## 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>
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<td>Honoraria/</td>
<td>Allergan, Bayer, Merck</td>
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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

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?

- 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
New Proposal: Consider PCOS as a “Modifier”, Not a Condition Itself Requiring Treatment

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

Note: Routine use of Metformin to treat “PCOS” is not appropriate
Revised 2003 PCOS Criteria (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

ACOG 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
- Endometrial cancer risk factors (but not cancer?)
- Mood disturbances and depression
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

Workup for PCOS: Overview

- Personal history
- Family history of endocrine, reproductive, metabolic disorders
- Physical examination
- Laboratory tests
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 acne, hirsutism, androgenic alopecia, acanthosis nigricans

ACOG Suggested Evaluation for PCOS: Laboratory 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 Screening Labs Cont.

- FBS + 2 hour glucose after 75 g load
  - 2-5 fold increased risk of DM
  - 40% PCOS have glucose intolerance
- No recommended screening test for insulin resistance
  - Little utility to routine testing of insulin levels in women with PCOS
    - Does not predict who will respond to therapy
- Fasting lipid panel

Treatments for PCOS: Androgen Excess

- Acne and hirsutism
  - Combination hormonal contraceptives or
  - GnRH agonists with estrogen-progestin add back

- Hirsutism
  - Spironolactone
  - Finasteride
  - Vaniqa® (eflornithine hydrochloride) Cream (sole source)
  - Electrolysis or laser
PCOS: changing women’s health paradigm

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: 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”

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

LH

Granulosa cells

FSH

Cholesterol

Androgen

Estrogen

Follicle

Androgen

Estrogen
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)

+ IGF-I or Insulin

LH alone

LUTEINIZING HORMONE (IU/L)
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
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

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

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<tr>
<th>Condition</th>
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<tr>
<td>Hyperandrogen + ovulatory dysfunction + PAO</td>
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<tr>
<td>Hyperandrogen + ovulatory dysfunction</td>
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<tr>
<td>Hyperandrogen + PAO</td>
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<tr>
<td>Normoweight controls</td>
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CVD 10-Year Mortality in Post-Menopausal Women With Clinical Features of PCOS

- 295 post-menopausal women in the NIH Women’s Ischemia Syndrome Evaluation
  - 25 had clinical features of PCOS
  - PCOS vs. non-PCOS women
    - Earlier menopause, more often smokers
    - + Tended to more angiographic CAD
    - 10-year mortality 28% vs 27%

- PCOS history not helpful in women with known CVD disease

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

CVD Screening Recommendations for PCOS (Excessive?)

- Testing needed for:
  - Fasting lipid profiles: Starting at 20
  - 2HGT with glucose and insulin measurements
  - Carotid intimal medial thickness starting age 30
  - CT-coronary calcium screening start age 45

- Treatments needed for:
  - Insulin resistance
  - Hypertension
  - Dyslipidemia

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

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>
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<tr>
<th>Variable</th>
<th>Simvastatin</th>
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<th>Metformin</th>
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<th>Simvastatin + Metformin</th>
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<td>6 Months</td>
<td>Baseline</td>
<td>6 Months</td>
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<td>8.7</td>
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<td>- 0.93</td>
<td>1.21</td>
<td>- 0.75</td>
<td>1.55</td>
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* P < 0.05 Simvastatin superior to Metformin

## 6 Month Outcomes Statin vs Metformin

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*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

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, 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

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\(^2\)

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<th>Non-Obese PCOS</th>
<th>All Control</th>
<th>Obese Control</th>
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<td>% OSA</td>
<td>47%</td>
<td>77%</td>
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Mental Health Disorders in PCOS

- Evaluation of 60 PCOS subjects over 22 months

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<th>Disorder</th>
<th>PCOS (%)</th>
<th>Controls (%)</th>
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<td>Total mood disorder</td>
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<td>Depressive disorder</td>
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<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>
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- 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%

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 Issues: Diabetes

- Testing with 2 hour 75g OGTT (0 and 2 hrs.) indicated for:
  - Hyperandrogenism with anovulation
  - Acanthosis nigricans
  - Obesity (BMI > 30 or > 25 in Asians)
  - Family history of T2D
  - Personal history of GDM
- Diet and lifestyle first choice
- Metformin may be used for IGT and T2D

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
Lifestyle modifications are the best approach to modify risks for cardiovascular disease and diabetes.

Calorie restriction rather than composition of diet itself.

Recent studies have suggested little benefit to the addition of Metformin above lifestyle therapy alone.

Data are insufficient to recommend insulin-sensitizing agents prophylactically to prevent diabetes in women with PCOS.

Endocrine Society: PCOS 2013

- **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

Orlistat vs Metformin in PCOS

- Metformin 500 mg 3 times daily (n = 11)
- Orlistat 120 mg 3 times daily (n = 10)
- Weight reduction
  - Metformin: 1.0%
  - Orlistat: 4.7%
- Compliance equal (~90%)
- Testosterone levels dropped in both groups
- No change seen in SHBG, fasting insulin levels or lipid profiles

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
PCOS Issues: Hirsutism

● Oral contraceptives traditional mainstay
  ◆ Decrease ovarian androgen production
  ◆ Increase SHBG

● Combined with antiandrogens to block androgen action at hair follicles
  ◆ Spironolactone (with effective contraceptive)
  ◆ Vaniqa topical therapy
  ◆ Flutamide (NG due to hepatotoxicity)

● Insulin-sensitizing agents little effect
● Electrolysis or laser treatment acceptable

Adolescent Girls with Androgen Excess: Really?

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<th>EE-CPA Baseline</th>
<th>EE-CPA 12 months</th>
<th>Low dose PioFluMet* Baseline</th>
<th>Low dose PioFluMet* 12 months</th>
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<td>13.5</td>
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<td>8.4*</td>
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<tr>
<td>Acne</td>
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<td>0.4</td>
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*Low dose Pioglitazone-Flutamide-Metaformin

Resveratrol

- Resveratrol = natural polyphenol
  - Found in grapes, nuts, berries
  - Anti-inflammatory, antioxidant, cardioprotective
- Reduces androgen production by thecal-interstitial by inhibition of Cyp17a1 mRNA expressions
  - No effect on progesterone production
- Cytostatic effects on granulosa cells
  - Reduces expression of vascular endothelial growth factor

Soy Isoflavones on Metabolic Status of PCOS

- Randomized blinded trial 50 mg/d soy isoflavones vs. placebo x 12 weeks

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<tr>
<th></th>
<th>Soy</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Insulin</td>
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<td>+ 2.8</td>
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<td>HOMA-IR</td>
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<td>Free androgen index</td>
<td>- 0.3</td>
<td>+ 0.2</td>
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<tr>
<td>Triglycerides</td>
<td>- 13.3</td>
<td>+ 10.3</td>
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</table>

- Biomarkers of oxidative stress reduced

ACOG Infertility Treatments in PCOS

- First line treatment for ovulation induction: clomiphene citrate
- Second line
  - Low dose gonadotropin
  - Ovarian drilling
  - Aromatase inhibitors
  - 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
- Are there subgroups of women with PCOS and CC-resistance in which CC + metformin beneficial

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>
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<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

New Proposal: Consider PCOS as a “Modifier”, Not Itself a Condition Requiring Treatment

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

- Focus on treating actual problems

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?