Diagnosis and Management of PCOS

Anita L. Nelson, MD
Professor Emeritus, Obstetrics & Gynecology,
David Geffen School of Medicine at UCLA
Clinical Professor Obstetrics & Gynecology,
University Southern California
Professor and Chair of Obstetrics & Gynecology,
Western University of Health Sciences

Women’s Healthcare Symposium
University of Missouri School of Nursing
July 17, 2018– Kansas City, MO
## Conflict of Interest Disclosure

Anita L. Nelson, MD

<table>
<thead>
<tr>
<th>Grants/Research</th>
<th>Agile Pharmaceutical, ContraMed, Estetra SPRL, Evofem Inc, FHI (MonaLisa), Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honoraria/Speakers Bureau</td>
<td>Allergan, Bayer, Merck</td>
</tr>
<tr>
<td>Consultant/Advisory Board</td>
<td>Agile, AMAG Pharma, Bayer, ContraMed, Merck, PharmaNest</td>
</tr>
</tbody>
</table>
Learning Objectives

At the end of this presentation, the participant will be able to:

● Describe the epidemiology and pathogenesis of polycystic ovarian syndrome.

● Discuss the diagnostic criteria and differential diagnoses for PCOS.

● Tailor therapies to meet the individual needs of women with PCOS.
Prevalence of PCOS

- Most common endocrinopathy of reproductive-aged women
- Complete syndrome thought to affect 5-10% of premenopausal women
  - Estimates rose to 15% using new definitions
- Functional androgen excess may affect up to 20% of reproductive-aged women
- Prevalence depends on definition used

Rotterdam Criteria for PCOS (2 out of 3 Criteria)

1. Oligo-ovulation or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic appearing ovaries (≥ 12 follicles 2-9 mm or ovarian volume > 10 mL) 

with

- Exclusion of other etiologies: congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome

Dysfunctions Observed in PCOS

- Abnormalities in ovarian steroidogenesis
- Abnormalities in follicular development
- Persistently rapid gonadotropin-releasing hormone pulses
- Excess of LH
- Insufficient FSH
- Insulin resistance
- Increased androgen production
- Reduced SHBG (sex hormone binding globulin)

What Does “PCOS” Diagnosis Say Clinically?

- Is the women with PCOS always
  - Obese?
  - Hirsute?

- Does she always have
  - Infrequent menses?
  - Acne?
  - Insulin resistance?
  - Increased risks for CVD? For DM?
  - Lower fertility
Proposal: Consider PCOS as a “Modifier”, Not a Condition Itself Requiring Treatment Until Definitions Stabilize

- Focus on actual problems in diagnosis
  - Obesity, with PCOS
    - OR
  - Hirsutism, with PCOS
    - OR
  - Anovulatory bleeding, with PCOS
- Focus on actual problems in treatment

Note: Routine use of Metformin to treat “PCOS” is not appropriate
ACOG 2018 Clinical Manifestations of PCOS

- Menstrual disorders
- Infertility
  - Ovarian hyperstimulation syndrome
  - Multifetal pregnancy
  - Gestational diabetes and hypertension
- Skin disorders
  - Hirsutism, acne, androgenic alopecia
- Insulin resistance
  - Metabolic syndrome; nonalcoholic fatty liver disease, sleep apnea; Type II DM
- Endometrial cancer risk factors (but not cancer?)
- Mood disturbances and depression

Liver Dysfunction in Obese, Hyperandrogenic, PCOS Women

- Non-alcoholic fatty liver incidence higher
  - Liver fat on MRA — higher
  - ALT levels higher
  - Hepatic steatosis on US greater
- Differences remain even after correcting for BMI, insulin resistance
- Also noted to have increase internal, visceral and subcutaneous fat

Obstructive Sleep Apnea (OSA)

- Obstructive sleep apnea greater in women > men\(^1\)
- OSA leads to higher levels of daytime sleepiness, anxiety and depression and reduced sleep quality
- Berlin questionnaire OSA risk\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>All PCOS</th>
<th>Obese PCOS</th>
<th>Non-Obese PCOS</th>
<th>All Control</th>
<th>Obese Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>% OSA</td>
<td>47%</td>
<td>77%</td>
<td>0</td>
<td>15%</td>
<td>63%</td>
</tr>
</tbody>
</table>

PCOS, Sleep Disordered Breathing and Metabolic Syndrome

- PCOS is associated with poor sleep quality, daytime sleepiness and risk for obstructive sleep apnea
- SDB is associated with glucose intolerance, insulin resistance, diabetes, hypertension and dyslipidemia
- Insufficient sleep is linked to decreased glucose tolerance
- Sleep debt may contribute to metabolic consequences of PCOS

Mental Health Disorders in PCOS

- Evaluation of 60 PCOS subjects over 22 months

<table>
<thead>
<tr>
<th>Disorder</th>
<th>PCOS (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mood disorder</td>
<td>56.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Binge eating</td>
<td>25.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

- Women diagnosed with PCOS should be routinely screened for mood disorders
- 4 page self administered questionnaire can diagnose 8 diseases
  - Sensitivity mood disorder 73%; Specificity 98%

Androgen Excess Manifestation: Acne

Ask about: Menstrual patterns, OC use, hair removal, family history

Look for: Alopecia, hirsutism, waist-to-hip ratio
PCOS Issues: Hyperandrogenism

- Hirsutism is good marker for PCOS
  - 70% PCOS women have hirsutism
  - *Must be evaluated biochemically*
  - Treatment (≥ 6 months) should focus on:
    - Reduction of androgen production
    - Decreasing fraction of Free T
    - Limit androgen bioavailability to hair follicle (increase SHBG)
- Acne and alopecia not good markers for PCOS

**Bart CJ. Hum Reprod. 2012;27(1):14-24.**
PCOS Differential Diagnoses

- Androgen secreting tumor
- Exogenous androgens
- Cushing syndrome
- Nonclassical congenital adrenal hyperplasia
- Acromegaly
- Genetic defects in insulin action
- Primary hypothalamic amenorrhea
- Primary ovarian failure/insufficiency
- Thyroid disease
- Prolactin disorders
- Medications

Workup for PCOS: Overview

- Personal history
- Family history of endocrine, reproductive, metabolic disorders
- Physical examination
- Laboratory tests
PCOS History Elements

- Personal history
  - Onset and duration of various signs of androgen excess
  - Menstrual history
  - Concomitant medications, including exogenous androgens
- Family history of endocrine, reproductive, metabolic disorders, cardiovascular disease, especially early onset in first degree relative

Screen for Other CVD Risks

- Cigarette smoking
- Obstructive sleep apnea
- Depression
- Anxiety
ACOG Physical Examination
Elements for PCOS

- Blood pressure
- BMI
- Waist circumference
  - > 35 inches is abnormal
- Presence of stigma of hyperandrogenism and insulin resistance:
  - Acne, hirsutism, androgenic alopecia,
  - Acanthosis nigricans

ACOG: PCOS Screening Tests

- Evidence of biochemical hyperandrogenemia
  - Total testosterone and SHBG
  - OR
  - Bioavailable and free testosterone
- Exclusion of other causes of hyperandrogenism
  - TSH
  - Prolactin
  - 17-hydroxy progesterone
  - Consider screening for Cushing or acromegaly

ACOG PCOS Screening Tests Cont.

- FBS + 2 hour glucose after 75 g load
  - No routine screening for insulin resistance
    - Does not predict who will respond to therapy
- Fasting lipid panel and metabolic syndrome
- Ultrasound evaluation
  - Determine polycystic appearance
    - >= 12 preantral follicles (1-9mm)
  - Identify endometrial abnormalities

ACOG: Optional Tests to Consider

- Gonadotropin determinations to identify cause of amenorrhea
- Fasting insulin levels in
  - Younger women
    - Women with stigmata of insulin resistance and hyperandrogenism
    - Women undergoing ovulation induction
- 24-hour urinary free cortisol excretion test or low-dose dexamethasone suppression test in women with late onset PCOS symptoms or stigmata of Cushing syndrome
- DHEAS if rapid virilization

ACOG: Optional Tests to Consider

- Screen for nonclassical adrenal hyperplasia (late-onset congenital adrenal hyperplasia) in higher risk women with a suspected diagnosis of PCOS
  - Ashkenazi Jews
  - Hispanics
  - Yugoslavs
  - Native American “Inuits” in Alaska
  - Italians
- Use fasting level of 17-hydroxyprogesterone in morning
  - Normal < 2-4 ng/mL
  - If abnormal, order ACTH stimulation test

Treatment for PCOS Menstrual Disorders

- Combination oral contraceptives are primary treatment
- Progestins provide endometrial protection but are associated with abnormal bleeding patterns
- Insulin-sensitizing agents
  - None of the antidiabetic agents is FDA-approved for this indication.
  - No studies longer than 1 year in PCOS
  - Metformin has safest risk-benefit ratio

Treatments for PCOS: Anovulatory Cycling

- Combination hormonal contraceptives: OCs, patches or vaginal rings
  - Cyclic, extended-cycle or continuous use
  - May not be appropriate for obese women over age 35
- Cyclic progestin (MPA, NETA)
  - Initiate 12-day therapy PRN no menses for 30-35 days
- Chronic progestin: DMPA, POPs, LNG-IUS
Treatments for PCOS
Androgen Excess

- Acne and hirsutism
  - Combination hormonal contraceptives

- Hirsutism
  - Spironolactone 25-100mg BID
  - Finasteride 1mg/d teratogenic
  - Flutamide 125-250 mg/day teratogenic, hepatotoxic
  - Vaniqa® (eflornithine) Cream (sole source)
  - Electrolysis or laser (better with eflornithine)

Treatment for PCOS Long Term Health

- Lifestyle modifications: first line therapy
  - Increase in exercise
  - Calorie restriction
    - More important than diet content

- Insulin-Sensitizing Agents
  - Can delay development of DM in those with impaired glucose tolerance
  - Little benefit to adding metformin to lifestyle

- Statins
  - Emerging data. Not yet for young women

- Combined hormonal contraceptives
  - No increase in DM or CVD

Adolescent Girls with Androgen Excess: Really?

<table>
<thead>
<tr>
<th></th>
<th>EE-CPA</th>
<th>Low dose PioFluMet*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td>BMI</td>
<td>23.0</td>
<td>23.9</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>13.5</td>
<td>9.1*</td>
</tr>
<tr>
<td>Acne</td>
<td>2.2</td>
<td>1.1*</td>
</tr>
<tr>
<td>SHBG</td>
<td>23</td>
<td>162</td>
</tr>
<tr>
<td>Total-T</td>
<td>58</td>
<td>30</td>
</tr>
<tr>
<td>LDL-C</td>
<td>81</td>
<td>105</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50</td>
<td>64</td>
</tr>
<tr>
<td>CRP</td>
<td>0.9</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Low dose Pioglitazone-Flutamide-Metaformin

Letrozole vs. Clomiphene for PCOS-Related Infertility

- Double-blind, multicenter trial up to 5 cycles
- 750 women 18-40: Rotterdam criteria PCOS
- Spontaneous menses or MPA withdrawal
  - Clomiphene: 50-150 mg daily CD 3-7
  - Letrozole 2.5-7.5 mg daily CD 3-7

<table>
<thead>
<tr>
<th>Cumulative rates</th>
<th>Letrozole</th>
<th>Clomiphene</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>27.5%</td>
<td>19.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Ovulation</td>
<td>61.7%</td>
<td>48.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

No differences in major congenital anomalies or pregnancy losses

ACOG Infertility Treatments in PCOS

- First line treatment for ovulation induction
  - Letrazole
  - Clomiphene citrate
- Second line
  - Low dose gonadotropin
  - Ovarian drilling
  - Add Metformin to clomiphene citrate

Where Did Metformin Go?

- Metformin alone is not indicated as a first-line agent for ovulation induction in infertile women with PCOS
  - Insufficient evidence metformin increase pregnancy or live birth rates better than placebo
  - Metformin + clomiphene citrate (CC) does not improve live-birth rates over CC alone
- There may be subgroups of women with PCOS and CC-resistance in which CC + metformin beneficial

Hormonal contraceptives: first line management
- Menstrual disorder
- Hirsutism/acne

Clomiphene: first line management
- Infertility

Metformin: beneficial for metabolic/glycemic abnormalities
- Limited or no value treating androgen excess, infertility, obesity or prevention of pregnancy complications

Lifestyle intervention: beneficial
- Overweight/obese women
- Other health benefits

Schematic representation of the change in emphasis from early age reproductive disorders to long-term metabolic and cardiovascular health.

Longitudinal Screening for CVD

- Each visit
  - BMI
  - Waist circumference
  - BP
- Every 2 years (sooner if weight gain)
  - Fasting lipid levels
- Every 1-5 years
  - 2 hour oral glucose-tolerance test (HbgA1c)

PCOS Issues

- Rotterdam definition created real problems
  - Adult women
  - Teens
- Lack of definition creates problems identifying etiology
- Insulin resistance may play role for some, but not all women with PCOS
  - Even if IR relevant, we can’t measure it in practice
- PCOS phenotypes and risks differ.
- What labs do we really need?
  - Testosterone assays very imprecise at these low levels and probably unnecessary
Small follicles are crowded at the surface of a spherical polycystic appearing ovary.
Polycystic Appearing Ovary (PAO)

- Any chronic anovulation causes PAO
  - 30-50% women with functional hypothalamic amenorrhea\(^1\)
  - 100% congenital adrenal hyperplasia and female-to-male transsexuals
  - 75% anovulatory women in randomized samples
- 30% asymptomatic women\(^{1,2}\)
- 48% controls in early follicular phase\(^3\)

PCOS Issues: Adolescents

- Do not diagnose PCOS until more than 2 years after menarche
- No agreement on diagnosis
  - All 3 Rotterdam elements needed
  - Hyperandrogenemia needed?
- Individual manifestations should be treated
  - Acne, obesity, irregular cycling

PCOS Issues: Ethnic Differences

- Asians: generally shorter, lower BMI, milder hyperandrogenic phenotype
- South Asians: higher prevalence of central obesity, metabolic syndrome and type 2 diabetes
- African American: higher prevalence of obesity, MetS, hypertension and CVD
- Hispanics: higher prevalence of obesity and metabolic syndrome and Type 2 diabetes
- Middle Eastern and Mediterranean: high prevalence hirsutism, lower metabolic syndrome

Lack of Definition Creates Problems Identifying Etiologies

- Stein Leventhal: thickened ovarian cortex
- Gonadotropin abnormalities: LH/FSH
- Insulin resistance
- Genetic/intrauterine predisposition
  - Exposure to endocrine disrupting chemicals
- Calcium dysregulation
- Adipocyte malfunction
- Sympathetic nervous system dysfunction
- Dysregulation of opioid system
- Dysbiosis of gut flora
2 Cell Hypothesis

Theca cells

FSH

LH

Granulosa cells

Follicle

Cholesterol

Androgen

Estrogen

Androgen

Estrogen

Theca cells

FSH

LH

Granulosa cells

Follicle
Ovarian Contributions to PCOS: Monolayer Cell Preparation

- PCOS theca cells had increased androgen production per cell
  - P-450 C17 selectively increased androgen production, decreased progesterone production
  - Effects of growth factors (Insulin, IGF-1, IGF-2)
    - PCOS increased androgen basal levels and LH stimulation
    - No overlap between normal and PCOS preparation
Model of LH-androgen Dose-response Curves

ANDROGEN (nmol/L)

LUTEINIZING HORMONE (IU/L)

+ IGF-I or insulin

LH alone
Impact of Selective Insulin Resistance in PCOS

- Insulin resistance in skeletal muscle and adipose cells leads to hyperinsulinemia

- Hyperinsulinemia affects organs that retain insulin sensitivity
  - Hypothalamus → increases appetite
    - increases GnRH
  - Adrenal → increases androgen production
  - Ovaries → increases androgen production
IR Associated With Defects in Plasminogen Activator System

- Decreased proteolytic enzyme plasmin
- Plasmin important in clot lysis, ovulation and implantation
- Plasminogen $\rightarrow$ plasmin regulated by plasminogen activator inhibitor 1 (PAI-1), which is overproduced due to elevated insulin levels.
- PAI-1 levels and activity elevated in PCOS women, which may explain anovulation and implantation problems
PCOS Issues: Insulin Resistance and the Metabolic Syndrome

- Not all PCOS phenotypes have similar metabolic risks
- Insulin resistance (IR) prevalent finding in obese women
  - 61-70% US PCOS women obese
- IR most severe in hyperandrogenism and chronic anovulation

Increased Risk of Type 2 Diabetes Mellitus

- Type 2 diabetes occurs at earlier age (20’s-30’s versus 50’s-60’s in general population)
  - Due to insulin resistance (IR) and $\beta$-cell dysfunction
- PCOS women ages 14-44:
  - 31.1% have (undiagnosed) glucose intolerance
  - 7.5% have diabetes
  - Risk also exists for young and lean women
- PCOS women ages 40-59:
  - 15% have Type 2 diabetes

PCOS and Gestational Diabetes

- Meta-analysis of 15 studies with 5,293 pregnant women
  - 721 PCOS; 4,572 controls
  - PCOS GDM RR = 2.89 (95% CI 1.68 – 4.98)
- **BUT**: Significant heterogeneity among studies
  - Dependence of outcome on study type
- Conclusion: “Higher risk of GDM in women with PCOS questionable”

PCOS and Cardiovascular Disease

- Markers for CVD higher in PCOS women\(^1\)
  - Evidence of higher mortality rates?
- 786 PCOS women (ovary biopsy) 30 year follow-up
  - No increased risk of CVD death
  - Nonfatal CVD events increased 3.4x
- 82,439 nurses – 14 year follow-up
  - Menstrual regularity vs. irregularity:
    - CHD RR 1.53 (95%, CI 1.24-1.90) after adjustment for confounders
    - Absolute risk very low
- PCOS not associated with worsening metabolic health postmenopausally\(^2\)
- Perhaps PCOS over-tested/over-treated?

PCOS Issues: CVD Markers

- PCOS greater CVD risk markers, obesity worsens
- Non-HDL cholesterol and waist circumference best indicators
- All markers worse in NIH criteria PCOS
- CVD risk assessment should include:
  - Psychological stress, BP, glucose, lipid panel, waist circumference, physical activity, nutrition and smoking
- Periodic CVD risk reassessment

ACOG CVD in PCOS

- Premenopausal women with PCOS have increased prevalence of subclinical atherosclerosis compared with controls
- “An increased risk and early onset of cardiovascular disease in women with PCOS is strongly suspected but less well documented”

Not all “PCOS” Women Share the Same CVD Risk Profile

- Percent of women with at least one CV risk:
  - Dyslipidemia, increased C-reactive protein, increased homocysteine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogen + ovulatory dysfunction + PAO</td>
<td>40%</td>
</tr>
<tr>
<td>Hyperandrogen + ovulatory dysfunction</td>
<td>20%</td>
</tr>
<tr>
<td>Hyperandrogen + PAO</td>
<td>5%</td>
</tr>
<tr>
<td>Normoweight controls</td>
<td>5%</td>
</tr>
</tbody>
</table>

PCOS: What’s in a Name?

- Names for each of 3 major phenotypes:
  1. Classic form: “Metabolic hyperandrogenic syndrome”
  2. Ovulatory form: “Polycystic ovary-hyperandrogenic syndrome”
  3. Normoandrogenic form: “Polycystic ovary anovulatory syndrome”

Androgen Assays

- Total testosterone assays relatively inaccurate at lower levels detected in women
  - Mass spectrometry – based assay better
- Free testosterone most sensitive test, but
  - Direct free-T assays “notoriously inaccurate”
  - Calculated free levels using free total T+ SHBG more accurate
- Why do either?¹

New Concepts of PCOS Etiology

- Adipocytes fill with free fatty acids as they grow
- Early small adipocytes are insulin resistant
- Large “too full” adipocytes undergo necrosis and induce inflammatory changes
### 6 Month Outcomes Statin vs Metformin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simvastatin Base-line</th>
<th>Simvastatin 6 Months</th>
<th>Metformin Base-line</th>
<th>Metformin 6 Months</th>
<th>Simvastatin + Metformin Base-line</th>
<th>Simvastatin + Metformin 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td># Menses*</td>
<td>2.4</td>
<td>+ 1.6</td>
<td>3.0</td>
<td>+ 1.1</td>
<td>2.6</td>
<td>+ 1.7</td>
</tr>
<tr>
<td>Ovarian Volume</td>
<td>21.9</td>
<td>- 2.99</td>
<td>21.3</td>
<td>- 1.24</td>
<td>20.6</td>
<td>- 1.49</td>
</tr>
<tr>
<td>BMI</td>
<td>23.5</td>
<td>- 0.35</td>
<td>24.7</td>
<td>- 0.93</td>
<td>24.8</td>
<td>- 1.35</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>9.1</td>
<td>- 1.1</td>
<td>9.7</td>
<td>- 0.84</td>
<td>8.7</td>
<td>- 1.0</td>
</tr>
<tr>
<td>Acne</td>
<td>1.19</td>
<td>- 0.93</td>
<td>1.21</td>
<td>- 0.75</td>
<td>1.55</td>
<td>- 1.06</td>
</tr>
</tbody>
</table>

* P < 0.05 Simvastatin superior to Metformin

---

6 Month Outcomes Statin vs Metformin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simvastatin</th>
<th>Metformin</th>
<th>Simvastatin + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
<td>Baseline</td>
</tr>
<tr>
<td>Total - T</td>
<td>0.84</td>
<td>- 0.22</td>
<td>0.84</td>
</tr>
<tr>
<td>DHEAS*</td>
<td>9.26</td>
<td>- 1.64</td>
<td>9.26</td>
</tr>
<tr>
<td>Total C*</td>
<td>190.7</td>
<td>- 35.4</td>
<td>174.4</td>
</tr>
<tr>
<td>LDL-C*</td>
<td>107.6</td>
<td>- 32.6</td>
<td>96.6</td>
</tr>
<tr>
<td>FBS</td>
<td>84.2</td>
<td>- 2.85</td>
<td>84.9</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>6.9</td>
<td>- 0.29</td>
<td>8.1</td>
</tr>
</tbody>
</table>

* P < 0.05 Simvastatin superior to Metformin

Enhanced Inflammatory Transcriptome in Granulosa Cells

- Periovulatory follicles of PCOS patients undergoing IVF vs. control patients
- PCOS granulosa cells express elevated transcripts encoding cytokines, chemokines and immune cell markers
  - Affects oocyte quality and embryo development, CLC formation and risk OHSS
- Obese PCOS patients formed distinct PCOS disease subtype
- Intrafollicular androgens and cytokines
  - Comprise local regulatory loop impacting granulosa cell expression of those factors

Endogenous Opioid System and PCOS

- **Central actions of opioid system**
  - Abnormal secretory patterns gonadotropins and prolactin
  - Paradoxical stimulation of LH release in PCOS
  - Affects behavior, appetite regulation, body temperature, respiratory activity, sleep-wake cycle, mood, cognition
  - Chronic administration opioid antagonist normalizes LH response to GnRH challenges

- **Peripheral effects of opioid system**
  - Carbohydrate metabolism, insulin resistance
  - Follicular maturation

PCOS Etiology: Dysbiosis of Gut Flora

- PCOS characterized by chronic state of inflammation and insulin resistance
- Poor diet
  - Increases gut mucosal permeability
  - Increase passage of lipopolysaccharide (LPs)
    - Gram negative colonic bacteria into systemic circulation
  - Resultant activation of immune system
    - Interfaces with IR, ↑ insulin → ↑ androgens

PCOS Issues

- Uncertainty exists as to whether PCOS increases CVD mortality
- Risk of endometrial cancer higher 2.7 [1.0-7.3]
  - More well differentiated cancers with good prognosis
- No support that PCOS increases ovarian or breast cancer risks
- Age may improve many manifestations
- General health status of postmenopausal women with prior PCOS not known

Pathogenesis of PCOS

- In a **low fuel** milieu, PCOS might confer resistance to “metabolic anovulation”
  - ↑ GnRH drive is slowed to permit folliculogenesis
  - Historically, a low fuel milieu was imposed (starvation) rather than elected (dieting)
- In a **normal or high fuel** milieu, women with PCOS develop insulin resistance and anovulation
  - Reduced diet-induced thermogenesis
  - Caloric “thriftiness”
Recognition of PCOS

- Recognition of patient with PCOS is important to prevent long-term sequelae of PCOS
- Traditionally, care has been fragmented among specialists, but need to be alert that one symptom suggests others
PCOS: Overall Goals of Treatment

- Reduce production and circulating levels of androgens
- Protect endometrium from unopposed estrogen
- Achieve normal body weight
- Lower risk for cardiovascular disease, diabetes
- Plan and prepare for pregnancies
ACOG Summary of Recommendations and Conclusions: Level A

- An increase in exercise combined with dietary change has consistently been shown to reduce diabetes risk comparable or better than medication.
- Improving insulin sensitivity with insulin-sensitizing agents is associated with a decrease in circulating androgen levels, improved ovulation rate and improved glucose tolerance.
- For women with PCOS, letrozole should be considered as first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate.
- The addition of eflornithine to laser treatment is superior in the treatment of hirsutism than laser alone.

ACOG Summary of Recommendations and Conclusions: Level B

- Women with a diagnosis of PCOS should be screened for type 2 diabetes and impaired glucose tolerance with a fasting glucose level followed by a 2-hour glucose level after a 75g glucose load.
- Women with PCOS should be screened for cardiovascular risk by determinations of BME, Fasting lipid and lipoprotein levels, and metabolic syndrome risk factors.
- Reduction in body weight has been associated with improved pregnancy rates and decreased hirsutism, as well as improvements in glucose tolerance and lipid levels.
- There may be an increase in pregnancy rates by adding clomiphene citrate to metformin, particularly in obese women with PCOS.
- If CC or letrozole use fails to result in pregnancy, the recommended second-line intervention is either exogenous gonadotropins or laparoscopic ovarian surgery.

ACOG Summary of Recommendations and Conclusions: Level C

- Combination low-dose hormonal contraceptives are most frequently used for long-term management and are recommended as the primary treatment of menstrual disorders.

- Women in groups at higher risk of nonclassical congenital adrenal hyperplasia and a suspected diagnosis of PCOS should be screened to assess the 17-hydroxyprogesterone value.

- A low-dose regimen is recommended when using gonadotropins in women with PCOS

- There is no clear primary treatment for hirsutism in PCOS

Proposal: Consider PCOS as a “Modifier”, Not Itself a Condition Requiring Treatment until Definitions Stabilize

* Focus on actual problems in diagnosis
  * Obesity, with PCOS
    * OR
  * Hirsutism, with PCOS
    * OR
  * Anovulatory bleeding, with PCOS

* Focus on actual problems in treatment

Note: Routine use of Metformin to treat “PCOS” is not appropriate
A 24 year old obese G1P1 woman who had gestational diabetes in her last pregnancy. Her menses now occur about every other month. Her waist circumference is 40 inches. Her triglycerides are 180.

- What tests would you order?
- What is your diagnosis?
- What would you recommend for her first line therapy?
- What would you do if that did not work?