgen levels and vice versa: (↑Insulin and ↓SHBG)

Insulin resistance in PCOS

- **Insulin resistance seen in 75% of lean and 95% of overweight/obese (1) and the exacerbation by obesity is greater in PCOS women vs controls (2)**
- The prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes is much higher in PCOS (regardless of BMI but exacerbated by obesity)
- 5 fold in Asia, 4 fold in the Americas and 3 fold in Europe (3)
- **Insulin augments** GnRH mediated gonadotropin release and LH mediated **androgen synthesis** in theca cells and anti müllerian hormone stimulation contributes to follicular arrest and ovulation disruption
- **Insulin inhibits** hepatic SHBG production with resulting higher levels of **bioavailable androgen**
- Lower IGF-1 binding protein, higher IGF-1 and more androgen production

1.Stepto NK, Cassar S, Joham AE, et al. Hum Reprod. 2013;28:777–784.
2.Cassar S, Misso ML, Hopkins WG, et al. Hum Reprod (Oxford, England). 2016;31:2619–2631.
3.Teede et al. Fertility and Sterility. Volume 110, Issue 3, August 2018, Pages 364-379.

Insulin resistance in PCOS

PCOS women should be tested for components of MetS, including glucose intolerance, dyslipidemia, hypertension, BMI/waist circumference, and nonalcoholic fatty liver disease:

- Assesses glycemic status at baseline (OGTT or A1c or FPG)
- Repeat q1-3 years based on risk factors.
- If high-risk (BMI > 25kg/m2 or in Asians > 23kg/m2, h/o IFG, IGT, GDM, FH T2DM, HTN, or high-risk ethnicity), an OGTT is recommended.
- A 75-g OGTT should be offered in all women with PCOS preconception or if not completed prior, then should be completed prior to usual 20 weeks gestation.

Androgens in PCOS

Disordered gonadotropin secretion:

LH > FSH or augmented release of LH vs FSH

Primary ovarian and adrenal hyperandrogenism:

Increased circulating and intrafollicular androgens, 20-30% with increased adrenal androgens (DHEA-S)

Testosterone primary source is the ovary in women.

DHEA-sulfate primary source is the adrenal gland in women.

Measuring testosterone in women

- Women are more sensitive to testosterone than men
- the changes in levels of testosterone that lead to hirsutism in women would cause no visible change in hair density/richness/quality in men
- Moderate changes in the levels lead to dermatologic symptoms (hirsutism, acne, hair loss)
- Severe changes lead to somatic changes with virilization (clitoromegaly, deepening of the voice, change in body structure)
- Total testosterone is the first line, most basic diagnostic parameter
  - 65% bound to SHBG, 30-34% bound to albumin, 2-3% free testosterone
- Reference ranges need to be established for each laboratory assay and should take into account time of the menstrual cycle and age.

PCOS: Endocrine Management
Case example 1

28 year old female presents for consultation. She tells me she was diagnosed with PCOS by her pediatrician around age 16 when she discussed her irregular menstrual cycles and weight gain.

She was prescribed COC and metformin.

However, she self discontinued both as she felt they were not working because she was still gaining weight.

She had secondary amenorrhea off the COC. She started using progesterone to induce cycles.

She is now in nursing school. She started to learn about her family health issues and came in as she desired better management of her own health issues.

PCOS: Endocrine Management
Case example 1

Menstrual history
- Menarche at age 11 or 12, no pregnancies.
- Irregular cycles through teens, then started COC at age 19 or 20. Off OCPs, had cycles that were up to 6 weeks apart that responded to progesterone. → **oligomenorrhea**

Hirsutism present on chin and around nipples.

Acne present in adulthood occasionally.

FH: T2DM in mother.

clinical hyperandrogenism

PCOS: Endocrine Management
Case example 1

Exam: BMI 53, 122/80, skin tags, acanthosis, hirsutism on chin, acne scars on face.

Labs: Elevated A1c, IGT, mixed hyperlipidemia, hyperandrogenism
A1c 6.4, 2hr gtt 96⇨150
TC 216, Trig 206, HDL 50, LDL 125.
Testosterone 87 (ULN 60)
TSH, prolactin, 17-OHP, late night salivary - all normal

Imaging – TVUS: Thickened endometrial lining, increased ovarian volume, Multiple follicles in periphery of ovaries (PCO morphology)

PCOS: Endocrine Management
Case example 1

- Started metformin. Had diarrhea on IR form but tolerated XR/ER form.
- Added liraglutide and titrated up to 1.8mg daily
- Started exercise - lifting weights 2 times per week, kickboxing once per week, tracking steps, cardio 2-3 times per week.
- Nutrition – meal planning, worked to eliminate regular soda, tracking calories.
- 1 year later – tolerating metformin 1500mg/day + liraglutide, lost 35 lbs, A1c improved to 5.4, menses every month (without COC), also restarted COC for management of hyperandrogenism with symptomatic improvement

PCOS: Endocrine Management
Lifestyle guidance

International PCOS Network Guidelines 2018:

Healthy eating & regular physical activity to improve symptoms and general health.

Multicomponent intervention with diet, exercise and behavioral strategies are recommended.

- No one diet stands out
- Focus on accountability, tracking and hypocaloric diet in weight loss phase
- Focus balanced and long term sustainable nutrition plan

Achievable goals (5-10% weight loss in 6 months) with goal setting and self monitoring.

Acknowledge psychosocial impact and mood disorders.

Healthy lifestyle may contribute to health and quality of life benefits in the absence of weight loss.

Benefits: improved ovulation, menstrual pattern, pregnancy rates, insulin regulation, lipids, inflammatory markers.

PCOS: Endocrine Management
Metformin

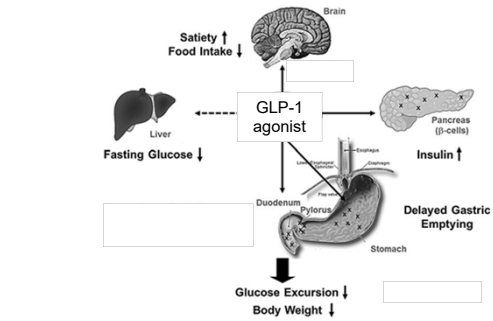
- Most popular, value, safe
- decreased hepatic glucose production and intestinal glucose absorption, improved peripheral glucose uptake
- 1.5-2.5 grams per day, 1-2 g/day if XR; divided doses with meals
- Dose response present
- SE: Nausea, diarrhea
- Pregnancy: Increased live births, reduced GDM, not 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)

PCOS: Endocrine Management
GLP based therapy

- Glucagon Like Peptide-1 (GLP-1): incretin hormone (along with GIP) secreted from the L cells in the distal small intestine after food intake with insulinotropic effect

- Biologic GLP-1 has a half life of 2 minutes with rapid inactivation by dipeptidyl peptidase 4 (DDP-4)

- Food → GI tract → secrets GLP-1 (and GIP) → acts on multiple targets



GLP-1/GLP-1 RA actions:

Target	Actions:
Pancreas	Augments insulin secretion in glucose dependent fashion Reduced glucagon secretion β-cells: more proliferation, less apoptosis; more insulin synthesis
Liver	Less glucose release, less glycogenolysis
GI tract	Slowed gastric emptying and motility
Heart	Reduced BP, improved myocardial contraction
Brain	Reduced appetite, increased satiety via vagus nerve and direct GLP-1 binding
Muscle	Increase glucose uptake and glycogen synthesis
Adipose tissue	Increased fatty acid uptake, lipolysis and glucose uptake
HPG axis	GnRH release from hypothalamus → improved LH production prior to ovulation and maturation of follicles Receptors on ovaries → proposed means for lower androgen levels seen in some studies

GLP based treatment in PCOS in obese and overweight women

Exenatide (alone or with metformin): benefits to menstrual pattern, weight management, inflammatory markers

Liraglutide (alone or with metformin): benefits to weight, insulin resistance, visceral fat, hepatic steatosis, 2 hour glucose tolerance, potential lower testosterone (higher SHBG), assisted pregnancy rates in IVF?

Do not use if contraindications: pregnancy, MTC, MEN2, pancreatitis, gastroparesis

Cost may be a barrier

PCOS: Endocrine Management Thiazoladinediones

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 make this less optimal of a choice.
Small cohorts with reduced DHEA-s and increased SHBG, improved menstrual regularity.

PCOS: Endocrine Management Orlistat

Reduces fat absorption, inhibits lipases, inhibits triglyceride absorption

120mg up to 3 times/day with meal and restrict dietary fat < 30%, add ADEK

Contraindicated: pregnancy, cholecystitis, obstructive bowel disease; caution in pancreatic or liver disease

SE: flatulence, steatorrhea, diarrhea, increased BMs (rare: kidney stones)

Medium weight loss effect.

PCOS: Endocrine Management
Other options

Acarbose: reduced glucose absorption from GI tract (50mg -100mg every 8 hours with first bite of a meal) but with GI side effects; medium 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

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

PCOS: Endocrine Management
Case example 2

A 25 year old female presents due to lack of return of menstrual cycles after stopping COC. She stopped COC 6 months ago. She has been attempting to become pregnant without success.

She reports menarche at age 11. By age 13, she was started on COC for acne.

She had at least 1 year of regular menstrual cycles prior to starting her COC but not much time without hormonal therapy to discern pattern.

Since stopping COC, she also notes weight gain (+26 lbs in 18 months, 10-15 lbs in last 6 months), fatigue and worsening acne. She has not noted hirsutism, headache, vision changes, nipple discharge or hot flashes.

Just prior to coming to my clinic, she was prescribed progesterone (provera). She took 10 day course and had a very light 2 day cycle.

She is referred with labs with elevated total testosterone at 106 (ULN 76), normal prolactin, TSH, random FSH of 5.2. Pelvic US with PCO morphology on right side.

PCOS: Endocrine Management
Case example 2

She has no chronic medical conditions.

Medications: medroxyprogesterone 10mg.

Family history – M: HTN, F: high cholesterol, MGM: T2DM, PGF: T2DM

Exam: BMI 35, BP 122/84, HR 86. Notable for dorsal fat pad, acne present on face/chest/shoulders, no hirsutism, no acanthosis, no striae.

More labs: T2DM by 2 hour glucose, hyperandrogenism

A1c 5.2, GTT 89 --> 1 hr 206 --> 2 hr 243

Androstenedione 325 (H), Testosterone 77 (ULN 60), DHEA-s normal, 17-OHP normal.

Dx: PCOS, T2DM.

PCOS: Endocrine Management
Case example 2

She later completes the rest of her labs:

Late night salivary cortisol 381 (<50-100)

24 hour urine:

CORTISOL, URINE: 50 (Ref 3.5-45 mcg/24 hr)

CORTISONE, URINE: 221 (Ref Range: 17 - 129 mcg/24)

1mg dexamethasone suppression test:

Cortisol 9.59 (<1.8)

MRI: 4 mm pituitary microadenoma

PCOS: Endocrine Management Case example 2

Patient underwent pituitary surgery.

2 weeks after surgery, she had a menstrual cycle. Next cycle was 1 month later. She became pregnant in the following cycle.

She had uneventful pregnancy and after was down 65 lbs, has regular menstrual cycles and no further symptoms.

PCOS: Summary points

PCOS is prevalent but diagnosis is not uncommonly delayed. Diagnostic criteria have changed over time and likely will continue to be updated.

Earlier intervention, serial monitoring and individualized management may reduce the risk for potential later life complications.

Management is focused on patient specific risks, concerns and clinical features with focus on quality of life and long term health benefit.

The differential diagnosis for irregular menses should be explored for all patients presenting with possible PCOS. Likewise, patients should have secondary endocrine causes excluded.

Metabolic Reproductive Syndrome may be a better way to conceptualize this disorder and a comprehensive, multidisciplinary approach to management is recommended.