PCOS: Overview and Treatment Options

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“Classic” PCOS

When fully expressed, manifestations include:

- Ovulatory dysfunction
- Androgen excess
- Polycystic Ovaries
- Obesity
PCOS - Pathophysiology

“Cysts”
- Actually follicles
- Follicles arrested in development accumulate in the ovary
- “PCOS women do not throw away their old follicles”
Follicle growth – 85 days

- Initial phase
  - 70 days
  - Previous to cycle where ovulation occurs
  - Gonadotropin independent

- Second phase
  - 14 days
  - Follicle development during menstrual cycle
  - Gonadotropin dependent
    - Initially FSH only
Hormone dynamics: PCOS

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<tr>
<th>FSH &amp; LH IU/L</th>
<th>Estradiol pg/mL</th>
<th>Progesterone ng/mL</th>
<th>17-OHP ng/mL</th>
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FSH: Follicle-stimulating hormone
LH: Luteinizing hormone

Normal vs. PCOS:
- Normal: Steady state, no persistent anovulation
- PCOS: Persistent anovulation
Hormone dynamics: PCOS

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Menses | Ovulation

Steady state | Persistent anovulation

Normal PCOS
- Low FSH levels
- High testosterone levels

Gonadotropin Independent: 70 days

Gonadotropin Dependent: 14 days
PCO is the end result or sign of the disease, not the etiology.
Polycystic ovaries: What is the underlying problem?

- Hyperandrogenism
- Hypothalamic-pituitary-ovarian (HPO) axis disturbance
- Insulin resistance and hyperinsulinemia
Polycystic ovaries: What is the underlying problem?

- Hyperandrogenism
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Normal female androgen production

Adrenal Cortex

- Androstenedione: 50%
- DHEA: 100%
- DHEAS: 90%
- Testosterone: 50%

Ovary

- Testosterone: 25%
- Androstenedione: 50%
- DHEA: 10%
- DHEAS: 50%
Normal female androgen production

Adrenal Cortex

- 25% to Testosterone
- 50% to Androstenedione
- 100% to DHEA
- 90% to DHEAS

Ovary

- 50% from Androstenedione
- 25% from Testosterone
- 10% from DHEAS
PCOS: Hyperandrogenism

- Excess androgen production comes from the ovary
- Excess LH and decreased FSH leads to increased androgens
PCOS: PATHOPHYSIOLOGY

- Hyperandrogenemia
- Disruption of hypothalamic-pituitary-ovarian axis (HPO)
- Insulin resistance
HPO AXIS:
LH AND FSH SECRETORY ABNORMALITIES

- Increased LH release
- Decreased FSH release
- Increased LH:FSH ratio

Arrested Follicles
HPO AXIS: LH AND FSH SECRETORY ABNORMALITIES

- Anovulation causes lack of progesterone: ↑LH
- Feedback effect of elevated androgens: ↓FSH, ↑LH
PCOS: PATHOPHYSIOLOGY

- Hyperandrogenemia
- Disruption of hypothalamic-pituitary-ovarian axis (HPO)
- Insulin resistance (IR)
Insulin resistance is a feature of PCOS in obese and non-obese women
EFFECTS OF HYPERINSULINEMIA

- In the ovary: Stimulates theca cells
  - Increased Testosterone production
- In the liver: Decreased SHBG production
  - Increased free Testosterone
PCOS: Insulin Resistance

- IR itself is not enough to cause PCOS
  - Only about 25% of reproductive-aged women with type 2 diabetes have PCOS
PCOS: Prevalence

- Affects 6-8% of reproductive age women
PCOS: Definition

NIH major criteria (all 3 required):

1. Chronic anovulation (oligo- or amenorrhea)
2. Clinical and/or biochemical evidence of hyperandrogenism
3. Exclusion of other causes of anovulation and hyperandrogenism

PCOS: Definition

- 2003 Rotterdam ESHRE/ASRM Consensus:
  - Exclusion of other disorders
  - Two of three required:
    - Chronic anovulation: *Oligo- or anovulation*
    - Clinical and/or biochemical signs of hyperandrogenism
    - Polycystic ovaries
      - ≥12 follicles measuring 2-9 mm
      - >10 ml ovarian volume (0.5 x length x width x thickness)

Fertil Steril; Jan 2004
Normal ovary

Polycystic ovary
PCOS: Definition

- Androgen Excess and PCOS Society consensus: (all 3 required)
  1. Hyperandrogenism (clinical and/or biochemical)
  2. Ovarian dysfunction (oligo-anovulation and/or polycystic ovaries)
  3. Exclusion of related disorders

Fertil Steril 2008
Diagnostic tests

- Anovulation:
  - Menstrual history
- Hyperandrogenism:
  - Physical exam:
    - Hirsutism (Ferriman-Gallway score > 6)
    - Acne
- Serum androgen levels:
  - Testosterone (> 50-80 ng/dL)
  - Free T (> 0.66 ng/dL)
  - DHEAS (> 2750 ng/mL)
- Pelvic Ultrasound
Diagnostic tests

- Anovulation:
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Tests of Exclusion

- Pregnancy: Serum beta-HCG
- Hyperprolactinemia: Prolactin
- Thyroid abnormalities: TSH
- Congenital Adrenal Hyperplasia: 17-OH progesterone
- Androgen secreting tumor:
  - Total Testosterone > 200 ng/dL
  - DHEAS > 700 mcg/dL
- Cushings syndrome: 24 hour urinary cortisol –if symptoms
Tests of Exclusion

- Pregnancy: Serum beta-HCG
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Additional tests

- **All PCOS**
  - Assess CV risk
    - Blood pressure
    - Fasting Lipids
    - Waist circumference
    - Screening for glucose intolerance / diabetes
      - 2 hour GTT
- **Chronic anovulation**
  - Endometrial biopsy – rule out endometrial hyperplasia
Additional tests

- All PCOS
  - Assess CV risk
    - Blood pressure
    - Fasting Lipids
    - Waist circumference
      - Screening for glucose intolerance / diabetes
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- Chronic anovulation
  - Endometrial biopsy – rule out endometrial hyperplasia
Prevalence of Glucose Intolerance/Diabetes

PCOS Patients

Glucose Intolerance
Diabetes
PCOS: Treatment

- Not trying to get pregnant
- Trying to get pregnant
PCOS: Not Trying to Get Pregnant

- Dysfunctional uterine bleeding
  - Oral contraceptives or cyclic progestins
  - Metformin – only if can not tolerate hormones
- Acne
  - Oral contraceptives
  - Anti-androgens
- Obesity
  - Lifestyle management - diet and exercise
- Glucose Intolerance
  - Lifestyle management
  - Metformin - if fail lifestyle
Oral contraceptives

- Treat dysfunctional uterine bleeding and acne
  - Use mono-phasic low dose estrogen
    - 20-35 mcg ethinyl estradiol
  - Non-androgenic progestin
    - (e.g. desogestrel, norethindrone)
    - desogen, mircette, ortho-novum, necon 1/35 or 0.5/35
Oral contraceptives - Acne

- Skin manifestations - Acne
  - Oral contraceptives
    - ↑SHBG leading to ↓bio-available androgen
    - Decrease LH leading to decrease ovarian androgens
    - Decrease adrenal androgens
Anti-androgens

- Reduce biochemical and clinical hyperandrogenism
- Improves menstrual cyclicity\(^2\)
  - teratogenic to male fetus – need birth control
- No improvement in metabolic abnormalities\(^2\)
PCOS and anti-androgens

- Spironolactone: K+-sparing diuretic with anti-androgen effect
  - Most common choice in U. S.
  - 50-100 mg/day have been reported to be effective $^{1,2}$
- Flutamide: androgen receptor blocker
- Finasteride: 5 alpha reductase inhibitor
Lifestyle

- Weight loss
  - Increase ovulation rates
  - Decrease hyperandrogenism, decrease insulin resistance
  - Increase implantation rates
Insulin sensitizers: Metformin

- Decreases hepatic gluconeogenesis
- Increases peripheral glucose uptake
  - muscle, adipose tissue
- Increases insulin sensitivity at the post-receptor level
- Major SE - Lactic acidosis (elderly)
Metformin

- In women with PCOS:
  - Restores spontaneous ovulation
    - 50% of women
  - No proof of endometrial protection
  - Minimal improvement in symptoms of hyperandrogenism
  - Facilitates weight loss
  - Improves lipid profile
  - Success in treatment not dependent on degree of insulin resistance
Metformin

- Treat DUB if hormones not tolerated
- Treat glucose intolerance if lifestyle management fails
PCOS: Infertility Work UP

- Ovarian reserve
  - AMH
  - Antral follicle count
- Fallopian tubes
  - HSG
- Uterus
  - HSG
  - Hydrosonogram
- Semen analysis
PCOS: Trying to Get Pregnant

- Ovulation induction
  - Clomiphene citrate
  - Metformin
  - Letrozole
Clomid

- Clomiphene Citrate
  - Estrogen receptor modulator
  - 65-80% ovulation rate
  - 30-50% pregnancy rate after 6 cycles
  - Starting Dose- 50mg
Metformin

- Metformin vs. Placebo
  - Increased ovulation rates, pregnancy rates
  - Better response when BMI <30
Metformin vs. Clomid

- Metformin vs. Clomid (Conflicting data)
  - Palomba et al. 2005
    - Ovulation rate equal
    - Higher pregnancy rates with Metformin (than Clomid)
  - Legro et al. 2007
    - Increased ovulation rates, pregnancy rates with clomid
    - Clomid + Metformin increased ovulation but not pregnancy
  - Zain et al. 2008
    - Increased ovulation with Clomid
    - Pregnancy rates equal
    - No benefit of Clomid + Metformin (ovulation or pregnancy)
PCOS: ovulation treatment

- Clomid – first line treatment
- If ovulatory with Clomid
  - No benefit with adding Metformin
- If Clomid resistant
  - Addition of Metformin could be helpful
  - Improve ovulation and pregnancy rates?
Clomid

- Increase dose of Clomid
  - 50mg (50%)
  - 100mg (22%)
  - 150mg (12%)
  - 200mg (7%)
  - 250mg (5%)

- Traditional method if not responsive
  - Progestin withdrawal between each cycle

FDA approved up to 100mg
Clomid Resistance

- **Adjunctive Treatments**
  - Clomid + Metformin
  - Clomid Stair Step
  - Clomid + Glucocorticoids
    - Dexamethasone 0.5mg, Prednisone 5mg

- **Alternative Treatments**
  - Letrozole
  - Surgical drilling
  - Gonadotropins + IUI
  - IVF
Clomid Resistance

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Clomid – When to Start?

- Historically
  - Induced endometrial shedding - Provera or OCP
    - Provera won’t work unless uterine lining is thick enough
  - Delays start by 2-3 weeks

- NOW – No withdrawal bleed
  - Ovulation rates higher without withdrawal bleed
  - Live birth rates higher without withdrawal bleed
    - Per ovulation
      - No withdrawal – 19.7%
      - Spontaneous or progestin withdrawal 3-5%

- Diamond et al. Obstetrics and Gynecology, 2012
Clomid Stair Step

- If not respond
  - Use increasing dose of clomid
  - Omit withdrawal bleed

- Hurst et al, AJOG 2009: 586-589
Methods

**Traditional**
- CC 50 mg for 5 days
- Serum Progesterone
- 10 mg MPA x 10 days
- Withdrawal Bleed
- CC 100 mg for 5 days
- Serum Progesterone

**Stair-step**
- CC 50 mg for 5 days
- U/S
- CC 100 mg for 5 days
- U/S
- Serum Progesterone

**Timeline**
- **Day 24**
- **Day 55**
Clomid Stair Step

- Decreased time to ovulation
- Increased rate of mild side effects
  - 40% vs 15%
- Higher ovulation rates
  - Cumulative Clomid effect
- Pregnancy rates equivalent in ovulatory cycles

- Hurst et al, AJOG 2009: 586-589
Letrozole

- Reversible, competitive aromatase inhibitor
- Blocks estrogen production from all sources
- Releases the hypothalamic/pituitary axis from negative feedback.
- Does not deplete estrogen receptors (ER) at target organs (so does not thin the endometrium)
Letrozole

- 2005 ASRM meeting: oral abstract –
  - 150 Letrozole OI births vs. 36,000 spont. deliveries
- Cardiac and locomotor anomalies overrepresented
- Despite many flaws of abstract (never published), Novartis sent out warning letter to physicians, advising against use of Letrozole
- Use of Letrozole decreased significantly
Letrozole

- 2006: multicenter Canadian study
- 514 Letrozole births vs. 397 CC births

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<th>Clomiphene Citrate</th>
<th>Letrozole</th>
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<td>Major Malformations</td>
<td>1.2%</td>
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<td>Cardiac anomalies</td>
<td>3%</td>
<td>1.8%</td>
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Letrozole vs. Clomid: NON PCOS

- Letrozole
  - lower number of mature follicles
- Similar ovulation rates, endometrial thickness
- Similar pregnancy rates
- Similar miscarriage rates
Letrozole vs. Clomid

- Double blind, randomized, multicenter trial
- 750 PCOS women
- Letrozole vs Clomid for ovulation induction – up to 5 cycles
- Findings:
  - Cumulative ovulation higher with letrozole (62 vs 48%)
  - Cumulative live birth rates higher with letrozole (27 vs 19%)
  - Similar pregnancy loss (30%)
  - Higher multiple rate with Clomid (7 vs 3%)
  - Similar rate of congenital anomalies

- Legro et al. NEJM 2014
PCOS: ovulation treatment

1. Letrozole
   - Stair step Letrozole

2. Clomid
   - Stair step Clomid
   - Clomid + Metformin

3. Injections
   - Drilling
   - IVF
Gonadotropins

- Gonadotropins (LH/FSH) - Injectable medications
- Performed with IUIs
- Long, intensive cycles
  - Low-dose and step up protocols
- Risks
  - Cancellation of cycles
  - High order multiples
  - OHSS
Laparoscopic Ovarian Surgery

- Ovarian Drilling
- Monopolar electrocautery treatment of the ovary
- Destruction of stromal tissue leads to decrease in androgen production
Laparoscopic Ovarian Surgery

- **Success rates**
  - ovulation 80-90%
  - conception 50-70%

- **Pros**
  - Improves endocrine abnormalities
  - Similar pregnancy rates to gonadotropins (3-6 months)
    - Decreased Multiples
    - No Hyperstimulation

- **Cons**
  - Adhesion formation - 20-40%
  - No long term data on continued ovulation
  - Surgical risks
  - Decreased benefit with BMI >30
IVF in PCOS patients

- Exaggerated E2 response to gonadotropins
- Greater # of oocytes recovered
- Lower # of mature oocytes
- Poor fertilization rates
- Lower embryo cleavage rates
- Lower implantation & pregnancy rates
- Increased miscarriage rates
- Increased risk of OHSS
  - metformin use may decrease incidence
Summary

- PCOS
  - Common Disorder
  - Complex underlying etiologies
  - Multiple treatment options that depend on ultimate goal
Thank you!