PCOS across the Lifespan: An Update on Treatment Strategies

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Conflict of Interest

• Financial conflict – none
• Research conflict
  – Funded research:
    • Ferring Pharmaceutical
    • Nora Therapeutics
• Off-label drug use
  – none

PCOS: Overview

- Characterized by oligo-ovulation, hirsutism, polycystic ovaries
- 5-10% Reproductive age females
- Pathogenesis unclear:
  - Androgen
  - Insulin
  - Pituitary
- Familial clustering: genetic etiology?

PCOS across the lifespan

Young Adult
Reproductive Age
Post Reproductive

Diagnosis
Fertility

Management of Symptoms:
  Cycle Control
  Hirsutism

Metabolic Alterations
Young Adult

Making the PCOS Diagnosis

PCOS: Diagnosis

Rotterdam Criteria
Must have at least 2 out of 3:
1. Oligo- or anovulation
2. Clinical and/or laboratory evidence of hyperandrogenism
3. Polycystic ovaries

Exclusion of other etiologies

PCOS Diagnosis: Anovulation

Anovulation

Oligo-anovulation
1. Less than 8 periods/year
2. Variable bleeding pattern
3. Amenorrhea rare
4. Unopposed estrogen increases risk

PCOS Diagnosis: Hyperandrogenism

Clinical Evidence
- Hirsutism
- Acne
- Male pattern alopecia

Lab Evidence
- Total Testosterone
- Free Testosterone
- DHEA-S
PCOS Diagnosis: Ovary

Ovary Criteria:

- 12 or more follicles measuring 2-9 mm in diameter
- Increased ovarian volume (>10cm³)

Controversy: Follicle Number

- Specificity concerns:
  Follicle cut off of 12 is too low

- Relevance concerns:
  Follicle count does not associate with metabolic abnormalities

Rotterdam Criteria for Polycystic Ovary Syndrome (PCOS)

- Modified from Johnstone 2010

Controversy: Follicle Number

- Specificity concerns:
  Follicle cut off of 12 is too low

- Relevance concerns:
  Follicle count does not associate with metabolic abnormalities
Metabolic Impact of Isolated PCO

**TABLE 2.** Age-adjusted LSM values among women with and without PCO-AFC, with differences and 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>PCO-AFC (n = 82)</th>
<th>Without PCO-AFC (n = 175)</th>
<th>Difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6</td>
<td>24.0</td>
<td>1.6</td>
<td>0.04-3.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.3</td>
<td>76.1</td>
<td>3.2</td>
<td>0.1-6.3</td>
<td>0.045</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>66.9</td>
<td>63.3</td>
<td>3.6</td>
<td>-1.6-7.6</td>
<td>0.59</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>5.08</td>
<td>4.23</td>
<td>0.84</td>
<td>-0.5-2.05</td>
<td>0.17</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.16</td>
<td>0.91</td>
<td>0.24</td>
<td>-0.05-0.54</td>
<td>0.10</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>173</td>
<td>173</td>
<td>0</td>
<td>-8-8</td>
<td>1.00</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>62.9</td>
<td>64.3</td>
<td>-1.4</td>
<td>-5.2-2.7</td>
<td>0.59</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>92.0</td>
<td>92.5</td>
<td>-0.5</td>
<td>-7.5-6.4</td>
<td>0.68</td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dl)</td>
<td>17.1</td>
<td>15.0</td>
<td>2.1</td>
<td>-0.3-4.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Total cholesterol to HDL ratio</td>
<td>2.89</td>
<td>2.83</td>
<td>0.010</td>
<td>-0.12-0.31</td>
<td>0.38</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>85</td>
<td>77</td>
<td>8</td>
<td>-6-21</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Johnstone 2010

Management: Uterine Protection

- **Unopposed estrogen = risk of hyperplasia**
- **Options for protection:**
  1. Cyclical Progestin
  2. Combined contraceptive
  3. Mirena IUD

Mechanism of OCP

- Protect the uterus
- Increase SHBG
- Inhibit of LH secretion
- Inhibit adrenal androgen secretion

Young Adult -> Reproductive Age

- Cycle control and uterine protection
- Hirsutism
- Acne
Management: Hyperandrogenism

**Acne**

**Hirsutism**

**Androgenic Alopecia**

**Mechanical Removal**

- Laser
- Electrolysis

**Pharmacologic**

- Oral Contraceptives
- Spironolactone
- Flutamide
- Finasteride
- Vaniqua

Mechanism of OCP

- Protect the uterus
- Increase SHBG
- Inhibit of LH secretion
- Inhibit adrenal androgen secretion

Summary: Hirsutism

- Direct Removal
- Oral Contraceptive
- Second Agent: Spironolactone
Androgenetic Alopecia:

Differential Diagnosis: Importance of History/Physical
- Telogen Effluvium
- Alopecia Areata

Treatment:
- FDA Approved option: Rogaine
- Oral contraceptive and Spironolactone 50 mg per day

Reproductive Age: Fertility

- Weight Loss and Lifestyle Change
- Clomid
- Metformin
- Letrozole
- Drilling
- Gonadotropins

Lifestyle Changes

87 women
- obese
- 79% PCOS

6 month group program
- regular exercise
- gradual dietary changes

67 patients completed program
- Mean change in BMI -3.7
- 27% spontaneous conception
- 53% conceived with assistance
- Increased self esteem
- Decreased anxiety/depression

20 patients dropped out
- No changes in BMI
- No conceptions

Clark et al Human Reproduction 1995

Lifestyle Change

- 40 women with PCOS/anovulatory infertility

Structured Exercise
3 sessions/wk week

Patient choice....

24 weeks

Hypocaloric Diet
High Protein
800 kcal deficit

Palomba et al Human Reproduction 2008
### Exercise vs. Diet: Results

<table>
<thead>
<tr>
<th></th>
<th>Exercise</th>
<th>Diet</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.8</td>
<td>25.8</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>33.1</td>
<td>33.2</td>
<td></td>
</tr>
<tr>
<td>Dropout</td>
<td>15%</td>
<td>35%</td>
<td>0.14</td>
</tr>
<tr>
<td>% Ovulatory</td>
<td>65%</td>
<td>25%</td>
<td>0.01</td>
</tr>
<tr>
<td>Pregnancy Rate</td>
<td>35%</td>
<td>10%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Palomba et al Human Reproduction 2008

### Lifestyle

- Lifestyle interventions may increase ovulations and chance of pregnancy
- Weight reduction may reduce pregnancy complications
- Lifestyle interventions should be considered first line

### Ovulation Induction: Mechanism

- Metformin: Improve insulin sensitivity
- Weight Loss: Improve insulin sensitivity
- Clomiphene Citrate (Clomid): Synthetic Antiestrogen
  - Convenient
  - Inexpensive
  - Long-standing first choice for ovulation induction in women with PCOS
How many women will ovulate with Clomid?

<table>
<thead>
<tr>
<th>Clomiphene Citrate dosage</th>
<th>Ovulatory (%)</th>
<th>Anovulatory (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/d 150 mg/d</td>
<td>13 (77%)</td>
<td>45 (23%)</td>
</tr>
<tr>
<td>50 mg/d</td>
<td>44 (57%)</td>
<td>58 (43%)</td>
</tr>
</tbody>
</table>

Number of patients: 199

Imani, B. et al. J Clin Endocrinol Metab 1998;83:2361-2365

Clomid: What are the chances for conception?

- 160 patients
- Normogonadotropic anovulation
- Successful response to clomid
- Normal SA
- BMI > 18.5

Metformin for ovulation

- Biguanide Insulin Sensitizer
- Category B
- Not FDA approved

Reproductive Medicine Network

- Multicenter
- Double blind
- 626 women with PCOS

Legro et al. NEJM 2007; 35:551-66
**Results of RMN PPCOS Trial**

- **OVULATION**: P<.001
- **Conception**: P<.001
- **Livebirth**: P<.001
- **Pregnancy loss**: P<.001

Legro et al. NEJM 2007; 35:551-66

**Live Birth Prediction Chart**

- Predictors of success:
  - Low hirsutism score
  - Lower BMI
  - Younger age
  - Shorter duration of infertility

Rausch M E et al. JCEM 2009;94:3458-3466

**PCOSMIC: Met/Clomid in BMI <32 and >32**

- Randomized double blind trial in New Zealand
- BMI >32 (n=65): placebo vs. metformin
- BMI <32 (n=106) CC vs. Met vs. CC/MET
- Six month treatment period

**Live Birth Rates**

- **BMI >32**
  - Placebo: 6%
  - Metformin: 16%
  - Clomid: 36%
  - Metformin: 29%
  - Clomid + Met: 43%

- **BMI <32**


**Metformin as Pre-Treatment: Results**

- **Pregnancy rate**: Metformin 52.6% Placebo: 40.4%

- Effect more pronounced in obese women

Obese Non-Obese

Morin-Papunen L et al. JCEM 2012;97:1492-1500
Aromatase Inhibitors

Clomiphene citrate vs. Letrozole

Summary: Fertility

- The first line treatment for ovulation induction remains lifestyle.
- Letrozole superior to Clomiphene citrate
- Metformin may add benefit as pre-treatment
- Gonadotropins are second line treatment
- IVF third line treatment or if over-stimulation cannot avoided

Post-reproductive PCOS and Insulin Resistance

Adapted from Dunail A, et al. JCEM 81: 942-947, 1996
Insulin and the Pathophysiology of PCOS

- Hyperinsulinemia
- Increased Free Androgen
- Clinical Hyperandrogenism
- Anovulation
- Decreased SHBG
- Fatty Liver
- Insulin Resistance
- Hyperglycemia
- Diabetes
- Cardiovascular disease

Prevalence of IGT or Diabetes

- Chicago n=122
- Penn State n=144
- Mt Sinai n=110
- Rezulin Collab Group n=408

Legro, et al. JCEM 1999; 84: 165-169
Azziz et al. JCEM 2001; 86: 1626-1632
Ehrmann et al. Diabetes Care 1999; 22:141-146

Prevalence of IGT and Diabetes

PCOS versus National population

- IGT
  - PCOS: 30%
  - Lean PCOS: 10%
  - NHANES: 1.6%

- T2DM
  - PCOS: 8%
  - Lean PCOS: 0%
  - NHANES: 2.2%

IGT Across the Lifespan

- Adolescents have impaired glucose tolerance 30% and TYPE 2 diabetes 7.4%
- Prevalence of Type 2 diabetes in perimenopausal women with history of PCOS is four fold higher compared to controls (32% vs 8%)

Palmert, MR et al JCEM 2002; 87:1017
Metabolic Syndrome

368 Non-diabetic PCOS patients (Ages 18-41)

- No Metabolic syndrome in Women with BMI <27 (n=52)
- Women with BMI > 30 had 13x chance of Metabolic syndrome


Meta-Analysis of BMI Matched Studies

Odds Ratio (95% CI) in women with PCOS compared to BMI controls
- Impaired glucose tolerance: OR: 2.54 (1.44, 4.47)
- Diabetes: OR: 4.00 (1.97, 8.10)


The Impact of BMI on IGT

Impaired Glucose Metabolism by BMI

Adapted from Legro, et al. JCEM 1999; 84: 165-169

PCOS Phenotypes

- Hyperandrogenism
- Oligo or Anovulation
- Polycystic Ovaries
Insulin Resistance and PCOS Phenotype

137 Italian women screened with insulin glucose clamp

Moghetti et al JCEM April 2013 Epub

Free Androgen Index and Metabolic Syndrome

Natural History of Insulin Resistance in PCOS

Moghetti et al JCEM April 2013 Epub

Progression to Type 2 Diabetes

- 67 Australian Women with PCOS followed for 6.2 years
- Mean BMI 29
- 2.2% annual conversion rate from normal glucose tolerance to impaired glucose tolerance (IGT) or Type 2 diabetes
- 8.7% annual conversion rate from IGT to DM


Progression and Population Attributable Risk

- Prospective Controlled Study
- 149 PCOS and 166 Controls followed for 8 years
- Diagnosis of T2DM made by fasting glucose or reported history

Among 242 white women
- 6.5 increase in RR when adjusting for age
- 4.0 increase in relative RR when adjusting for BMI
- 25-36% population attributable risk based on a 6-10% prevalence of PCOS in general population

Talbott et al. Journal of Women’s Health 2007; 16:191

Progression of Insulin Resistance

- 16% conversion per year from NGT to IGT
- 2% conversion/year from IGT to DM2
- 2 fold increase over controls

Legro et al. JCEM 2005; 90:3236-32

Progression of Insulin Resistance

- Cohort of women with PCOS (n=255)
- Followed for at least 10 years (mean 16.9)
- 42 developed T2DM
- IR 1.05 per 100 person years

Age Standardized Rate of Type 2 Diabetes

PCOS 39.3%
Italian Population 5.8%
**Why is Screening Important?**

- Identify T2DM requiring intensive treatment
- Identify hyperglycemia in patient considering pregnancy
- Identify IGT or IFG that could benefit from treatment
- Motivate!

**Criteria for Defining Impaired Glucose Metabolism**

<table>
<thead>
<tr>
<th>Test</th>
<th>WHO 2006</th>
<th>ADA 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>Impaired 110-125 mg/dl</td>
<td>Impaired 100-125 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Diabetes &gt;126 mg/dl</td>
<td>Diabetes &gt;126 mg/dl</td>
</tr>
<tr>
<td>2 hour Glucose Challenge</td>
<td>Impaired 140-199 mg/dl</td>
<td>Impaired 140-199 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Diabetes &gt;200 mg/dl</td>
<td>Diabetes &gt;200 mg/dl</td>
</tr>
</tbody>
</table>

**Screening Recommendations**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Who to screen</th>
<th>Screening Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>All patients with PCOS</td>
<td>Fasting glucose, Consider OGTT</td>
</tr>
<tr>
<td>American College of Obstetrics and Gynecology</td>
<td>All patients with PCOS</td>
<td>Fasting glucose, OGTT</td>
</tr>
<tr>
<td>ADA</td>
<td>Asymptomatic individuals under age of 45 if overweight with additional risk factors, including PCOS</td>
<td>Fasting glucose, OGTT in patients with IFG or if high level of concern.</td>
</tr>
<tr>
<td>ASRM and ESHRE</td>
<td>Obese women with PCOS, consider non-obese women with additional risk factors</td>
<td>OGTT</td>
</tr>
<tr>
<td>Androgen excess Society</td>
<td>All patients with PCOS</td>
<td>OGTT</td>
</tr>
</tbody>
</table>

**Screening: OGTT is Key**

Patients with abnormal OGTT with normal fasting glucose

Legro R S et al. JCEM 1999;84:165-169
Screening

- Population based study
- OGTT administered to 105 consecutive women with PCOS referred to an academic REI clinic
- Mean age 28, Mean BMI: 25.5
- Prevalence of abnormal OGTT was 28%
  - 23% had IGT and
  - 5% had diabetes
- If ADA recommendations were followed 1/7 women with PCOS would have missed dx


Implications of Impaired Glucose Metabolism

Funagata Diabetes Study
Patients with normal glucose, IGT and IFG
Only IGT had poor outcomes

Impaired glucose tolerance

Impaired Fasting Glucose

Prevention and Treatment

- Multi-center, 4 year study
- 3234 people with impaired glucose tolerance and mean BMI of 34
- 45% of participants from higher risk minority groups
- Interventions:
  - Metformin (850 mg bid)
  - Structured Lifestyle (goal of 7% weight loss)
  - No intervention
- Ended study 1 year early

Diabetes Prevention Trial: Results

Conversion to Diabetes:
- Placebo: 29%
- Metformin 22%
- Lifestyle 14%

Risk reduction
- Metformin 31%
- Lifestyle 58%

Indian Diabetes Prevention Project

Persistent Impaired Glucose Tolerance
Mean BMI = 26
Mean ages = 45

Controls
n=136
Lifestyle diet and exercise advice and scores for adherence n=133
Metformin (500mg) n=133
Metformin and Lifestyle n=129

Indian Diabetes Prevention Project

Cumulative Incidence of diabetes 3 years:
- Controls: 55%
- Lifestyle: 39%
- Metformin: 41%
- Both: 40%
- Risk reduction of 28%

Physical Activity in the Real World

- Cross sectional study of 150 women with PCOS (Rotterdam)
- Assessed adherence to Department of Health and Human Services guidelines for exercise-150 minutes of moderate or 75 minutes of vigorous exercise per week

PHYSICAL ACTIVITY

- Did not meet DHHS Guidelines
- Met DHHS Guidelines

- Active women more likely to be white (72% vs. 46%) and nulliparous (64% vs. 40%)
Physical Activity in the Real World

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not Active</th>
<th>Active</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index kg/m2</td>
<td>33.7</td>
<td>29.9</td>
<td>.009</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98</td>
<td>89</td>
<td>.03</td>
</tr>
<tr>
<td>Weight fluctuations (kg)</td>
<td>28.0</td>
<td>19.2</td>
<td>.008</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>94.0</td>
<td>87.8</td>
<td>.04</td>
</tr>
<tr>
<td>OGTT (mg/Dl)</td>
<td>122.3</td>
<td>105.4</td>
<td>.07</td>
</tr>
<tr>
<td>Sex hormone-binding globulin (nmol/L)</td>
<td>40.4</td>
<td>68.4</td>
<td>.006</td>
</tr>
<tr>
<td>Depression</td>
<td>5.5</td>
<td>3.6</td>
<td>.005</td>
</tr>
</tbody>
</table>

Lamb et al Am J of Obste Gynecol 2011; 204:352-356

Recommendations for Management

Consensus Recommendations for treatment of individuals with IFG, IGT or both

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG or IGT</td>
<td>Lifestyle modification (5-10% of weight loss and moderate intensity physical activity 30 minutes per day)</td>
</tr>
<tr>
<td>Individuals with IFG and IGT and any of the following</td>
<td>Lifestyle and/or metformin</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;35</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>Elevated TRIG</td>
<td></td>
</tr>
<tr>
<td>Reduced HDL</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>AIC &gt;6.0</td>
<td></td>
</tr>
</tbody>
</table>

Nathan et al Diabetes Care 2007 30: 753-760

Summary: Metabolic Risk

- Insulin resistance and diabetes is common in PCOS and appears likely to translate into increased cardiovascular events even when controlling BMI
- Risk factors are increased BMI, family history of diabetes, and PCOS with hyperandrogenism and increased ovarian volume
- Screening with OGTT is most sensitive screening method
  - Obtain fasting lipid profile as well
- Lifestyle is mainstay of treatment for IGT
- Pharmacologic intervention should be considered in select patients

UCSF Multidisciplinary Clinic for PCOS

Pre-visit
- One month off OCP’s and anti-androgen therapy
- Questionnaires
- Complete Laboratory Panel

Visit One
- Reproductive Endocrine
- Ultrasound
- Dermatologist
- Genetic counselor

Visit Two
- Reproductive Endocrine
- Nutritionist
- Psychologist

Clinical Care
Research Framework
Thank You