Practical Points about Patients with PCOS and Hyperandrogenic Anovulation

Margaret E Wierman MD
Professor in Medicine, OBGYN,
Director Pituitary Adrenal and Neuroendocrine Program,
University of Colorado Anschutz Medical Campus,
Chief of Endocrinology, RMRVAMC

Disclosures: grant reviewer Pfizer, Pituitary investigator grants Corcept, Novartis, Ionis
Hyperandrogenic Anovulation
Differential Diagnosis

- Polycystic Ovarian Syndrome
- Ovarian or adrenal tumor
- Iatrogenic: exogenous androgen administration or exposure, other drugs
- Obesity-induced Hyperandrogenic Anovulation
- Congenital adrenal hyperplasia
- Other: Cushing’s syndrome, prolactinoma
Case 1:

- 19 yr old Hispanic female presented with hirsutism, acne, and irregular menses since menarche age 11
- Hirsutism since age 9 on face, chin, around breasts and below umbilicus, no virilization
- Periods ALWAYS irregular, 3 in last year, one in response to medroxyprogesterone withdrawal
- Gradual weight gain, difficulty losing diet lifestyle
- Family hx: Type 2 diabetes, obesity, hyperlipidemia
Case 1:
Case 1:

• Anabolic appearance, BMI 29
• Terminal hair lip, chin, neck; no temporal recession, gr II acne, no clitoromegaly
• **Timed Labs** *(days 1-5 of induced cycle)*:
  • `LH 15 mIU/ml, FSH 5 mIU/ml (normal 2-15),`
  • Testosterone 70ng/dl (nl <40ng/dl), DHEAS 400ng/ml (nl 50-350)
  • A1C 5.7 (nl 4-6)
## PCOS Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligomenorrhea (8 or less menses a year)</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperandrogenism (clinical or biochemical, any androgen)</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Polycystic Ovary on US (greater than 10ml size and &gt;20 follicles)</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

**To meet criteria for PCOS**

- Must have first 2
- Need 2 of 3
- Need androgens + one other

All of the above have exclusion of other cause, CAH, ovarian or adrenal tumor, elevated prolactin
Hirsutism

Ferriman Gallway Score

>4-6 is abnormal pending ethnicity
PCOS: Treatment Options

- No pregnancy desired
  - **Regularize menses**: OCPs with constant, less androgenic progestin, or cyclic progesterone (endometrial shedding, increase SHBG)
  - Avoid levonogestrel IUD?
  - **Treat hirsutism**: spironolactone: 50-100mg/ d (antiandrogen), local control: electrolysis
  - **Diet and lifestyle**
  - **Insulin sensitizer**: most of data on metformin
    Role in halting progressive weight gain, improving androgen levels and insulin resistance
  - Other: D-chiroinositol, myoinositol? NO
PCOS Pathogenesis

Genetics complex: GWAS still no discrete targets

Case 2:

- 28 yr old woman with PCOS here to discuss planned pregnancy
- Hx: menarche age 10, PCOS dx at 18, irregular menses, acne and hirsutism and US showing increased ovarian volume and multiple follicles
- Intermittently on oral contraceptives and spironolactone; 6 mo ago started metformin alone and menses more regular
- Weight: 140 (63.6kg), 160 (72.7kg) now 180 (82kg) BMI 31.9
- BP: 130/80, obese WF with acanthosis, Gr II acne no virilization.
- Urine pregnancy negative
Case 2

Which of the following treatments in this woman with PCOS would be most effective in induction of ovulation to achieve a live birth?

A) Letrozole
B) Clomiphene citrate
C) Human menopausal gonadotropins
D) Cabergoline
E) Progesterone suppositories
**Metformin vs Clomiphene**

- Patients given metformin 850XR rather than meal time dosing, Patients quite obese

**TAKE HOME:**

- Metformin improves insulin resistance, lipids, sometimes weight
- Clomiphene induces ovulation

When to consider combination: ? risk Gestational diabetes, complications

But...Letrozole is better than Clomiphene

- 750 patients: L 2.5mg vs CC 50mg d3-8 for 5 mo
- Definition: Anovulation+HA or PCOS ovaries
- Live births: 27.5% vs 19.1% L vs CC
- Congenital anomalies 4 vs 1 L vs CC
- Ovulation rate: 62% vs 48% L vs CC
- Pregnancy loss 32% vs 29%, Twin 3.4% vs 7.4%
- Fatigue and dizziness (L) vs Hot flashes (CC)

Live Births Letrozole vs Clomiphene Stratified by Maternal Weight

Algorithm 5: Assessment and treatment of infertility

1st line non-pharmacological management for infertility

1st line pharmacological management for infertility
- Letrozole* (consider Letrozole as 1st line therapy)
- Clomiphene citrate
- Clomiphene citrate + metformin
- Metformin*

Lifestyle interventions

2nd line pharmacological/surgical management
- Gonadotrophins
- Laparoscopic ovarian surgery

3rd line management could be other appropriate interventions including IVF

* Off label prescribing: Letrozole, COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

Teed HJ. Clin Endocrinol (Oxf). 2018 Sep;89(3):251-268
Should we recommend diet, wt loss and/or insulin sensitizers?  YES

• Several studies showing improved outcome for induction of ovulation with pretreatment diet/weight loss protocols
• Weight loss and OCP improvements in multiple domains related to quality of life, depressive symptoms, and anxiety disorders in overweight/obese women with PCOS
• ALSO Ovulation rate 65% vs 45%; Live birth 25% vs 8.5% in response to clomiphene
• PreRx exenatide 4.3 vs 2.3KG increased response to metformin and pregnancy rates(43.60% vs 18.70%, P < .05)

Case 3:

- 33 yr old woman with PCOS irregular menses,
- G2P2 with induction of ovulation
- BMI 32, stable hirsutism
- On metformin and oral contraceptive
- **Wants to know what are the longterm complications of PCOS?**
PCOS Across the Lifespan

- **Cancer Risks**: endometrial
- **Metabolic Risks**: DM2, metabolic syndrome
- **Cardiovascular Risks**: markers but unclear if disease
- **Other**:
  - Obstructive sleep apnea
  - Nonalcoholic liver disease (NALD, NASH)
  - Depressed Mood
PCOS women get Endometrial Cancer EARLY

- Retrospective analysis of prevalence of PCOS in 128 pts with EC vs 83 controls.
- Increased risk in women less than 50 yrs
- Cycle with OCP or Progestin

Pillay et al. Hum Reproduction 21:924, 2006;
Teed HJ. Clin Endocrinol (Oxf). 2018 Sep;89(3):251-268
Risk of Diabetes

### Gestational diabetes, impaired glucose tolerance and type 2 diabetes

Regardless of age, gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are increased in PCOS, with risk independent of, yet exacerbated by obesity.

Glycaemic status should be assessed at baseline in all with PCOS and thereafter, every one to three years, based on presence of other diabetes risk factors.

In high risk women with PCOS (including a BMI > 25kg/m² or in Asians > 23kg/m², history of abnormal glucose tolerance or family history of diabetes, hypertension or high risk ethnicity) an oral glucose tolerance test (OGTT) is recommended. Otherwise a fasting glucose or HbA1c should be performed.

An OGTT should be offered in all with PCOS when planning pregnancy or seeking fertility treatment, given increased hyperglycaemia and comorbidities in pregnancy.

If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation

- **3-5 fold increased risk of T2D**, higher with obesity
- Assess glycemic status at *diagnosis, then every 1-3 years*
- In obesity/family history of T2D: *OGTT, otherwise fasting glucose or HbA1c*
- Pre-pregnancy OGTT or < 20 weeks, then again 24-28 weeks

Teed HJ. Clin Endocrinol (Oxf). 2018 Sep;89(3):251-268
Will GLP-1 RA treatment help in PCOS?

- **Randomized trial of Exen, Exen+Met or Met, 24 weeks, 60 women**
  - Weight loss 6.0±0.5 kg in Exen+Met; 3.2±0.1 kg Exen; 1.6±0.2 kg Met
  - ↓ 2 hour glucose, better HOMA-IR
  - ↓SHBG and FAI, ↑ menses

- **Randomized trial of Lira, Lira+Met or Met, 12 weeks, 40 women**
  - Weight loss 6.5±2.8 kg in Lira+Met; 3.8±3.7 kg Lira; 1.2±1.4 kg Met
  - ↓ 2 hour glucose, no change in HOMA-IR
  - No change in androgens

- **LIPT –STUDY -randomized trial of liraglutide, 26 weeks, 65 women**
  - GLP-1 treatment: N=44, 5.2 kg loss, ~2% liver fat loss per $^1$H-MRS
  - Placebo: N=21, 0.2 kg gain, ~1% liver fat loss
  - ↓ Free testosterone, fasting glucose, ovary size, ↑ SHBG
  - No change in Matsuda, fasting lipids

Frossing S, Diabetes Obes Metab. 2018

Elkind-Hirsch K, JCEM 2008

Key Studies in Progress

• 18 trials in ClinicalTrials.gov

- **DAPA, EQW, DAPA/MET ER and PHEN/TPM ER in Obese Women With Polycystic Ovary Syndrome (PCOS) - NCT02635386**
- **135 women**, randomized to 5 therapies for **24 weeks**
- SGLT-2, Exenatide weekly, Exenatide +SGLT-2, SGLT-2 +Metformin ER, Phentermine/Topomax
- Started enrolling 2016

- **Liraglutide 3mg (Saxenda) on Weight, Body Composition, Hormonal and Metabolic Parameters in Obese Women With PCOS (SAXAPCOS) - NCT03480022**
  - **92 women, 2:1 Drug Placebo**
  - Started enrolling 9/2018
Metaanalysis of Risk for STROKE and Nonfatal CHD in Women with PCOS

Figure 1. Meta-analysis of stroke and coronary heart disease (CHD) in women with PCOS. This figure includes a forest plot comparing the risk of nonfatal stroke in women with PCOS compared to controls in the older age group (mean > 45 y) (top) and a forest plot comparing risk of nonfatal CHD in women with PCOS compared to controls in the older age group (bottom) (mean > 45 y). CI, confidence interval; M-H, Mantel-Haenszel. [Adapted from S. A. Anderson et al: Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: a systematic review and meta-analysis. Int J Cardiol. 2014;176:486–487 (173), with permission. © Elsevier.]
CVD and Weight Management

<table>
<thead>
<tr>
<th>Cardiovascular disease risk and weight management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All with PCOS should be offered regular monitoring for weight change and excess weight, in consultation with and where acceptable to the individual. Monitoring could be at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the individual. Weight, height and ideally waist circumference should be measured and BMI calculated.</td>
</tr>
<tr>
<td>• BMI categories and waist circumference should follow World Health Organisation guidelines also noting ethnic and adolescent ranges.</td>
</tr>
<tr>
<td>• Consideration for Asian and high risk ethnic groups including monitoring waist circumference.</td>
</tr>
<tr>
<td>All with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk.</td>
</tr>
<tr>
<td>If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD.</td>
</tr>
<tr>
<td>Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, measurement should be guided by the results and the global CVD risk.</td>
</tr>
<tr>
<td>All women with PCOS should have blood pressure measured annually.</td>
</tr>
<tr>
<td>CVD risk in women with PCOS remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting awareness and consideration of screening.</td>
</tr>
</tbody>
</table>

- Monitor *weight every 6-12 months*
- Assess individual **CVD risk factors**
- **Lipids** at diagnosis then per CVD guidelines
- **Blood pressure** checked annually

Teed HJ. Clin Endocrinol (Oxf). 2018 Sep;89(3):251-268
PCOS: Other Risks

• Obstructive Sleep Apnea: increased in PCOS patients
  • Known to be independent risk for stroke and MI in men; what about women?
  • Related to BMI?

• Liver Steatosis: Increased risk of fatty liver
  • Related to BMI?

• Mood: assess QOL, depression higher
OSA in PCOS correlated to BMI

Mokhlesi B Fert Steril 2012
PCOS and NAFLD Metaanalysis

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95%CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerda, C (2007)</td>
<td>2.95 (1.00, 8.75)</td>
<td>12.21</td>
</tr>
<tr>
<td>Zheng, RH (2008)</td>
<td>2.86 (1.27, 6.45)</td>
<td>14.89</td>
</tr>
<tr>
<td>Vassilatou, E (2010)</td>
<td>2.33 (1.02, 5.35)</td>
<td>14.72</td>
</tr>
<tr>
<td>Qu, Z (2010)</td>
<td>2.09 (1.42, 3.09)</td>
<td>19.00</td>
</tr>
<tr>
<td>Faisal, A (2012)</td>
<td>46.00 (12.35, 171.38)</td>
<td>10.26</td>
</tr>
<tr>
<td>Zueff, LF (2012)</td>
<td>3.14 (1.30, 7.60)</td>
<td>14.19</td>
</tr>
<tr>
<td>Karoli, R (2013)</td>
<td>5.86 (2.56, 13.43)</td>
<td>14.73</td>
</tr>
<tr>
<td>Overall (I-squared = 73.6%, p=0.001)</td>
<td>3.93 (2.17, 7.11)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effect analysis

Figure 2. Correlation Between NAFLD and PCOS
Ramezani-Binabai et al Hepatitis Monthly 2014 14: 23235
Case 4:

• 64 yr old WF presents with severe hirsutism
• Hx of infertility and irregular menses in 30’s
• Early menopause after treatment for breast ca
• Hx of R breast cancer ’94 ER+, chemo, xrt, SERMx5 yrs, recurrent ’99 now on letrozole (aromatase inhibitor block E production)
Drugs that cause Hirsutism

- Androgens alone or with estrogens
- Anabolic steroids
- Some OCPs with androgenic progestins
- Minoxidil
- Phenytoin
- Diazoxide
- Cyclosporine
- Aromatase inhibitors in the face of increased prohormones: ie NCCAH, PCOS?

Treating Hirsutism in Women with Hyperandrogenism

Removing hair
- Electrolysis
- Eflornithine hydrochloride
- Shaving
- Plucking
- Waxing

Treating underlying cause
- OCPs (drospirenone vs norethindrone)
- Spironolactone
- Finasteride
- Flutamide
- Metformin or TZD
- Weight loss

Case 4:

- 37 yr old woman referred for virilization
- Menarche age 12, regular menses until age 33, weight gain over 30 months, 2-3 menses then amenorrhea
- She denies exogenous drugs
- Exam: BP: 160/90, BMI-32, anabolic appearing, low voice, full beard, breast atrophy, male hair pattern, clitororomegaly
Case 4: Too Much

- Labs: LH-1.5, FSH- 2.2 mIU/ml,
- **T-450 ng/dl (nI<40)**, DHEAS 240ng/ml (nl to 260),
- E 45 pg/ml, Prl 6, Hct 52, creatinine 1.4
- What other diagnostic tests should be performed?
- What is the cause of her virilization?
Hyperandrogenic Anovulation: When to consider a Tumor

- **Rapid onset** of symptoms and signs in a woman with previously normal menses
- **Location** of hirsutism: upper back and chest and abdomen
- **Virilization**: temporal recession, anabolic phenotype, loss of breast tissue, clitoromegaly
- **Procedure**: Vaginal US, ? CT adrenals

Rothman and Wierman 2011 Clin Endo 75:160-4; Alpanes m et al JCEM 2012 97:2584-2588
Hyperthecosis

• Nests of luteinized stromal cells in the ovarian stroma
• Scattered throughout the stroma of the ovary, rather than being confined to areas around cystic follicles as in PCOS

• Ovarian stromal cells produce androstenedione; peripheral estrogen production is increased, can predisposes to endometrial carcinoma
• can occur in postmenopausal women

• Severe hirsutism and virilization in postmenopausal women are more often due to ovarian hyperthecosis than virilizing ovarian tumors
• Often associated with insulin resistance and hyperinsulinemia
Ovary with Sertoli Leydig Cell Tumor
Hyperandrogenism: Tumors

- **Ovarian** (T>200ng/dl), 10% of ovarian tumors
  - Sertoli-Leydig cell
  - Hilar cell tumor
  - Lipoid cell tumor
- **Adrenal** (DHEAS>8-900ng/ml)
  - Adrenocortical adenoma or carcinoma
  - Virilizing T secreting tumor only T is high (rare)
- **Treatment**: Surgery, GnRH agonists?

Male pattern balding pre- and post- tumor removal

Obesity Induced Hyperandrogenism

- History of normal menarche, regular menses
- Progressive weight gain without problems then surpass "threshold weight" with onset of irregular menses, hirsutism and acne
- Cysts on ovaries due to anovulation
- Successful weight loss reverses phenotype

? Role of weight loss drugs vs insulin sensitizers?
Case 5:

• 22 yr old college senior presents with irregular menses and acne. Menarche was age 15, athlete in school, missed periods age 17-18, some stressors
• Hirsutism upper lip, below umbilicus
• BMI 20
• What is the next step?
  • Prolactin
  • HCG
  • Testosterone, DHEAS
Not Everything is PCOS

• **Hypothalamic amenorrhea**: GnRH pulse generator defect (3-5% women)
  • Usually stressed women, usually not hirsute
  • Often thin but can be normal or overweight with eating disorder or mood disorder
  • Can have cysts on ultrasound due to anovulation
  • **Low normal LH=FSH low estradiol**
  • Risk of E deficiency
  • Treat with oral contraceptives to replace E, regularize menses
PCOS: Take home

- **Common**: 8-10% women
- **Anovulation, clinical /biochemical hyperandrogenism, insulin resistance**
- Obesity in 60++%
- **Risks**: infertility, obesity, metabolic syndrome (HTN, dyslipidemia), early diabetes
- Less established: endometrial cancer, ? Stroke, CAD, ?OSA, NAFLD (role of BMI)

- Dx requires early and continued intervention by health care providers
Hyperandrogenic Anovulation Differential Diagnosis

- Polycystic Ovarian Syndrome
- Ovarian or adrenal tumor
- Iatrogenic: exogenous androgen administration or exposure, other drugs
- Obesity-induced Hyperandrogenic Anovulation
- Congenital adrenal hyperplasia
- Other: familial hirsutism, Cushing’s syndrome, prolactinoma
Role of NK3 in GnRH induced LH secretion

KNDy neuron (in hypothalamus)

GnRH neuron (in hypothalamus)

MЛЕ4901 inhibits NK3R on the KNDy neuron...

...which leads to a reduction in GnRH hyperpulsatility...

...resulting in lower LH and T levels.

NK3 receptor antagonists: early days

- ESN364 Ogeda -> Astellas Pharmacueticals
- AZD4901/MLE490 (was AZD2624) Millendo Therapeutics

- AZD4901 in 6 Healthy women
  - 40 mg orally twice daily for 5 days, Day 5-10 of cycle
  - No change in LH, lower estrogen, smaller follicles, thinner endometrium

- ESN364 in 24 healthy, normal cycling women
  - placebo or 20, 60, or 180 mg each day for 21 days
  - dose-dependently decreased basal LH, not FSH
  - decreased estradiol and progesterone
  - delayed ovulation, decreased endometrial thickening, impeded follicular maturation, longer menstrual cycle

- WHAT ABOUT IN PCOS? Stay tuned

Fraser GL, JCEM 2016 Feb;101(2):417-26