PCOS: Evaluation and Treatment

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Potential conflicts of interest

- None
Case Study - 24 year old female

- CC: Irregular menstrual cycles, weight gain

- Menarche - age 13. At age 16 her periods became irregular and infrequent, 45 days to 6 months apart, LMP 3 months ago which lasted 9 days and was very heavy

- Reports 15-20 lb weight gain over the past year

- Notes excessive hair growth on upper lip, chin, mid-sternum

- Reports worsening acne on her face, chest and back over the past year.
Physical exam

On exam:
- BP 122/80, Wt: 224 lbs, Ht: 5’4” BMI: 38.5
- Generalized obesity with velvety, dark brown pigmentation at the nape of neck
- Dark hairs on upper lip; scattered hair on chin, chest
- Scattered acne noted on face/chest/upper back
- Terminal hairs on linea alba below umbilicus
What’s her diagnosis?

Could she have PCOS?

- How to we confirm the diagnosis?
- How to treat her symptoms?
OBJECTIVES

1. Understand the pathophysiology of Polycystic ovarian syndrome (PCOS)
2. Review the diagnostic criteria from NIH/Rotterdam/Androgen excess society
3. Review the treatment options available for PCOS
Presence of “polycystic ovaries” confirmed by pelvic ultrasound is required to make a diagnosis of PCOS

- True
- False
Which of the following organs is sensitive to the action of insulin in PCOS women

a. Liver  
b. Skeletal muscle  
c. Ovary
What is the long term complication most commonly associated with PCOS?

a. Invasive endometrial carcinoma
b. Osteoporosis
c. Diabetes mellitus
d. Impaired glucose tolerance
e. Sleep apnea
Which of the following hormones increases SHBG production?

(a) Insulin
(b) Testosterone
(c) Progesterone
(d) Estrogen
(e) IGF-1
The best test/s to diagnose pre-diabetes in women with PCOS

a. Fasting glucose

b. OGTT

c. HbA1c

d. 2 hour post glucose challenge insulin
History

- **1935**

- **1980** Link to hyperinsulinemia and impaired glucose tolerance

PCOS – Epidemiology

- Most common endocrinopathy in reproductive age group women
  - 5-10% are affected
  - Symptoms typically begin during adolescence

- Most common cause of female infertility

- But still underdiagnosed and undertreated
Pathophysiology

- a) primary neuroendocrine defect
- b) increased production of ovarian androgens
- c) defect in the action and secretion of insulin
  - Pituitary dysregulation
  - Insulin resistance Ovarian hyperandrogenism
Pathophysiology of PCOS

Menstrual cycle

MenstrualCycle2_en.svg
https://www.metaboliceffect.com/pcos/
Pathophysiology of PCOS

Possible mechanism by which insulin resistance leads to the clinical manifestations of PCOS

Figure from Uptodate, Originally adapted from Mantzoros, CS, Flier, JS, Adv Endocrinol Metab 1995; 6:193. 333.
Diagnosis of PCOS
History & Physical exam

- **Presence of androgenic symptoms** (acne, hirsutism, alopecia)

- **Reproductive health** (menarche, past and present cycle, oligo-/amenorrhoea, menorrhagia, miscarriage, infertility)

- **Lifestyle factors** (changes in body weight, eating and exercise habits)

- **Weight, BMI, BP**

- **Waist circumference**

- **Acne, hirsutism, scalp hair thinning, acanthosis nigricans**

- **Abdominal striae**

- **Frontal balding, deepening of the voice, broadening of the shoulders, breast atrophy**

- **Ferriman Gallaway scoring**

Teede HJ., Hum Reprod 2018
Grading of severity of hirsutism

Ferriman Gallaway Score

Mild
Hatch R., Am J Obstet Gynecol 1981; 140:815
Moderate
Teede HJ., Hum Reprod 2018
Severe
>25
Various criteria used to diagnose PCOS

- Hyperandrogenism
- Oligo-anovulation
- Polycystic ovaries on ultrasound

<table>
<thead>
<tr>
<th>NIH 1990</th>
<th>Rotterdam criteria 2003 (2/3 required)</th>
<th>Androgen Excess Society 2006 (2/3 required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenism</td>
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<tr>
<td>Menstrual irregularity</td>
<td>Menstrual irregularity</td>
<td>Menstrual irregularity (or)</td>
</tr>
<tr>
<td>Exclusion of other etiologies</td>
<td>Polycystic ovaries on ultrasound</td>
<td>Polycystic ovaries on ultrasound</td>
</tr>
<tr>
<td></td>
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All possible phenotypes based on the presence or absence of oligo anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome (PCOS).

Aziz, Fertil Steril 2006
Hyperandrogenism

- Various Androgens
- Which Testosterone?
- Which assay?

Original data from DeVane, Am J Obstet Gynecol 1975; 121:496, figure from uptodate
Teede HJ., Hum Reprod 2018
Polycystic ovaries

- Excessive size is defined as an ovary with a **volume** >10 cubic mL in adults.

- Excessive **follicle number** is defined as >20 follicles per ovary. These follicles are typically 2 to 9 mm in diameter.

When can USG be used for dx?
- Transducer frequency bandwidth?
- No: of follicles per ovary?
- Ovarian volume?

Image from Uptodate Courtesy of Robert L. Rosenfield, MD

Teede HJ, Hum Reprod 2018
## Exclusion of other etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Diagnostic test/s</th>
</tr>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>TSH</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Late onset non classic CAH</td>
<td>17 OH progesterone</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>HCG</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>24 hour urine cortisol</td>
</tr>
<tr>
<td>Androgen secreting tumor</td>
<td>Testosterone, DHEAS</td>
</tr>
<tr>
<td>Primary ovarian insufficiency</td>
<td>FSH, estradiol</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
<td>FSH, LH, estradiol, progesterone</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>IGF1</td>
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Treatment of PCOS
Treatment of PCOS

Rx priorities

**Patient concerns:**
- Current issues
  - Menstrual irregularities
  - Cosmetic concerns
  - Weight issues
  - Infertility

**Additional concerns for the Physician**
- Future issues
  - Endometrial Cancer Risk
  - DM type 2 Risk
  - Dyslipidemia Risk
  - Cardiovascular Risk
MANAGEMENT OF PCOS

ANOVULATION
- Irregular menstrual cycles (Prevent endometrial hyperplasia)
  - Infertility (Induce ovulation)

HYPERANDROGENISM
- Hirsutism (eg Decrease androgens)
  - Acne
  - Alopecia

METABOLIC RISKS
- IGT/DM (Lifestyle measures)
  - Obesity
  - Dyslipidemia
A. Irregular Menstrual Cycles
A. Irregular menstrual cycles

1. **Combined Estrogen-Progestin contraceptive pills**
   - Progesterone prevents endometrial hyperplasia
   - Estrogen increases SHBG levels
   - Decreases pituitary LH secretion and ovarian/adrenal androgen secretion

2. **Periodic progesterone withdrawal**
   - Cyclic Medroxyprogesterone acetate
     - 5-10mg po qd X 10-14 days
   - Cyclic Micronized progesterone
     - 200mg po qd X 10-14 days
     - (contraception needed)
   - Norethindrone 0.35 mg daily
   - Levonorgestrel-releasing IUDs

3. **Weight loss**
4. **Metformin**
   - restores ovulatory cycles, ?endometrial protection
OCPs lower free testosterone concentration and decreases hair growth

- Normalization of the serum free testosterone concentrations in seven women with PCOS after the initiation of therapy with OCP containing estradiol 30 mcg and norethindrone acetate 1.5 mg

- Changes in hair growth rates, determined by photography, in hirsute women treated with ethinyl estradiol 30 g and desogestrel 0.15 mg

Data from: Raj SG. Obstet Gynecol 1982
Data from: Dewis P. Clin Endocrinol (Oxf) 1985; 22:29
B. Hyperandrogenic symptoms
B. Rx of Hyperandrogenic symptoms

Combination Rx better than single agents

<table>
<thead>
<tr>
<th>HIRSUTISM</th>
<th>ACNE</th>
<th>HAIR LOSS</th>
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<tr>
<td>Combined OCP</td>
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<td>Antiandrogen</td>
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<tr>
<td>Eflornithine cream</td>
<td>Benzoyl Peroxide</td>
<td>Minoxidil</td>
</tr>
<tr>
<td>Laser</td>
<td>Topical antibiotic</td>
<td></td>
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<tr>
<td>Electrolysis</td>
<td>Tretinoin cream</td>
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- Oral EP contraceptive pills
  - Decrease bioavailable testosterone levels
- Spironolactone (off label use)
  - Androgen receptor antagonist
- Eflornithine cream
  - Inhibits the enzyme ornithine decarboxylase
- Laser photoepilation
  - Selective absorption by melanin and destruction of hair follicles

Teede HJ, Hum Reprod 2018
C. Metabolic & Other Risks
C. Metabolic & other risks

- **Screen for**
  - Impaired GT/Type 2 DM
  - Obesity
  - Dyslipidemia
  - Hypertension
  - Obstructive sleep apnea
  - Depression & anxiety

- **Treatment**
  - Lifestyle measures: Diet, exercise, and behavioral strategies
  - Weight loss
  - Insulin sensitizers
  - Appropriate referral for OSA and depression

Teede HJ, Hum Reprod 2018
Prevalence of impaired glucose tolerance and diabetes in women with PCOS

Study Design:

a) 122 PCOS women had a standard OGTT

b) A subset of 25 women had OGTT after 2 years.

Results:

- Glucose tolerance abnormal in 45%, 35% had IGT and 10% had DM
- Women with DM compared to those with normal glucose tolerance had a 2.6-fold higher prevalence of first-degree relatives with DM and were significantly more obese

Prevalence of IGT and DM

- Among the subset with IGT, the fasting glucose concentration was poorly predictive of the 2-h level.

- The glucose concentration at 2 hr during the fu OGGT was significantly higher than that of the first study.

- Women with PCOS should have periodic OGGT.

Weight loss

- Improvement of menstrual function with 5-10% weight loss, variable response
- Improves pregnancy rates
- Decreased need for ovulation induction
- Normalization of hyperandrogenemia
- Few data on improvement of hirsutism
- Diet: energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day)
- Exercise: moderate (250 minutes/week) or vigorous intensity (150 minutes/week) + muscle strengthening
- SMART - (Specific Measurable, Achievable, Realistic and Timely), goal setting and self-monitoring

Teede HJ, Hum Reprod 2018
Kiddy DS Clin Endocrinol (Oxf) 1992;36:105–111
Escobar-Morreale HF J Clin Endocrinol Metab. 2005;90:6364–6369
Bariatric surgery outcomes

- PCOS women with morbid obesity underwent bariatric surgery
- Weight loss (41 +/- 9 kg after 12 +/- 5 months
- Menstrual cycles/ovulation restored
- Insulin resistance improved
- Androgen levels decreased
- Hirsutism scores improved

Cardiovascular risk

- **Nurse’s Health Study:** increased dose response risk of CVD/events in the presence of increasing oligomenorrhea

- More angiographic CAD and worsening CV event-free survival in premenopausal women with irregular menses and hyperandrogenemia - WISE (*Women's Ischemia Syndrome Evaluation*) study

- Increased carotid intimal medial thickness noted in studies examining subclinical atherosclerosis in premenopausal women with PCOS

- No prospective studies yet on cardiovascular events in women with PCOS.
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Summary: PCOS

- The most common endocrine disorder in women and the most common cause of chronic anovulation

- Other major features are hyperandrogenism and insulin resistance

- Long term risks: Infertility, type 2 DM, dyslipidemia, cardiovascular risks, sleep disordered breathing, endometrial hyperplasia and carcinoma

- Treatment depends on the needs of the patient, at the same time focusing on preventing long term health issues.
Thank you