Update in Management of Polycystic Ovary Syndrome (PCOS)

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Disclaimer

• I have/had an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization:
  – I have received a grant(s) or an honorarium from a commercial organization:
    • Ferring Pharmaceuticals, EMD Serono, Merck
  – I am currently participating in or have participated in a clinical trial within the past two years:
    • Ferring Pharmaceuticals

• I do intend to make therapeutic recommendations for medications that have not received regulatory approval (i.e. “off-label” use of medication).

• No financial or in-kind support was received from a commercial organization to develop this presentation
Objectives

• Diagnostic Criteria and Work-up of PCOS

• Symptomatology Management
  – Infertility
  – Hirsutism

• Long-Term Complications
  – Diabetes
  – Endometrial Cancer

PCOS – Diagnosis

• Stein-Leventhal Syndrome
  – First Described in 1935

  – Women with amenorrhea, infertility, hirsutism, and enlarged polycystic ovaries

  – Resumption of ovulation with ovarian biopsy

### PCOS - Diagnosis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Must meet both criteria</td>
<td>Must meet two of three criteria</td>
<td>Clinical and/or biochemical evidence of hyperandrogenism</td>
</tr>
</tbody>
</table>

- **Clinical and/or biochemical evidence of hyperandrogenism**
- **Menstrual dysfunction**
- **Oligo- or anovulation**
- **Ovarian dysfunction or polycystic ovaries**
- **Polycystic ovaries**

**ESHRE/ASRM** – European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine

**NIH/NICHD** – National Institutes of Health/National Institute of Child Health and Human Disease

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### PCOS – Diagnosis

**History and Physical**
- Anovulation
- Hirsutism

**Laboratory Testing**
- Midluteal Progesterone
- Total Testosterone
- Fasting Glucose

**Imaging**
- Pelvic ultrasound

**Exclusion of other Causes**
- TSH
- Prolactin
- 17-OH Progesterone
PCOS – Diagnosis

• What is Biochemical Hyperandrogenism
  – Free androgen index > 5
    • FAI = (Total Testosterone (nM)/SHBG (nM)) X 100
  – Total testosterone > 1.7 nM

• What is a Polycystic Ovary?
  – Normal ovary with volume > 10 mL
  – ≥ 12 follicles between 2-9 mm in ovary
    • 50% normal women under age 30
  – ≥ 25 follicles between 2-9 mm in ovary more specific

PCOS and AMH

AMH 4.9 ng/ml – 97% specific and 92% sensitive for PCOS

PCOS – Diagnosis Take Home Points

- Making diagnosis helpful but not critical
  - More important to exclude other etiologies
    - Thyroid dysfunction
    - Hyperprolactinemia
    - Congenital Adrenal Hyperplasia
    - Androgen secreting neoplasms (T usually > 2-fold upper range)

- Ultrasound helpful but not critical
  - Must be endovaginal
  - Request ovarian volume and number of follicles per ovary

PCOS - Infertility

- Confirm Oligo-or anovulation
  - Menstrual cycle intervals > 35 days
  - Midluteal progesterone < 10 nM

- Semen testing recommended
  - Repeat if abnormal
  - Refer if total motile count (TMC) persistently < 10 million
    - TMC = (Volume (mL) X Motility (%)) X Conc (10^6/mL)/100

- Tubal patency testing optional - based on risk factors
PCOS – Preconception Interventions

• Obese (BMI > 29) age 18-39 infertile women

• RCT to lifestyle intervention for 6 months before treatment vs immediate fertility treatment

• Primary outcome
  – Vaginal birth of healthy singleton at term within 24 months of randomization


<table>
<thead>
<tr>
<th></th>
<th>Intervention Group N = 289</th>
<th>Control Group N = 285</th>
<th>RATE RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anovulation</td>
<td>128 (44.3%)</td>
<td>141 (49.5%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal Birth Healthy Live Singleton</td>
<td>76 (27.1%)</td>
<td>100 (35.2%)</td>
<td>0.77 (0.60-0.99)</td>
</tr>
<tr>
<td>Live Birth</td>
<td>123 (43.9%)</td>
<td>153 (53.9%)</td>
<td>0.82 (0.69-0.97)</td>
</tr>
<tr>
<td>Natural Conception</td>
<td>73 (26.1%)</td>
<td>46 (16.2%)</td>
<td>1.61 (1.16-2.24)</td>
</tr>
<tr>
<td>Ovulation Induction</td>
<td>34 (12.1%)</td>
<td>64 (22.5%)</td>
<td>0.54 (0.37-0.79)</td>
</tr>
</tbody>
</table>

PCOS – Preconception Interventions

Van Oers AM et al. Hum Reprod 2016;31:2704-13

PCOS - Infertility

For Primary Care Provider

- Ovulation Induction
  - Metformin (off-label)
  - Clomiphene (on-label)
  - Letrozole (off-label)

For Fertility Specialist

- Ovulation Induction
  - Gonadotropins
  - Laparoscopic Ovarian Drilling

- IVF
PCOS-Ovulation Induction

• Metformin
  – Oral biguanide/insulin sensitizer
  – May be used alone, or in conjunction with clomiphene
  – Initial studies
    • Ovulation rates 90% with metformin and clomiphene
    • Ovulation up to 75% with metformin and clomiphene in clomiphene resistant patients


PCOS-Ovulation Induction

• Clomiphene Citrate
  – Selective Estrogen Receptive Modulator (SERM)
  – Shown to induce ovulation in 1961
  – Ovulation rates of 70-80%
  – Pregnancy rates of 30-40%
  – Twin pregnancy rates 5-7%
PCOS-Ovulation Induction

• Letrozole
  – Aromatase inhibitor
  – Adjuvant treatment estrogen receptor positive breast cancer
  – First described in 2000 for ovulation induction
  – Number of small studies showing similar success to clomiphene

Mitwally MF et al. Reprod Technol 2000. 10:244-47

PCOS – Ovulation Induction

• Practical questions for the Family Physician/OBGYN
  – What drug is “best”
  – How do I use the drugs
  – How do I monitor for effectiveness
  – How should I counsel my patients
### PPCOS 1 - Ovulation Induction

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene N = 209</th>
<th>Metformin N = 208</th>
<th>Combination therapy N = 209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>49.0%</td>
<td>29.0%</td>
<td>60.4%</td>
</tr>
<tr>
<td>Conception</td>
<td>29.7%</td>
<td>12.0%</td>
<td>38.3%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>23.9%</td>
<td>8.7%</td>
<td>31.1%</td>
</tr>
<tr>
<td>Twins</td>
<td>4.0%</td>
<td>0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Live Birth</td>
<td>22.5%</td>
<td>7.2%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

Legro R et al., N Eng J Med; Feb 8, 2007

### PPCOS 2 - Ovulation Induction

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene N = 376</th>
<th>Letrozole N = 374</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>48.3%</td>
<td>61.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conception</td>
<td>35.8%</td>
<td>46.5%</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Twin birth</td>
<td>6.9%</td>
<td>3.9%</td>
<td>0.49</td>
</tr>
<tr>
<td>Live Birth</td>
<td>19.1%</td>
<td>27.5%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Legro R et al., N Eng J Med; July 10, 2014
### PPCOS – Ovulation Induction

#### How to Use the Ovulation Induction Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Letrozole</th>
<th>Clomiphene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>2.5 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Cycle day 3-7 (5 days)</td>
<td></td>
</tr>
<tr>
<td>Recommended maximum cycles</td>
<td>6 ovulatory cycles</td>
<td></td>
</tr>
<tr>
<td>Confirmation of ovulation</td>
<td>Cycle day 21-23 progesterone &gt; 10 nM</td>
<td></td>
</tr>
<tr>
<td>Indication for dosage increase</td>
<td>Absence of ovulation</td>
<td></td>
</tr>
<tr>
<td>Dosage increase</td>
<td>2.5 mg daily increment</td>
<td>50 mg daily increment</td>
</tr>
<tr>
<td>Maximal daily dose</td>
<td>7.5 mg daily</td>
<td>150 mg daily</td>
</tr>
</tbody>
</table>

#### PCOS – Ovulation Induction

- **Practical Points**
  - Remind intercourse timing – one of:
    - Ovulation predictor kits
      - Day before and day of ovulation best chance of conception
      - Kits typically positive 1-2 days before ovulation
      - 7% false positive rate
    - Intercourse every other day from cycle day 10-20
      - Greater frequency neither helpful or harmful

- Multiple pregnancy rate
  - 4-7% twins
  - Higher order multiples <1%
PCOS – Persistent Anovulation

• Refer to Fertility Specialist

• Management Options
  – Addition of Metformin to oral ovulation induction agents
  – Laparoscopic ovarian drilling
  – Gonadotropins
  – IVF

PCOS - Hirsutism
PCOS - Hirsutism

• Therapy includes
  – Androgen suppression
  – Peripheral androgen blockade
  – Mechanical/cosmetic destruction of unwanted hairs

• Hormonal/Medical therapy requires > 6 months

• Removal of unwanted hairs most effective after medical therapy

PCOS - Hirsutism

• Oral Contraceptive Pill (OCP) first line treatment

• No clinical differences between OCPs for hirsutism

• Yaz/Yasmin have theoretical advantages
  – Drospirenone 3 mg has spironolactone activity

• Diane 35 has theoretical advantages
  – Cyproterone acetate an antiandrogen
PCOS - Hirsutism

- Spironolactone
  - Aldosterone-antagonist, mild-diuretic
  - Better effect seen with dose 100-200 mg daily
    - After time, can lower dose to maintenance 25-50 mg daily
  - Hyperkalemia risk
    - Use with caution in elderly and diabetic
PCOS - Hirsutism


PCOS – Diabetes

IGT

DM2

PCOS - Diabetes

• Screening for DM2 for PCOS
  – BMI > 30
  – BMI > 25 for Asian population
  – Acanthosis nigricans
  – Family History of GDM or DM2

• Fasting glucose vs 75 g-OGTT

PCOS - Diabetes

• Prevention of Type 2 Diabetes
  – RCT of 3234 people at risk for DM2
    • Fasting glucose 5.3-6.9 mM or
    • Glucose 7.8-11 mM - 2 hr post 75g glucose load

  – Three groups
    • Lifestyle Modification (goal of 7% weight loss and 150 minutes physical activity/week)
    • Metformin 850 mg po bid
    • Placebo

Diabetes Prevention Program Research Group; N Engl J Med; 346: 393-403
PCOS and Diabetes

Diabetes Prevention Program Research Group; N Engl J Med; 346: 393-403

PCOS and Endometrial Cancer
PCOS and Endometrial Cancer

• Risk Factors for Endometrial Cancer (EC)
  – Obesity
  – Unopposed Estrogen
  – Infertility
  – Hypertension
  – Type 2 Diabetes

• 2.9- fold greater risk of EC with PCOS

• 9% Absolute Lifetime Risk

PCOS and Endometrial Cancer

• Preventative measures for EC in PCOS not known

• OCP treatment of menstrual irregularity protective against endometrial cancer
  – 50% reduction in ever users of OCP
  – Greater risk reduction with longer OCP use
  – Risk reduction lasts even > 20 years after discontinuing

• Levonorgestrel IUS may have similar reduction risk
PCOS and Endometrial Cancer


QUESTIONS?