Metabolic Syndrome & PCOS, and Reproductive Considerations

Anne Moore, DNP, WHNP/ANP-BC
## Disclosures

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<th>Anne Moore, DNP, WHNP/ANP-BC, FAANP</th>
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Objectives

1. List the symptoms associated with PCOS
2. Discuss the etiology of PCOS.
3. Compare treatment strategies for management of PCOS patients.
History of PCOS
Stein Leventhal Syndrome

• 1935 Dr.’s Stein and Leventhal published report on 7 women with:
  – Amenorrhea
  – Hirsuitism
  – Enlarged ovaries

• Theorized that thickened ovarian capsule prevented ovulation

• Supported wedge resection as treatment
History of PCOS

• Later criteria included:
  – Oligomenorrhea
  – Hirsuitism
  – Obesity
  – Cystic, enlarged ovaries
PCOS Prevalence

5% to 14% of reproductive age women

5 million women in US

Features of PCOS

- Genetics
- Lifestyle/obesity

Hormonal changes:
- Androgens
- Insulin

Androgens:
- Ovarian follicles/anovulation/estrogen

Insulin:
- Diabetes
- Cardiovascular risk/metabolic syndrome

Menstrual disturbances:
- Hirsuitism/acne
- Menstrual disturbances

Psychosocial issues: body image, self esteem, depression, anxiety
# PCOS Complications by Age

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<tr>
<th>Clinical Concerns</th>
<th>Prenatal</th>
<th>Childhood</th>
<th>Adolescence</th>
<th>Reproductive Years</th>
<th>Peri- and Post-Menopause</th>
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National Institutes of Health. 2012
Pathophysiology

• May be related to multiple issues:
  – Hypothalamic pituitary ovarian dysfunction

• Increased LH
  – Increased LH (pulse frequency/amplitude - increased LH:FSH ratio
    • Stimulates ovary to increase androgen production
  – Decreased FSH
    • No dominant follicle

• Peripheral conversion of androgen precursors

• Decreased SHBG – increased free testosterone
Pathophysiology

- Ovarian dysfunction
  - Increased androgen production
  - Apoptosis dysfunction

- Adrenals
  - Increased:
    - adrenocortical production of androgens
    - DHEAS (40 to 70%)
PCOS Pathophysiology

- Hypothalamus
  - GnRH pulse generator
- Pituitary
- Ovary
  - LH
  - FSH
  - Androgens
- Skeletal muscle
  - Adipocytes
- Chronic hyperinsulinaemia
- Insulin resistance

## PCOS Diagnostic Criteria

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<td>- Chronic anovulation</td>
<td>- Oligo- and/or anovulation</td>
<td>- Clinical and/or biochemical signs of hyperandrogenism</td>
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<tr>
<td>- Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies, e.g., congenital adrenal hyperplasia)</td>
<td>- Clinical and/or biochemical signs of hyperandrogenism</td>
<td>- Ovarian dysfunction (Oligo-anovulation and/or polycystic ovarian morphology)</td>
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<td>(Both criteria needed)</td>
<td>- Polycystic ovaries (Two of three criteria needed)</td>
<td>(Both criteria needed)</td>
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What do ovaries of women with PCO look like?

- Surface area may be doubled
- Volume may be increased 3 fold
- Thickened tunica(capsule)
- Presence of “string of pearls”....up to 100 follicles on ovarian periphery
Polycystic Ovary: String of Pearls
Clinical Features of PCOS
Hyperandrogenism

- Hirsuitism, acne, male pattern balding, and/or male distribution of body hair

Hirsutism

Latin *hirsutus* = shaggy, hairy

Excessive growth of terminal hair in typically male sexual sites.
Assessing for Hirsutism

Ferrimen-Gallwey

Ferriman D. J Clin Endocrinol Metab. 1961.
What about insulin resistance?

• Hyperinsulinemia results from insulin resistance in skeletal muscle and adipose tissue

• Organs that are impacted:
  – Hypothalamus – increases appetite and GnRH
  – Adrenals and ovaries – increased androgen production
Acanthosis Nigricans

- HAIRAN syndrome: HyperAndrogenic Insulin-Resistant Acanthosis Nigricans

acanthosis nigricans.
Insulin Resistance and PCOS

- Increased insulin levels can stimulate androgen production
- Insulin can stimulate adrenal steroidogenesis - enhances sensitivity to adrenocorticotrophic hormone; increases pituitary LH release
- Insulin-lowering therapies - restore menstrual cycles in some anovulatory women with PCOS
- Defects in insulin receptors found in up to 1/2 of women with PCOS

PCOS and Type II DM

• PCOS in women aged 14-44
  – 31% have (undiagnosed) glucose intolerance
  – 7.5% have diabetes
  – Risk also with lean women

• PCOS in women aged 40-50
  – 15% have type 2 diabetes

ACOG: 2009 - PCOS

- Menstrual disorders
- Infertility
  - Hyperstimulation of ovaries
  - Gestational diabetes/HTN
- Dermatologic disorders
  - Acne, hirsuitism, alopecia
- Insulin resistance
  - Metabolic syndrome
  - Sleep apnea
- Endometrial cancer
- Mood disorders/depression
ACOG: 2009 PCOS Differential Diagnosis

- Androgen producing tumor
- Acromegaly
- Congenital adrenal hyperplasia
- Cushings syndrome
- Exogenous androgens
- Hyperprolactinemia
- Hypothalamic amenorrhea
- Ovarian failure
- Thyroid disorder
Evaluation of PCOS

• Personal history
• Family history: endocrine, reproductive, metabolic
• Physical examination
• Laboratory tests
Personal History

- Weight over time
- Hirsuitism: onset, progression, treatments
- Menstrual history: menarche, interval, duration, mittleischmertz, premenstrual symptoms; onset of irregularity
- Obstetric history: complications, GDM
- Medications: androgens, anabolic drugs
- Voice changes
- Known medical problems
- Surgeries
- Depressive symptoms
ACOG: 2009 Evaluation of PCOS

- BP
- BMI
- Waist circumference: > 35 inches is abnormal
- Acne, hirsuitism, alopecia, acanthosis nigricans
PCOS Management: Diagnostic Evaluation

- Blood pressure
- BMI
- Waist circumference
- Skin and hair exam
- Labs
  - Testosterone (total and SHBG or bioavailable and free)
  - TSH, prolactin, 17-hydroxyprogesterone
  - 2 hour oral GTT
  - Fasting lipid and lipoprotein levels
- Ultrasound: ovaries and uterus

Association Between Weight Gain and PCOS

- Up to 50% of women with PCOS are moderately obese or overweight
- Obesity is usually the android type, with increased waist-to-hip ratios
- When present, obesity worsens insulin resistance and increases the risk for diabetes and cardiovascular disease

PCOS Labs

• Metabolic evaluation
  – 2 hr GTT (FBS < 100 WNL)
    • Most sensitive for determination of glucose tolerance
    • Recommended by ASRM and AES
  – Fasting lipid panel
    • Total cholesterol
    • LDL
    • HDL
    • Triglycerides
Interpreting OGTT

Fasting
• Normal < 100
• Impaired 100-125
• Diabetes >126

2 hour OGTT
• Normal < 140
• Impaired 140-199
• Diabetes 200

No recommended screening test for insulin resistance – little utility for routine tests
  – Does not predict who will respond to therapy
PCOS: Lipid Panel

• Typical for PCOS patients
  • Elevated LDL
  • Elevated triglycerides
  • Decreased HDL
  • Decreased apolipoprotein A-I

ACOG Evaluation PCOS: Ultrasound

• Presence of polycystic ovary
  – >12 follicles 2-9mm diameter
  – Ovarian volume > 10 cm/3

• Endometrial abnormalities
ACOG 2009: Optional Testing

• Gonadotropin levels to evaluate amenorrhea
• Fasting insulin
  – Younger women
  – Significant hyperandrogenism
• 24 hour urinary free-cortisol excretion test
  – Late onset PCOS
  – Symptoms of Cushings
PCOS: Treatment Goals

- Decrease production/circulating levels of androgen
- Endometrial protection
- Normalize body weight
- Decrease risk of CVD
  - Decrease hyperinsulinism
- Pregnancy planning
PCOS: Treatment Goals

• Weight loss
  – 15% is helpful
  – Low fat, low calorie
  – Exercise
ACOG 2009: CVD Prevention in PCOS

• Lifestyle modification
  – Diet
    • Low glycemic/high fat yielded more improvement than high glycemic/low fat
      – Lower insulin resistance
      – Lower BP, triglycerides, CRP

PCOS Management: Metabolic and Cardiovascular Risk Reduction

- Regular screening
  - BMI, waist circumference, blood pressure
  - Fasting glucose or OGTT, lipid profile

- Lifestyle modification
  - Weight reduction
  - Exercise

- Drug therapy
  - Metformin

Metformin

• Doses:
  – 500mg TID
  – 850mg BID
  – Igm BID
    • Begin with 500 mg with largest meal of day
    • Increase to 1500 to 2000 mg daily
  – Generic extended release (500 mg, 750 mg)
    • Entire dose with dinner

• Side effects
  • Diarrhea, nausea
  • Decreased B12
Metformin

- Suppresses gluconeogenesis
- Facilitates transport of glucose into cells
- Increases peripheral insulin sensitivity
- Lowers androgens, weight, LDL, BP
- Resumption of menses and ovulation – WITH weight loss
PCOS: Sleep Disorders

- PCOS a/w poor sleep quality, daytime fatigue, sleep apnea
- Insufficient sleep a/w impaired glucose tolerance
- Sleep debt contributes to metabolic problems a/w PCOS

Tasali E, et al. J. Clin Endocrinol Metab. 2006; 91(1): 36042
PCOS Treatments: Androgenic Blockers

• Spironalactone 25-200 mg/day
  – Monitor for hyperkalemia

• Used in conjunction with hormonal contraception
PCOS Management: Hirsutism and Acne

- Mechanical methods
- Ovarian suppression with low androgenic-activity progestin
  - Norgestimate
  - Desogestrel
  - Drospirenone
- Antiandrogens (with contraception)
- Eflornithine cream

PCOS Treatments: Dermatologic

• Acne
  – Astringents
  – Antibiotics

• Hirsuitism
  – Bleaching
  – Electrolysis
  – Laser
  – Eflornithine hydrochloride 13.9% (Vaniqa)
    • BID
    • Add to laser?
Laser & intense pulsed light

• Selective phototricholysis. A light source sufficient to penetrate to the follicular bulge & the papillae is directed at the hair by probe.
• All areas
• May give permanent hair reduction, efficient, painless
• Dark hair required, expensive, scarring, skin pigmentation, repeated treatments usually necessary
PCOS Effects on Menses and Fertility

- Oligomenorrhea
- Amenorrhea
- Reduced fertility
- Dysfunctional uterine bleeding
- Risk of ovarian hyperstimulation and multifetal pregnancy
- Endometrial hyperplasia or carcinoma

PCOS: Anovulation

- Combined hormonal contraception:
  - COC’s
  - Patch
  - Ring
    • Extended/continuous cycling
    • May NOT be good choice for women >35 who are obese

- Cyclic progestin
  - 12 days if no menses X 35 days

- Chronic progestin
  - DMPA, POP’s, LNG/IUC
PCOS: Hormonal Contraception

• Estrogen increased SHBG – decreased free testosterone
• Suppresses gonadotropin dependent ovarian and adrenal androgens
• No change insulin sensitivity
• ANY estrogen/progestin should help
  – Norgestimate: less androgenic
  – Levonorgestrel: more androgenic
Picking the Right Birth Control: U.S.MEC

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

**Key:**
1. No restriction (method can be used)
2. Advantages generally outweigh theoretical or proven risks
3. Theoretical or proven risks usually outweigh the advantages
4. Acceptable health risk (method not to be used)

Updated June 2012. This summary chart only contains a subset of the recommendations from the US MEC. For complete guidance, see http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.

Most contraceptive methods do not protect against sexually transmitted infections (STIs). Consistent and correct use of the male latex condom reduces the risk of STIs and HIV.

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<th>Combined pill, patch, ring</th>
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</table>

For more details and criteria, refer to the full chart in the source link provided.
PCOS Management: Menstrual Cycle Regulation and Fertility

- **Not attempting to conceive**
  - Birth Control*
  - Birth Control & anti-androgen
  - Metformin *(if IGT or DM2)*

- **Attempting to conceive**
  - Clomiphene Citrate
  - Gonadotropins
  - Ovarian drilling
ACOG 2009: PCOS & Infertility

- Weight loss
- Ovulation induction
  - Clomiphene citrate
  - Metformin if BMI >35
  - Ovarian drilling
  - Low dose gonadotropins (FSH)
  - Add metformin to clomiphene citrate
Aromatase Inhibitors

• Progestin induced withdrawal bleed
• Used days 3-7 of cycle
• Referral to fertility specialists
PCOS Contraception Considerations

- Choice of contraception
- Timing of desire to conceive
- Teratogens
- Obesity effects on efficacy
- Weight gain

ACOG. Obesity Project.
Stop for Pregnancy

ACE-I
ARB
Statins
ASA
Hypoglycemics
Anti-androgens

PCOS Management Strategies

• Focus on actual problems
  – Obesity with PCOS OR
  – Hirsuitism with PCOS OR
  – Anovulatory bleeding with PCOS

• Use of metformin can be adjuvant therapy but not indicated for treatment of PCOS
PCOS: Significance

PCOS: most common endocrine problem in women of reproductive age

Symptoms include:
- acne
- hirsuitism
- alopecia
- menstrual cycle abnormalities
- obesity/inability to lose weight

PCOS: undiagnosed/untreated can result in

Health risks including:
- metabolic syndrome
- obesity
- infertility
- endometrial (uterine) hyperplasia/cancer
- recurrent/persistent ovarian cyst formation.
- depression
- sleep apnea
Lipid Modification

Insulin Resistance Reduction

Normalizing Glucose

Normalizing Blood Pressure

PCOS: Metabolic Syndrome Risk Reduction
Patients Report Experiencing Poor Coordination

Percent U.S. adults reported in past two years:

- Your specialist did not receive basic medical information from your primary care doctor: 13%
- Your primary care doctor did not receive a report back from a specialist: 15%
- Test results/medical records were not available at the time of appointment: 19%
- Doctors failed to provide important medical information to other doctors or nurses you think should have it: 21%
- No one contacted you about test results, or you had to call repeatedly to get results: 25%
- Any of the above: 47%

Summary

• The correlation between diabetes and PCOS is strong
• Patients with PCOS are at increased risk of metabolic and cardiovascular complications as well as features such as hirsutism and acne.
• Reproductive health implications include effects on fertility, menstrual cycle, and pregnancy
PCOS Provider Resources

- American College of Obstetrics and Gynecology (http://www.acog.org)
- Boston Children's Hospital (http://youngwomenshealth.org)
- Hormone Foundation (http://www.hormone.org)
- PCOS Foundation (http://www.pcosfoundation.org)


