PCOS

- Stein-Leventhal syndrome
- 5-10% estimated prevalence
- Most common endocrinopathy in GYN
- Ovulatory dysfunction
- Heterogeneous presentation
- No definitive genetic or environmental factors
- Theory – enhanced CYP17 activity in ovary and decreased insulin receptor activity peripherally
Poly – Case Presentation
- 28 yo Hispanic female G0
- Married
- Irregular periods
- Desires pregnancy

Consensus on diagnostic criteria for PCOS

Rotterdam 2004 criteria 2 out of 3
1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries on ultrasound
*Exclusion of other etiologies

ESHRE and ASRM 2004

"Mimickers"
- CAH, Congenital Adrenal Hyperplasia
- Androgen-secreting tumors
  - Ovarian vs. adrenal
- Cushing syndrome
- Ingestion of exogenous androgen
## Pertinent History

- Ovulatory frequency
- Serum and/or clinical androgen status
  - Hirsutism
- Ovarian imaging / Pelvic US
- Galactorrhea
  - Prolactin
- Hypothyroid
  - TSH
- Diet, exercise, weight
- Medication
  - Partners who use topical androgen products
- Family history
- Social history

## Hyperandrogenism

**Clinical hyperandrogenism**
- Hirsutism: excessive growth of terminal hair in women in a male like pattern
- Acne 10-15%
  - Inflammatory acne in adolescents, moderate to severe
- Alopecia: weak marker unless associated with anovulation 5%

## Hirsutism

- Visual scoring: modified Ferriman-Gallwey score
- 50% of women with unwanted hair score < 5 had PCOS
- Less prevalent in East Asian or in adolescence
- Ask patient about strategies and frequency of hair removal/waxing

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*Reference: Souter et al., Am J Obstet Gynecol. 2004*
Hyperandrogenism

Biochemical hyperandrogenism
- Total Testosterone is not a sensitive marker in females
  - TT > 200 ng/dL, r/o ovarian androgen tumor
- Free testosterone T: equilibrium dialysis or calculated
- Isolated elevations in DHEA-S 10% or elevated Androstenedione 10%
  - DHEA-S > 700 ug/dL, r/o adrenal androgen tumor
- 20-40% will have normal androgens

Menstrual dysfunction

- Oligomenorrhea fewer than nine menses per year or amenorrhea
  - Cycles > 35 days
- Anovulatory cycles:
  - Dysfunctional uterine bleeding
  - Decreased fertility
  - Endometrial hyperplasia
- Usually starts at menarche and the postpubertal phase
Menstrual irregularities in adolescent

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary amenorrhea</td>
<td>Lack of menarche by 15 y of age or by 1 years after the onset of breast development^</td>
</tr>
<tr>
<td>Secondary amenorrhea</td>
<td>Over 60 d without a menstrual period after initially menstruating</td>
</tr>
<tr>
<td>Oligomenorrhea (infrequent AUB)</td>
<td>Postmenarcheal year 1: average cycle length &gt;60 d (&gt;4 periods)</td>
</tr>
<tr>
<td>Postmenarcheal year 2: average cycle length &gt;60 d (&gt;4 periods)</td>
<td></td>
</tr>
<tr>
<td>Postmenarcheal years 1-6: average cycle length &gt;45 d (&lt;3 periods)</td>
<td></td>
</tr>
<tr>
<td>Postmenarcheal years ≥7: cycle length &gt;10-40 d (≤8 periods)</td>
<td></td>
</tr>
<tr>
<td>Excessive anovulatory AUB?</td>
<td>Menstrual bleeding that occurs more frequently than every 21 d (19 d in yr 1) or in excessive facts (&gt;7 d or beaues &gt;1 pad or tampon every 1-2 h)</td>
</tr>
</tbody>
</table>

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Ultrasonographic PCOM:
Polycystic ovaries morphology

- > or = 12 follicles (2-9mm)
- Increased ovarian volume > 10cm³
- In either ovary

*Polycystic-appearing ovaries → present in 30% population

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AMH : Anti-Mullerian hormone

- AMH was suggested as a surrogate for PCOS
- AMH > 4.7 ng/ml (35 pmol/L):
  - Sp: 79.4%, Se: 82.8 %
  - AUC: 0.87
- May be useful
- Problems with standardization of the assay

Iliodromiti et al. JCEM. 2014
BMI
- Up to 50% women are obese or overweight
- Lean / Thin PCOS
- Obesity
  - Insulin resistance
  - Low sex-hormone binding globulin (SHBG) $\Rightarrow$ Increase relative levels free serum testosterone
  - Elevated estrogen
    - Adipose aromatase conversion of androgens $\Rightarrow$ estrogens
    - Increased risk of DM and cardiovascular disease

Insulin Resistance or DM
- PCOS population
  - IR: 31%
  - Type II DM: 7.5%
- Other associations
  - Obstructive Sleep Apnea, 5-10 times more
  - Depression, odd ratio for abnormal depression scores: 4.03 (2.96-5.5)
  - Metabolic syndrome

Poly’s History
- One of 6 children
- Mother has insulin-dependent type 2 DM
- Menarche age 14
- 4 menses per year
- Continuing weight gain
Physical exam

- Skin/ body changes
  - Acne
  - Male pattern hair loss
  - Abdominal striae
    - Consider other signs of Cushing’s
      - Dorsocervical or supracervical fat pad
      - Centripetal obesity
      - Muscle wasting

- Dorsocervical or supracervical fat pad

- Centripetal obesity

- Muscle wasting

Physical exam

- Acanthosis nigricans
  - Presence in dorsal neck, axillae, beneath breast, and/or pannus consistent with insulin resistance

- HAIR-AN syndrome
  - Hyperandrogenism, insulin resistance- acanthosis nigricans

Physical exam

- Clitoris enlargement / clitoromegaly
  - Normal 1.5-2 cm long, <1cm base diameter
  - More commonly found with high androgen levels associated with adrenal or ovarian neoplasms
Poly’s Physical exam

- BP 110/70, Pulse 72, Wt 192lb, Ht 5’3, BMI 34.5
- Moderate facial hirsutism – dark, thick facial hair on the upper lips and sideburns
- Bilateral axillary hyperpigmentation
- Tanner V breast, no nipple discharge
- Obese, no striae, “apple” shape, waist circumference 43in
- Normal vulva, clitoris 4mm
- Normal uterus, slightly enlarges ovaries

Recommended PCOS Testing

- Labs
  - bHCG
  - TSH
  - PRL
  - Glucose tolerance test → 2hr, 75g OGT
  - or HbA1c
    - 5.7-6.4% = insulin resistance
    - >6.5% = diabetes
  - Pelvic ultrasound

  - TSH to exclude hypothyroidism
  - Prolactin to exclude hyperprolactinemia
  - Many hyperandrogenic patients may have prolactin levels slightly above normal

Blood Test Levels for Diagnosis of Diabetes and Prediabetes

- Diabetes: A1C (percent) 6.5 or above, Fasting Plasma Glucose (mg/dL) 126 or above, Oral Glucose Tolerance Test (mg/dL) 200 or above
- Prediabetes: A1C 5.7 to 6.4, Fasting Plasma Glucose 100 to 125, Oral Glucose Tolerance Test 140 to 189
- Normal: A1C About 5, Fasting Plasma Glucose 99 or below, Oral Glucose Tolerance Test 129 or below

Definitions: mg = milligrams, dl = deciliter
For all these tests, within the prediabetes range, the higher the test result, the greater the risk of diabetes.
Other Possible Labs

- FSH and estradiol E2
  - R/o hypogonadotropic hypogonadism or premature ovarian insufficiency
  - Consider LH and P4
    - Previous LH:FSH ratio > 2-3
      - suggestive of PCOS
  - Total testosterone
  - Dehydroepiandrosterone sulfate DHEAS
    - Rapid virilization, r/o adrenal neoplasm

- Early morning fasting 17-hydroxyprogesterone (17-OHP) in follicular phase ➔ r/o 21-hydroxylase Nonclassical Congenital Adrenal Hyperplasia CAH
  - High risk populations, i.e. Ashkenazi Jews, Hispanics
  - Draw with P4 to see where in cycle
    - Physiologically elevated in the luteal phase
  - If > 200 ng/dL ➔ ACTH Cortrosyn stim test

- Other consideration
  - Endometrial biopsy in patients at high risk for endometrial hyperplasia

Poly's Test Results

- bhCG negative
- TSH normal
- PRL normal
- Hispanic risk factor: 17-OH P normal
- 2hr GTT 135
- Pelvic US – multiple peripheral cysts <10mm in size
Management

<table>
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<tr>
<th>Recommendation</th>
<th>Frequency</th>
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<tr>
<td>BP, Waist –hip ratio and BMI</td>
<td>Every visit</td>
</tr>
<tr>
<td>Complete lipid profile</td>
<td>Every two years (sooner if risk additional factors or weight gain)</td>
</tr>
<tr>
<td>2 hour GTT</td>
<td>Every 3-5 years (sooner if risk additional factors: obese, advanced age, GDM, or family history of Type 2 diabetes)</td>
</tr>
</tbody>
</table>

Endocrine society, 2013

Exclusion of “Mimickers”

- Non-classic adrenal hyperplasia 2%
  - Fasting am follicular 17-hydroxyprogesterone
  - If > 200 ng/dL → ACTH stimulation test

- Cushings syndrome 0.14%
  - R/o if patient is hypertensive and has Cushing’s stigmata
  - 24-hour urinary free cortisol

TREATMENT
Treatment

I. Insulin resistance and glucose intolerance

II. Hirsutism and acne

III. Oligomenorrhea and amenorrhea

IV. Ovulation Induction

I- Insulin resistance and glucose intolerance

• **Weight loss is first line therapy**
  • Important in treating overweight / obese patient
    • Goal at least 5-7% of body weight
  • No unique weight-loss regimen targets excess adiposity specific to the syndrome
    • Calorie-restrictive

I- Insulin resistance and glucose intolerance

■ Metformin
  • GI upset in 10-25%
  • Weight loss
  • Metformin ER Qhs titrate up to 1500-2000mg
    • 1 week 500mg, next week 1000mg, following 1500mg
  • Risk of lactic acidosis, followup with Cr and LFTs

*Limited evidence of metformin alone for fertility*
II- Hirsutism and acne

First line: Oral Contraceptives
- Suppress LH and androgen production
- Increase SHBG
- Choice of OCP is controversial
  - At least 30ug ethinyl estradiol
  - Levonorgesterel and Norethindrone
  - Norgestimate and desogestrel
  - Drosperinone (Yaz, Yasmine: VTE?)
- Potential adverse effects: insulin resistance, glucose tolerance, and coagulability

II- Hirsutism: Other options

- Anti-androgenic therapy
  - Spironolactone or flutamide
    - Spironolactone 100-200 mg/day
    - Rare complication of flutamide → fulminant hepatic injury
  - Finasteride, 5α-reductase inhibitor

* Contraception essential
  - Male fetus may undergo feminization

II- Hirsutism: Other options

- Eflornithine (Vaniqua, topical)
  - Irreversibly inhibits ornithine decarboxylase, necessary for hair growth
  - Effect seen over 4-8 weeks

- Combine w/ mechanical, cosmetic, laser therapy
III- Oligomenorrhea and amenorrhea – not desiring pregnancy

- Oral contraceptives
  - E+P
  - Reduce LH and androgen production
  - Ethinyl estradiol component \( \rightarrow \) increases SHBG
  - Some progestins with anti-androgenic potentials at the receptor
- Cyclic progesterone
  - Not a contraceptive

FERTILITY MANAGEMENT

IV: Ovulation Induction

- Patients who desire pregnancy
- Long history with Clomiphene citrate
  - SERM
  - Estrogen agonist-antagonist
    - Binds to hypothalamic receptors \( \rightarrow \) senses a decrease in estrogen \( \rightarrow \) increases GnRH
IV- Ovulation induction

- **Clomiphene citrate**
  - Start 50mg daily on cycle day 3 for five days
  - If failed, increased to 100, followed by 150mg daily
  - ~50% ovulate with 50mg, another 25% at 100mg
  - 6 month live birth rate 20-40%
  - Multiples risk <10%

- **Letrozole**
  - Aromatase inhibitor
  - Blocks androgens to estrogens
  - Off-label use
  - Letrozole 2.5-5 mg
  - Multiples risk <10%
  - *Shown to be superior to clomiphene citrate for ovulation induction (PPCOS II trial 2014, RCT)*

*Legro et al, NEJM, 2014*
IV- Ovulation induction

- Ovulation monitoring and Timed intercourse
  - LH urinary ovulation predictor kits (OPKs)
    - Ideally check early afternoon
  - Intercourse same day and next 2 days
  - Transvaginal ultrasound, midcycle ~ day 12
    - Follicle(s) > 18-20mm, +response
    - Consider ovulation trigger with Ovidrel/hCG 250mcg SQ, intercourse at least twice within 36 hours

- Ovulation confirmation
  - Temperature charting
  - Serum Progesterone (cycle day 21)

- Metformin
  - Numerous studies
  - Limited evidence for Metformin alone in fertility
  - PPCOS I trial, 2007: Clomiphene, Metformin, or Both
    - Metformin, alone or with Clomiphene did not improve live birth rates

Metformin: Pregnancy in Polycystic Ovary Syndrome I (PPCOS I)
IV- Ovulation induction
- If non-responsive, a higher dose of Letrozole or Clomiphene may be initiated without inducing menses
  - “Stair-step” protocol
  - High as Clomiphene 150-200mg or Letrozole 7.5mg
- Clomiphene and Letrozole
  - No associated congenital anomalies
- If resistant, considering adding glucocorticoids
  - Dexamethasone 0.5 – 2mg during the follicular phase (cycle 3 to 12)

Other Fertility Treatments
- Injectable gonadotropins → increase risk of OHSS and higher multiples
- IVF
- Laparoscopic ovarian drilling
  - Multiple perforation in ovarian stroma → decrease androgens
  - No improvement over other medical therapies
  - Concern compromise to ovarian reserve

Poly’s Treatment Plan
- Letrozole 2.5 - 5 mg for 3 to 6 cycles with timed intercourse
- Induce withdrawal bleeding
  - Oral MPA 10mg daily x 10 days
  - Oral micronized P4 200 - 400mg daily x 10 days
- Some evidence better pregnancy outcomes without inducing a withdrawal bleed
PCOS Highlights

- Diagnose using Rotterdam 2 out of 3:
  1. Oligo- and/or anovulation
  2. Clinical and/or biochemical hyperandrogenism
  3. Polycystic ovaries on ultrasound

- Exclude other common etiologies
  - bhCG
  - Prolactin
  - TSH

PCOS Highlights

- Evaluate for insulin resistance or diabetes
  - 2hr GTT or HA1c
  - If positive → Metformin ER, titrate up to 1500-2000mg Qhs

- Other test, based on risk factors and/or presentation
  - Total testosterone TT
  - DHEA-S
  - FSH, LH, E2, P4
  - AMH
  - 17OH-P with P4, morning fasting follicular
  - Urinary 24hr cortisol

PCOS Highlights

- Not desiring pregnancy
  - Protect the uterus → OCPs

- Desiring pregnancy
  - Start with Letrozole 2.5-5mg
  - Reasonable to try 3 to 6 cycles of ovulation induction
THANK YOU!

QUESTIONS?
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