What is and What is not PCOS (Polycystic ovarian syndrome)?

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No disclosures
Learning Objectives

• Discuss clinical vignettes and formulate differential diagnosis while evaluating a patient for polycystic ovarian syndrome.

• Identify an organized approach for diagnosis of polycystic ovarian syndrome and the associated disorders.
DISCUSSION

Clinical vignettes of differential diagnosis

Brief review of Polycystic ovarian syndrome (PCOS)

Therapeutic approach for PCOS

Clinical vignettes – Case based approach for PCOS

Summary
• 25 yo Hispanic F, referred for 5 years of amenorrhea. Diagnosed with PCOS, was on metformin for 2 years. Self discontinuation. Seen by gynecologist

• Progesterone withdrawal – positive.
  
  OCP’s – intolerance (weight gain, headache).

  Denies galactorrhea. Has some facial hair (upper lips) – no change since teenage years. No neurological symptoms, weight changes, fatigue, HTN, DM-2.

• Currently – plans for conception.

• Pertinent P/E – BMI: 24 kg/m², BP= 120/66 mm Hg. Fine vellus hair (upper lips/side burns).
## CASE - 1

<table>
<thead>
<tr>
<th>Labs</th>
<th>Values</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>2.23</td>
<td>0.3 – 4.12 uIU/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>903</td>
<td>1.9-25 ng/ml</td>
</tr>
<tr>
<td>CMP/CBC</td>
<td>unremarkable</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>33</td>
<td>0-400 pg/ml</td>
</tr>
<tr>
<td>Progesterone</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td>3.3</td>
<td>0-77 mIU/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>2.8</td>
<td>0-153 mIU/ml</td>
</tr>
</tbody>
</table>

**NEXT BEST STEP?**
Hyperprolactinemia

- Reported Prevalence of Prolactinomas: of clinically apparent prolactinomas ranges from 6 –10 per 100,000 to approximately 50 per 100,000.

- Rule out physiological causes/drugs/systemic causes. Mild elevations in prolactin are common in women with PCOS.

- MRI pituitary if clinically indicated (to rule out pituitary adenoma).

<table>
<thead>
<tr>
<th>Prl &gt;100 ng/ml</th>
<th>Moderate Prl =50-100 ng/ml</th>
<th>Mild Prl = 20-50 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically associated with subnormal estradiol concentrations.</td>
<td>Low normal or subnormal estradiol concentrations.</td>
<td>Insufficient progesterone secretion.</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>Amenorrhea OR Oligomenorrhea</td>
<td>Anovulation/Infertility.</td>
</tr>
<tr>
<td>Hot flashes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prolactin-secreting pituitary tumors in amenorrheic women: a comprehensive study Endocr Rev. 1980
J Clin Endocrinol Metab, February 2011
CASE - 2

27 yo F, previous h/o eating disorder (anorexia nervosa) Treated and cleared by psychiatrist a year ago.

• 4 years of amenorrhea treated with OCP’s and Metformin.
• Referred for evaluation of oligomenorrhea, fine facial hair. One menstrual cycle since OCP/MTF discontinuation x 8 mths. BMI = 21

<table>
<thead>
<tr>
<th>Lab</th>
<th>Initial visit</th>
<th>Follow up (8 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (0.3 – 4.12 uIU/ml)</td>
<td>0.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Prolactin (1.9-25 ng/ml)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Estradiol (0-400 pg/ml)</td>
<td>25.5</td>
<td>75 (Resumption of menstrual cycles)</td>
</tr>
<tr>
<td>Progesterone LH (0-77 mIU/ml)</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>FSH (0-153 mIU/ml)</td>
<td>20.4</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>A1C</td>
<td>5.0</td>
<td>-</td>
</tr>
<tr>
<td>17 OH progesterone</td>
<td>Normal</td>
<td>-</td>
</tr>
</tbody>
</table>
Functional hypothalamic amenorrhea

- Low energy availability (from decreased caloric intake, excessive energy expenditure, or both) and stress are common causes of hypogonadotropic hypogonadism in women.

- As many as half of patients with PCOS with a nonhyperandrogenic PCOS phenotype (i.e., oligomenorrhea and polycystic ovarian morphology on ultrasound) may have FHA.
CASE - 3

• 34 yo F, G2P2, referred for oligomenorrhea x 3 years.
• Menstrual cycles 1-2/year, previously monthly. On Metformin 500 mg bid for 1 year for diagnosis of PCOS.
• No exposure to OCP’s. Progesterone withdrawal – minimal spotting.

• Pelvic ultrasound – Presence of polycystic ovaries.
• TSH/Prl = normal.
• LH = 23 (0-77 mIU/ml)
• FSH = 105 (0-153 mIU/ml)
• Estradiol = 75
• Progesterone 0.5
• Total Testosterone = 38 (2-45 ng/dl), Free Testosterone = 6.8 (0.1-6.4 pg/ml)
Primary ovarian insufficiency (POI)

Premature ovarian failure/Premature menopause: Menopause before age 40 years.
Age-specific incidence for spontaneous POI: ~ 1 in 250 by age 35 years and 1 in 100 by age 40 years.
- elevated serum gonadotropins and
- low serum estradiol concentrations

- Symptons: hot flashes and vaginal dryness.
- Intermittent ovarian function seen in 50-75% of patients with spontaneous POI
- Autoimmune – screen for hypothyroidism/adrenal insufficiency
- Karyotyping

• 32 yo F, referred by Gynecologist. Oligomenorrhea, mild clitoromegaly, inability to conceive.
• Reports coarse facial hair, coarse hair around linea alba, lower back, sternal area – similar since teenage years.
• Oligomenorrhea. No exposure to OCP. Trial of Metformin – GI intolerance
• Family h/o similar phenotype and difficulties in conception.
Non congenital adrenal hyperplasia

- **Late-onset congenital adrenal hyperplasia**: can present in adult women with anovulation and hirsutism and is due almost exclusively to genetic defects in the steroidogenic enzyme, 21 hydroxylase (CYP21)

- **Incidence:**
  - Fasting level of 17- hydroxyprogesterone should be obtained in the morning. A value <2 ng/ml is considered normal.
  
- In adult women, the diagnosis of NCCAH is strongly suggested by a basal 17- hydroxyprogesterone value >200 ng/dL (6 nmol/L) and confirmed with an ACTH stimulation test.

- **Treatment** – OCP’s, Spironolactone (combined with contraception). Use of glucocorticoids only if anovulatory infertility (for ovulation induction).

Approach to the patient: the adult with congenital adrenal hyperplasia. Auchus RJ, Arlt W J Clin Endocrinol Metab. 2013
What is PCOS?

1. Hyperandrogenism (clinical, biochemical or both)
2. Ovulatory dysfunction
3. Polycystic ovarian morphologic features (on ultrasound).
Ovulatory dysfunction

Unpredictable menses at intervals of less than 21 or more than 35 days.

• Oligo-ovulation
• Anovulation
• Oligomenorrhea
• Amenorrhea
• Menorrhagia
Hyperandrogenism

Clinical: hirsutism, seborrhea, acne, and androgenic alopecia.

- Stigmata of insulin resistance – skin tags, acanthosis nigricans.

Biochemically: supranormal levels or estimates of circulating endogenous androgens

- Free Testosterone by equilibrium dialysis OR Calculated Free Testosterone (Total T and SHBG)

The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome. Fertility and Sterility, February 2009
Ferriman and Gallwey score

- Hirsutism scoring system of Ferriman and Gallwey. The nine body areas possessing androgen-sensitive pilosebaceous units are graded from 0 (no terminal hair) to 4 (frankly virile). [Reprinted with permission from R. L. Rosenfield: Clin Endocrinol Metab 15: 341-362, 1986 (1) © W. B. Saunders Co.]
# Diagnostic criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>National Institutes of Health</th>
<th>Rotterdam</th>
<th>Androgen Excess and PCOS Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenism*</td>
<td>Hyperandrogenism required</td>
<td>Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required</td>
<td>Hyperandrogenism required</td>
</tr>
<tr>
<td>Oligo-ovulation or anovulation†</td>
<td>Ovulatory dysfunction required</td>
<td>Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required</td>
<td>Either ovulatory dysfunction or polycystic ovarian morphologic features required</td>
</tr>
<tr>
<td>Polycystic ovarian morphologic features‡</td>
<td>Not applicable</td>
<td>Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required</td>
<td>Either ovulatory dysfunction or polycystic ovarian morphologic features required</td>
</tr>
<tr>
<td>No. of combinations that meet criteria for the polycystic ovary syndrome</td>
<td>Two (hyperandrogenism plus ovulatory dysfunction; hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features)</td>
<td>Four (hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features; hyperandrogenism plus ovulatory dysfunction; hyperandrogenism plus polycystic ovarian morphologic features; ovulatory dysfunction plus polycystic ovarian morphologic features)</td>
<td>Three (hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features; hyperandrogenism plus polycystic ovarian morphologic features)</td>
</tr>
</tbody>
</table>

* Evidence of hyperandrogenism can be clinical, biochemical, or both.

† Ovulatory dysfunction frequently manifests as unpredictable menses at intervals of less than 21 or more than 35 days, but it may also be present in patients who have hyperandrogenism with apparent eumenorrhea.

‡ Polycystic ovarian morphologic features are defined as 12 or more antral follicles (2 to 9 mm in diameter) in either ovary, an ovarian volume that is greater than 10 ml in either ovary, or both.
US features/images

• The sole presence of polycystic ovaries should not be considered as the *sine qua non* for PCOS because polycystic ovaries are common in young healthy women.

• Polycystic ovaries can be observed during pubertal development, and in patients with hypothalamic amenorrhea and hyperprolactinemia.

Ovarian Cyst
A classic reference indicating the prevalence of various presenting clinical symptoms and complaints among a large cohort of women with PCOS (N = 1089) culled from 187 previously published papers. The frequency is still relevant to today’s population of women with PCOS.

Pathophysiology

Persistently rapid GnRH pulses
Excess of LH
Insufficient FSH secretion

Many women with PCOS have Insulin resistance.
Hyperinsulinemia

Excessive Ovarian androgen production
Ovulatory dysfunction

Enhances Ovarian and Adrenal androgen production
Increase Androgen bioavailability

SHBG

Why is it a health problem?

- Insulin resistance and Hyperinsulinemia
- Metabolic diseases – Prediabetes, DM-2, Dyslipidemia, Obesity, Sleep apnea, NAFLD
- Infertility
- Pregnancy complications – Gestational Diabetes, Pre-eclampsia.
- Depression/Anxiety
Initial workup

Laboratory:
• Documentation of biochemical hyperandrogenemia:
  **Total testosterone and SHBG (for calculated free testosterone) OR bioavailable/free testosterone**

• Exclusion of common causes of menstrual disturbances:
  **Thyroid-stimulating hormone levels**
  **Prolactin**
  **17-hydroxyprogesterone**

• Evaluation for metabolic abnormalities
  - 2-hour oral glucose tolerance test, HbA1C, Fasting serum glucose
  - Fasting lipid panel
  - AST/ALT (Hepatic enzymes)
Workup

Other considerations:

• **Fasting insulin levels** in younger women, those with severe stigmata of insulin resistance and hyperandrogenism

• **Gonadotropin determinations** (LH, FSH) to determine cause of amenorrhea

• 24-hour urine test for urinary free cortisol with late onset of PCOS symptoms or stigmata of Cushing syndrome

Therapeutic Goals

PCOS SEEKING FERTILITY

PCOS NOT SEEKING FERTILITY
Therapeutic Goals

FERTILITY
• Weight loss 5-10% in Obese.
• Fertility specialist (*Clomiphene citrate/Gonadotropins/IVF*)

HIRSUTISM
• Mechanical hair removal.
• OC (Oral contraception)
• Spironolactone (combined with contraception)

IRREGULAR MENSES
• OC
• METFORMIN may improve ovulatory function.
• Lifestyle modifications.

GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME.
Endocrine Practice: December 2015
Table 2. Anticipated Effects of Common Therapeutic Options for the Polycystic Ovary Syndrome.‡

<table>
<thead>
<tr>
<th>Therapeutic Option</th>
<th>Clinical Hyperandrogenism</th>
<th>Ovulatory Function</th>
<th>Endometrial Protection</th>
<th>Reliable Contraception</th>
<th>Cardiovascular Risk</th>
<th>Practical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (if patient overweight)</td>
<td>Reduced androgen levels likely, but effect on hirsutism uncertain</td>
<td>Variable improvement</td>
<td>Yes, if normal ovulatory function is restored†</td>
<td>No (may increase pregnancy risk)</td>
<td>Expected improvement</td>
<td>No specific diet or exercise regimen has been proved to be superior in the polycystic ovary syndrome.</td>
</tr>
<tr>
<td>Mechanical hair removal</td>
<td>Improvement expected</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typically required even when pharmacologic therapy is used. One example is ethinyl estradiol (35 μg) plus norgestimate (0.25 mg), but no specific estrogen—progestin combination has been proved to be superior in the polycystic ovary syndrome. Daily ethinyl estradiol doses of 20 to 35 μg are acceptable. Progestins with low androgenic potential include norgestimate, desogestrel, gestodene, and drospirenone; among these, norgestimate may be associated with lower risk of venous thromboembolism. Medical eligibility (i.e., potential contraindications) should be considered before and during treatment.§</td>
</tr>
<tr>
<td>Oral combined hormonal contraceptives</td>
<td>Improvement expected</td>
<td>Reliable suppression</td>
<td>Yes</td>
<td>Yes</td>
<td>Increased risk of venous thromboembolism; potential increase in blood pressure, triglyceride, and HDL cholesterol levels; possible increase in cardiovascular events (all effects reversed after discontinuation)</td>
<td></td>
</tr>
<tr>
<td>Spironolactone¶</td>
<td>Improvement expected</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Spironolactone may be started at 50 mg twice daily, increasing to 100 mg twice daily as needed. Pregnancy must be strictly avoided in patients who receive spironolactone.</td>
</tr>
<tr>
<td>Metformin</td>
<td>Reduced androgen levels likely, but effect on hirsutism unlikely</td>
<td>Variable improvement</td>
<td>Yes, if normal ovulatory function is restored†</td>
<td>No (may increase pregnancy risk)</td>
<td>Reduced hyperinsulinemia; probable reduced risk of impaired glucose tolerance and type 2 diabetes mellitus; favorable effects on lipid levels possible; possible weight loss (modest); theoretical but unproven benefit with respect to long-term risk of cardiovascular disease</td>
<td>Gastrointestinal side effects of metformin may be limited by starting at a low dose (500 mg daily with a meal), gradually increasing to 1000 mg twice daily with meals.</td>
</tr>
<tr>
<td>Progestin (episodic administration)</td>
<td>—</td>
<td>—</td>
<td>Yes**</td>
<td>—</td>
<td>—</td>
<td>Oral micronized progesterone (200 mg at bedtime) or oral medroxyprogesterone acetate (5–10 mg daily) for 10–14 days every 1–3 mo.</td>
</tr>
<tr>
<td>Progestin-only contraceptive pills</td>
<td>Variable suppression††</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>Only norethindrone (0.35 mg/day without a hormone-free week) is available in the United States.</td>
</tr>
</tbody>
</table>
Current guidelines on PCOS:

- Recommend against the routine use of metformin in obese women with PCOS except in women with glucose intolerance who have failed lifestyle interventions.

- Recommend metformin as an adjuvant therapy for infertility to prevent OHSS (Ovarian hyperstimulation syndrome) in women with PCOS undergoing IVF

Legro et al Guidelines on PCOS J Clin Endocrinol Metab, December 2013
Other drugs

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>X</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INSULIN SENSITIZERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td>NOT RECOMMENDED (due to safety concerns. No Randomized control trials in PCOS patients).</td>
</tr>
<tr>
<td>Inositolès</td>
<td></td>
<td>NOT RECOMMENDED (due to lack of benefit).</td>
</tr>
<tr>
<td>STATINS</td>
<td></td>
<td>RECOMMENDED in women with PCOS who meet current indications for statin therapy.</td>
</tr>
</tbody>
</table>

Legro et al Guidelines on PCOS J Clin Endocrinol Metab, December 2013
• Initial labs prior to referral:
  TSH, Prolactin, CBC, CMP- normal.
• Other evaluation:
  Total T = 51 (2-45 ng/dl)
  Free T = 7.1 (0.1-6.4 pg/ml)
  LH = 14, FSH = 4. 17 OH progesterone = 96 (<185 ng/dl)
  A1C = 4.9%
  Lipid – wnl
26 yo F referred for evaluation of abnormal insulin and testosterone levels, R/o insulinoma. CT abdomen no masses, + mild hepatomegaly.

Reports oligomenorrhea. BMI = 35, Acanthosis nigricans +. BP = 146/90. Coarse facial hair+ (chin).

Glucose = 84, TSH = 1.4, A1C = 5.6%, Tg = 187 (<150).
Differential Diagnosis
(Hirsutism+Ovulatory dysfunction)

• Non-congenital Adrenal Hyperplasia
• Syndromes of Severe Insulin Resistance
• Hyperprolactinemia
• Hypothalamic amenorrhea
• Premature ovarian insufficiency
• Hyperthecosis of ovary
• Thyroid Abnormalities
  • Cushing’s Syndrome
  • Androgen-Secreting Ovarian or Adrenal Tumors
  • Idiopathic Hyperandrogenism
  • Idiopathic Hirsutism
  • Androgenic Anabolic Steroid Usage
  • Medications: Danazol, Phenothiazines, Corticotropin or ACTH analogues, Valproate
Summary

• **PCOS** – Complex polygenic disorder. Diagnosis of exclusion.

• Perform a thorough Clinical exam and Basic Biochemical evaluation for ruling out common etiologies of hyperandrogenism/anovulatory cycles.

• Women with PCOS tend to be insulin resistant, obese, and at risk for diabetes and an adverse cardiovascular risk profile.

• Treatment tends to be symptom based, with focused treatments for infertility, obesity, hirsutism, irregular menses and metabolic abnormalities.
THANK YOU