Polycystic Ovarian Syndrome
G. Wright Bates, Jr., M.D.
Reproductive Endocrinology and Infertility

PCOS Objectives

- Review epidemiology and pathophysiology
- Discuss diagnosis of PCOS
- Highlight reproductive and medical sequelae
- Review treatment options

I will discuss off label use of metformin and letrozole

I have no relevant conflicts of interest to disclose.

PCOS epidemic
“a widespread occurrence”

- 4 – 12% prevalence
- Up to 32% of sisters affected
- 40 – 80% of PCOS patients are obese
- Up to 28% of obese hispanic women have PCOS
- 63% of patient at UAB REI are overweight or obese

http://clinicaltrials.gov/ct2/show/NCT01319162
PCOS 2004 Consensus

• Irregular or Absent Ovulation
• Clinical and/or biochemical signs of androgen excess
• At least one ovary with 12 or more follicles (2 – 9mm) and increased ovarian volume (at least 10 ml)


PCOS: Must EXCLUDE or at least CONSIDER other endocrinopathies

• Thyroid
• Pituitary
• Androgen Excess
  • T, Androstenedione, DHEAS
• Adrenal
  • CAH (17-OH progesterone)
  • Cushing’s (24 hr urine cortisol)

PCOS Metabolic Abnormalities

• PCO women have greater hyper-insulinemia and insulin resistance than weight-matched controls
• Insulin resistance independent of effect of obesity
• Insulin augments androgen response to LH
• Insulin suppresses SHBG
Consequences of Chronic Anovulation—Syndrome X

- Abnormal uterine bleeding
- Hirsutism, acne
- Increased risk of endometrial Ca, possibly breast cancer
- Increased risk of CVD, PVD
- Hypertension, Hyperlipidemia
- Increased risk of DM in patients with hyperinsulinemia

Metabolic Syndrome

- Abdominal obesity (waist circumference)
  - Men > 102 cm (>40 in)
  - Women > 88 cm (>35 in)
- Triglycerides 150 mg/dL
- HDL cholesterol
  - Men < 40 mg/dL
  - Women < 50 mg/dL
- Blood pressure > 130/85 mm Hg
- Fasting glucose > 110 mg/dL

Pathophysiology

- Multiple Etiologies
- Follicular arrest and atresia
  - Follicles ripen prematurely and commit to atresia before stage where healthy oocytes can be sustained
  - Granulosa cells grow abnormally slow and their cell death may contribute to atresia
- Acquired obesity
PCOS Pathophysiology: Obesity

- Android Fat Distribution
- Increased Insulin Resistance
- Hyperinsulinemia
- Increased production of ovarian and adrenal androgens

Methods Used to Assess Ovulation

- REGULAR CYCLE / Moliminal Symptoms
- Basal body temperature chart
- Midluteal phase serum progesterone (> 3 ng/mL, ideally greater than 10)
- Luteal phase endometrial biopsy
- Detection of LH in the urine
- Cervical Mucous
- Ultrasound observation of follicular development and/or rupture
- Electronic monitoring

Diagnostic Evaluation - Anovulation

- Essential
  - TSH
  - Prolactin
  - Semen Analysis
  - Progesterin challenge and FSH if amenorrhea

- Recommend
  - Ovarian Reserve Testing
  - Hysterosalpingogram

- Consider
  - Androgens: Testosterone, 17-OH progesterone, DHEAS
  - Ovarian Reserve Testing
    - FSH, estradiol
    - AMH
**Treatment of Obese PCOS Patients with Anovulation**

Weight loss remains first line therapy
- Improves hormonal profiles
  - Lower androgens
  - Lower glucose and lipid levels
- Improves spontaneous resumption of menses and pregnancy
- Improves response to ovulation induction

**PCOS and Exercise**
- 3 month exercise regimen (92 min / week)
- 5% reduction in BMI and improved glucose dynamics
- 60% had return of menstrual cycle

Vigorito C, JCEM 2007;92:1379

Palomba S, Hum Reprod 2008;23:642

**Diet and Exercise CC-Resistant PCOS**
- 96 overweight/obese CC-resistant PCOS patients
- RCT
  1. 6 weeks SET and hypocaloric diet
  2. Observation for 2 weeks then cycle CC
  3. 6 weeks SET and hypocaloric diet, with CC after 2 weeks

Palomba S, Hum Reprod 2010;25:2783
Lifestyle Recommendations

- Stop smoking/limit alcohol and caffeine
- Weight Reduction
  - Low caloric diet, 1000-1200 kcal/day
  - 10% body weight reduction in 6 months
- Exercise
  - Regular physical exercise
  - Minimum 30 min moderate intensity 3 times/week
- Medical treatment/Bariatric Surgery

Fertil Steril 2008;90:21

---

Optimum Diet for PCOS: Low carbohydrate?

![Graph showing weight change over time with different diets](image)

Larsen, NEJM, Nov 2012

---

Bariatric Surgery

- Improved endocrine profile
- Enhanced Fertility
  - Lower efficacy of oral contraceptives
- Reduced miscarriage
- Improved pregnancy outcome
- Enhanced sexual functioning

Merhi, Z.O., Fertil Steril, 2009
Acne

- Most combination OCPs probably improve mild – moderate acne
- 3 formulations “indicated”
  - Ortho Tri-Cyclen (norgestimate)
  - Estrostep (Norethindrone acetate)
  - Yaz (drospirenone (DRSP) *
  - *also indicated for PMDD

Hirsutism

- Liberal use of hair removal techniques
  - Electrolysis, laser, depilation
- Antiandrogens
  - Cyproterone acetate (Diane), Flutamide, Finasteride
  - Spironolactone
    - Start at 100 mg a day up to 300 mg a day in obese girls
    - Requires up to 6 months
    - Polyuria polydipsia, nausea, headache, GI upset
- OCPs (Yaz or Yasmin)
- Efornithine Hydrochloride (Vaniqa)
  - Expensive, slow and may worsen acne

Metformin

- biguanide antihyperglycemic agent approved for the management of type 2 diabetes
- decrease blood glucose levels
  - suppress hepatic glucose output
  - decrease intestinal absorption of glucose
  - enhance peripheral glucose uptake and utilization
- Only oral agent approved for pediatric use

Barbieri RL. Obstet Gynecol 2003;101:785
Metformin and PCOS

- Decreases insulin secretion levels & LH
- Increased SHBG
- Decreases androgens
  - Total T 38%
  - Free T 58%
  - Androstenedione 58%
- Reduction in BMI
- ??Improved ovulation & pregnancy rates (OI & IVF)
- ??Reduced miscarriage rates


Metformin For Menstrual Irregularity and Anovulation

- Women with PCOS and irregular menses given metformin alone for six months, typically 50% resumed regular menses
- In adolescents with PCOS treated with metformin, most individuals required 4-6 months before ovulatory menses occurred


Metformin vs. Weight Loss

- RCT of 143 subjects (BMI> 30)
- 850 mg Bid vs placebo
- All received dietary counseling
- Only weight loss correlated with return of normal menstrual cycles (not metformin, initial BMI, age)
- Metformin reduced androgens and waist circumference

Medical/Surgical Treatment Options for Infertility

- Clomiphene Citrate (CC) / Timed Intercourse (TI) or Intrauterine Insemination (IUI)
- Letrozole / TI or IUI
- Metformin
- Gonadotropins (FSH or HMG) / IUI
- Surgical Intervention - Ovarian Diathermy
- In Vitro Fertilization (IVF)

Adjuncts to Ovulation Induction (Clomiphene or Letrozole)

- Metformin
- Oral Contraceptive Suppression
- Dexamethasone
- Ovarian Drilling
- Gonadotropins

PPCOS I

- RCT of 626 women with PCOS
  - Oligo or anovulation
  - Elevated androgens
- Randomized to Metformin, Clomiphene Citrate or combination for 6 cycles
- Metformin stopped with positive BhCG
- Significantly better pregnancy rate with CC or combination
- No significant difference in SAB rate
- Higher multiple rate with CC (6%)

Oral Contraceptive Pretreatment

- 48 patient with CC resistance
- 89 cycles
- CC 100 mg 5-9 alone vs. OCPs followed by CC
- Ultrasound monitoring, hCG

Branigan EF, Estes MA. Am J Ob Gynecol 2003;188:1424

ESHRE / ASRM-Sponsored PCOS Consensus Workshop

- First Line: Clomiphene Citrate
- 2nd Line: Gonadotropins
  L/S Ovarian Surgery
- 3rd Line: IVF
- Metformin for glucose intolerance
- Insufficient evidence to recommend Letrozole

Fertil Steril, 2008 Feb

Conclusions:

PCOS represents a spectrum of clinical presentations

Lifestyle modification is key!
- Weight loss
- Exercise
- Avoidance of refined sugars / carbohydrates
Lifestyle intervention improves body composition, hyperandrogenism (high male hormones and clinical effects) and insulin resistance in women with PCOS

No improvement in glucose, lipids or reproductive health

Cochrane Review 2011

Recommendations

• Contraception a must if pregnancy not desired
• Treat Symptoms – Hirsutism, Acne, Infertility
• Team approach
• Metabolic Syndrome Screen – lipids, HgbA1C, etc
• PPCOS II – Letrozole vs. Clomiphene Citrate
  • Enrollment complete – results pending