My Approach to PCOS

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Current consensus among most professional societies requires 2 of 3 criteria:
- Androgen excess
- Irregular menses/anovulation
- Polycystic ovarian morphology on ultrasound (AACE/ACE/AES propose 25 or more follicles per ovary)

5-20% of all women of reproductive age

Legro et al, 2013
PCOS signs
Associated comorbidities

- Obesity (60-80%)
- Type 2 diabetes (7-10%)
- Chronic hypertension
- Metabolic syndrome
- Obstructive sleep apnea
Managing PCOS

Glucose Intolerance
Obesity
Hirsutism
Acne
Infertility
Irregular Menses
OCPS
Metformin
Spironolactone
Clomid
Letrozole
Myo-Inositol
Managing PCOS

Glucose Intolerance
Obesity
Hirsutism
Acne
Infertility
Myo-Inositol?
Irregular Menses
OCPS
Metformin
Spironolactone
Clomid
Letrozole
The Patient: Symptoms

- Menstrual History
- Acne
- Hirsutism
- Current BMI and change over time
- Infertility
The Patient: Goals

- Menstrual regulation
- Treatment of acne and hirsutism
- Weight loss
- Fertility
Evaluation

- My goal in evaluation is NOT to make or break a PCOS diagnosis according to AACE/AES/PCOS guidelines
- Rather, it is to determine disease state and health risks
- For targeted treatment
Evaluation: Irregular menses

- Menstrual pattern: amenorrhea, oligomenorrhea, metrorrhagia
- Urine hcg, TSH, prolactin
- If uncertainty as to ovulation, serum progesterone ~1 week prior to expected menses
Evaluation: Irregular menses

- Endometrial biopsy to assess for hyperplasia with atypia in cases of metrorrhagia over the age of 35

- Ultrasound:
  - Structural abnormalities contributing to metrorrhagia
  - 25 or greater antral follicles per ovary, and/or volume > 10 mL
Differential diagnosis: Irregular menses

- Evaluation limited to selected patients with other signs or symptoms

- Hypothalamic amenorrhea:
  - Low BMI, recent weight loss or intense exercise, no hyperandrogenism
  - FSH, LH, estradiol

- Primary ovarian insufficiency:
  - Hot flashes, vaginal dryness
  - FSH and estradiol, AMH
Evaluation: Hirsutism, acne, or alopecia

- History: onset, rate of progression
- Physical examination:
  - Modified Ferriman-Gallwey
  - Acne
  - Alopecia
  - Skin tags
  - Virilization (clitoromegaly, voice)
Evaluation: Modified Ferriman-Gallwey
Table 2: Acne grading method by Cook et al.,\textsuperscript{11} using photographic standards

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Up to 3 small scattered comedones and/or small papules are allowed.</td>
</tr>
<tr>
<td>2</td>
<td>Very few pustules or 3 dozen papules and/or comedones; lesions are hardly visible from 2.5m away.</td>
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<tr>
<td>4</td>
<td>There are red lesions and inflammation to a significant degree; worthy of treatment.</td>
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<tr>
<td>6</td>
<td>Loaded with comedones, numerous pustules; lesions are easily recognized at 2.5m.</td>
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<tr>
<td>8</td>
<td>Conglobata, sinus or cystic type acne; covering most of the face.</td>
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Cook et al, 1979
Evaluation: Hyperandrogenism

- Documenting a detailed physical examination facilitates assessment of response to treatment
Evaluation: Hyperandrogenism

- 17-hydroxyprogesterone to rule out non-classic congenital adrenal hyperplasia
  - >200 ng/dl requires ACTH stimulation test

- Free testosterone by equilibrium dialysis is the most sensitive androgen (i.e., highest proportion of women will be positive)
Evaluation: Selected patients

- Virilization, mFG >15 or rapid onset of symptoms: rule out androgen-secreting tumors
  - Early morning total testosterone > 200 ng/dl
  - DHEAS > 700-750 µg/dl

- Obesity, hypertension, violaceous striae, muscle wasting
  - 24-hour urinary free cortisol to rule out Cushing’s syndrome

- Skin thickening, hyperhidrosis, macrognathia, bony changes
  - Serum IGF-1 to rule out acromegaly
Evaluation: Obesity and Metabolic Syndrome

- All women with PCOS should be screened for metabolic syndrome (3 of 5, per AHA guidelines):
  - BMI >30 kg/m²
  - Waist circumference >35 inches
  - Blood pressure > 130/85
  - Fasting lipids (HDL <50 mg/dl, triglycerides >150 mg/dl)
  - 2 hour, 75 gram oral glucose tolerance test (fasting glucose >100 mg/dl)
Evaluation: Obesity and Metabolic Syndrome

- Assess historical factors: smoking, family history of early cardiovascular disease
- Refer or treat for new diagnoses of hypertension or diabetes
Evaluation: Depression

- Major depressive disorder is more common in women with PCOS (OR 3.8)

- All women with PCOS should be screened for depression and anxiety
  - Hamilton Depression Rating Scale, Beck Depression Inventory

Mansson, 2008
Evaluation: Obstructive sleep apnea

- Women with PCOS are:
  - 30 times as likely to have sleep disordered breathing
  - 9 times as likely to have daytime sleepiness, after adjustment for BMI

- Women with symptoms of snoring and/or daytime sleepiness should undergo polysomnography

Vzontgas, 2001
Evaluation: Infertility

- Cycle length >35 days usually indicates anovulation
- 10-15% of hyperandrogenic women with regular menses are anovulatory
- Best assessment is serum progesterone 1 week prior to expected menses
- Semen analysis (10% severe oligozoospermia)
- HSG (5% bilateral tubal obstruction)

Legro et al, 2013
Treatment: Irregular menses

- Oral contraceptives as first line (contraceptive patch and vaginal ring as well)
- Effective for acne and hirsutism
- No evidence to support any particular dose or formulation
- Contraindications in PCOS are the same as in other populations
Alternatives for irregular menses

- Levonorgestrel IUD
- Progestin-only pills
- Cyclic oral progestin
- Etonogestrel implant
- Depot medroxyprogesterone acetate
Treatment: Hirsutism

- “Patient-important” hirsutism is an indication for treatment

- OCPs are first-line pharmacologic treatment
  - Mean change in mFG -8.

- If OCPs are contraindicated, antiandrogens may be used, but adequate contraception is necessary

Martin, 2008
Treatment: Hirsutism

- Hair removal: Laser, electrolysis, mechanical removal
- Spironolactone 50 mg bid
  - Mean change in mFG -4.8
- Finasteride 5 – 7.5 mg daily
  - Similar efficacy to spironolactone, 30-60% decrease in hirsutism
Treatments to avoid

- Flutamide: Hepatotoxicity, which has been fatal in case reports
- Metformin: ineffective
  - Change in mFG -1.5
- Glucocorticoids: limited efficacy, severe side effects
- Topical therapy: finasteride, eflornithine
  - Limited efficacy, high cost
Treatment: Obesity

- No strong evidence to support a particular diet in improving weight loss, menstrual cyclicity, or fecundity in PCOS.

- Studies in other populations have demonstrated benefit for a variety of diet types:
  - Atkins (low carbohydrate, high fat and protein)
  - Weight Watchers (calorie counting/points based)
  - Zone diet (30% protein/40% carbohydrate/30% fat)

Atallah, 2014
Potential benefits of exercise

- Exercise interventions associated with a 50-60% rate of resumption of ovulation (Harrison et al, 2011)

- Palomba et al (2008) reported a 35% pregnancy rate over the course of a 24 week intervention with exercise for 30 minutes, 3 times per week.

- Mario et al (2016) noted decreased serum androgens, FAI, BMI, and waist circumference in active versus sedentary women with PCOS
Obesity: Medical and surgical therapy

- ACC/AHA/The Obesity Society recommend consideration of bariatric surgery for:
  - BMI >40
  - BMI >35 with an obesity-related comorbidity

- The Endocrine Society recommends pharmacotherapy as an adjunct to lifestyle modification:
  - BMI > 30
  - BMI >27 with a comorbidity

ACC, 2014; Aprovian, 2015
Treatment: Impaired glucose tolerance

- First line treatment is lifestyle modification (diet and exercise)
- Metformin
  - Less effective than lifestyle modification in preventing progression to diabetes among those with impaired glucose tolerance
  - Secondary treatment for irregular menses if contraindications to hormonal options
- Inositols: Inadequate data to suggest a benefit
Infertility: Ovulation induction

- No need for a progestin withdrawal bleed prior to initiation of therapy
  - 5% live birth with random start versus 1.6% with progestin withdrawal (Diamond, 2012)

- PPCOS I trial: Clomiphene is more effective than metformin in inducing ovulation and achieving live birth in PCOS (Legro et al, 2007)

- PPCOS II Trial: Letrozole is superior to clomiphene citrate in inducing ovulation and in achieving pregnancy (Legro et al, 2014)

- Clomiphene or letrozole may be used in a “stair-step” fashion with sequential dose increases without progestin withdrawal (Deveci et al, 2015)
  - Decreased time to ovulation
A practical approach to ovulation induction

- Initiate letrozole at 5 mg daily for 5 days after a negative pregnancy test and baseline ultrasound
- Increase in a stair-step fashion to 7.5 mg daily x 5 days
- Increase length of therapy to 10 days
- Add clomiphene citrate in increasing dose (50 to 150 mg)
- Monitor with ultrasound and urine hCG
Ovulation induction: Adjuncts when standard therapies fail

- Dexamethasone 1 mg bid for 10 days concurrent with clomid/letrozole
- Metformin extended release 1500 mg daily
- Naltrexone 50 mg daily
- Gonadotropins: A short course at a low dose if there is follicular development to 14-16 mm but maturity is not achieved
- No benefit for IUI in PCOS (Abu Hashim et al, 2011)
Ovulation induction: Laparoscopic ovarian drilling

- Cochrane review with meta-analysis of 9 RCTs found LOD to be equal to alternative medical therapies in achieving live birth in women with PCOS (34% LOD versus 38% other therapies)
  - Lower rate of multiple gestation was significant only in comparison to gonadotropins

- Liu et al, 2015: RCT demonstrated higher live birth rates in women randomized to letrozole 2.5 mg days 5-10 than laparoscopic ovarian drilling (38% vs. 23%)
Miscarriage in PCOS

- Data is mixed on whether miscarriage is more common in women with PCOS (no difference to 3-fold increased risk)
- In IVF, no higher risk in PCOS compared with other diagnoses when matched for BMI (Provost, 2015)
- Obesity and insulin resistance are associated with increased rates of miscarriage in PCOS women
- Meta-analysis suggests metformin decreases risk of miscarriage (Feng et al, 2015)
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