Reproductive Gynaecology and Infertility

PCOS

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Disclosure

❖ No conflict of interest
❖ Pilot study (Bromocriptine for PCOS patient)
Objectives

- Key points
- Prevalence
- Background and pathophysiology
- Endocrinological and Metabolic dysfunctions
- Management
Key Points

❖ PCOS is recognized as a common cause of *menstrual irregularity*, *androgen* excess and *infertility*

❖ PCOS is *systemic disease* that impacts lipid levels, glucose handling and increases the risk for central obesity

❖ Approximately *50%* of patients with PCOS will also have *obesity*
Key Points

- Long-term health risks *diabetes mellitus, dyslipidemia, hypertension and cardiovascular diseases*

- Infrequent ovulation, *deficient progesterone secretion*. Increased risk for endometrial *hyperplasia or cancer*
Key Points

❖ Therapeutic approaches to PCOS should include life-style changes aimed at weight reduction such as exercise and a low glycemic index diet.

❖ 35% of PCOS patients have insulin resistance and up to 10% will have Diabetes, therefore a 2 hr GTT is recommended as a baseline, then repeat at 3-4 year intervals
Key Points

❖ **Oral contraceptives** are an effective treatment for the patient who does not want to conceive.

❖ **Lifestyle Modification**: (an increase in exercise combined with dietary change) has consistently reduced diabetes risk comparable to or better than medication.
PCOS: Prevalence

- PCOS affects 6-9% of reproductive age women
- “The most common endocrine disorder in women of reproductive age”

Published online. JCEM Oct 22 2013
Genetics of PCOS

- **Familial clustering** of hyperandrogenism, anovulation, and polycystic ovaries suggests an underlying genetic basis or cause.
- At least one group of patients with a *heritable X-linked form* of PCOS has been described, with a widely varying phenotype.
- Studies in large families have suggested *autosomal-dominant* inheritance, with premature balding as the male phenotype.
Clinical presentation

Presenting symptoms:
• Irregular bleeding
• Androgen excess
• Infertility

Associated with
• Central obesity
• Diabetes
• Insulin resistance
Genetics of PCOS

- Nearly 50% of sisters of women with PCOS have elevated total or bioavailable testosterone concentrations, and approximately 35% of mothers also are affected.

- The first degree relatives of women with PCOS also exhibit other metabolic abnormalities such as dyslipidemia, which may predispose to an increased risk for cardiovascular disease.
Diagnosis

2003 ESHRE/ASRM-sponsored PCOS Consensus Workshop

Revised Criteria: (2 or more conditions)

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries: Sonographic findings
   • *Exclusion of other etiologies; CAH, Cushing’s syndrome, androgen-secreting tumor*

Fertil Steril 2004; 81: 19-25
Diagnosis

Ultrasound Criteria: PCOS Diagnosis 2003 ESHRE/ASRM consensus workshop

At least one of the following in any one ovary:

- **12 or more follicles measuring 2-9 mm in diameter**
- Increased ovarian volume (>10 cm³)
PCOS: A Diagnosis of Exclusion

- If there are no signs of androgen excess: may need no testing
- Consider 17-OH P in ethnic groups at risk
- Testosterone level may be helpful as some ethnic groups do not have a high density of hair follicles and hyperandrogenism can be missed
When do you send possible PCOS patient for Pelvic Ultrasound?

A. If they don’t meet the clinical or laboratory criteria
B. If they have abnormal uterine bleeding
C. If they wish to conceive
D. Always
Diagnosis

PCOS: test by symptoms

• Clinicians should evaluate *irregular cycles*
  ❖ TSH
  ❖ prolactin
  ❖ FSH

• And should evaluate *androgen excess*
  ❖ 17-OH P
  ❖ Testosterone
  ❖ If Cushings suspected: salivary cortisol
PCOS: difficult diagnosis

- *Teens* and *perimenopausal* patients will often have irregular cycles
- No consensus on lab testing for these age groups
- Diagnosis rarely made by sonographic evidence
Diagnosis

• But *hyperandrogenism is never normal*
• Focus on the source of androgen excess to guide therapy
PATHOGENESIS OF PCOS

- Genetic
- Environmental

↑ Androgens
↑ Insulin

↓ Insulin Resistance
Endocrine

↑ Sensitivity to LH
Genetic
IR, IGF-BP1
P450c-17α
↓ SHBG

Normal Ovaries → Polycystic appearing ovary → PCOS
Insulin Resistance in Polycystic Ovary Syndrome

- Increased glucose
- Increased insulin
- Increased free androgen
- Decreased SHBG
- Excessive androgen production

Insulin Resistance in Polycystic Ovary Syndrome

- Increased insulin resistance
- Increased glucose
- Increased free androgen
- Decreased SHBG
- Ovarian theca: Excessive androgen production
- Pancreas

**Insulin Sensitivity (IR) in PCOS:** Glucose Clamp Study  
*(Dunaif et al. Diabetes 1989;38:1165)*

<table>
<thead>
<tr>
<th></th>
<th>Glucose Utilization (mg/Kgm per min)</th>
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<tbody>
<tr>
<td>Obese PCO</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>Obese Non-PCO</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>Non-Obese PCO</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>Non-Obese Non-PCO</td>
<td>7.4 ± 0.2</td>
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</tbody>
</table>

**Conclusion:** 1. PCOS women have significant insulin resistance.  
2. PCOS & obesity have a synergistic effect on glucose utilization.
High prevalence of impaired glucose tolerance and diabetes in obese PCOS patients

- Study of 122 women with PCOS (mean BMI 37.1)
  - 35% had IGT and 10% DM
- Over a 2.5 year follow-up period, of those that were normal at baseline, 45% developed IGT and 9% developed DM

Ehrmann et al Diabetes Care, 1999
PCOS: Metabolic Sequelae

• Ovarian hyperandrogenism - most consistent
• Insulin Resistance: Hyperinsulinemia
• Decrease in SHBG
  ↑ free T leading to Hirsutism
  ↑ free estradiol leading to ↑Endometrial Ca risk
• Unopposed E Production: E1 > E2
• Inappropriate LH/FSH Secretion
• Hyperprolactinemia, usually mild
Long term risks

- Psychologic disorder (Anxiety, Depression)
- Diabetes Mellitus DM2
- Cardiovascular Disease
- Metabolic syndrome
- Obstructive Sleep Apnea OSA
- Acanthosis Nigricans
- Endometrial Hyperplasia or Cancer
- NAFLD or NASH

Long-term Consequences of Polycystic Ovary Syndrome
Green-top Guideline No. 33 November 2014

Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline
J Clin Endocrinol Metab, December 2013, 98(12):4565–4592
Long term risks

Pregnancy complications

• Gestational Diabetes Mellitus GDM
• Hypertensive disorder of pregnancy
• Preterm Premature Rupture of Membrane
• Preterm Labor and delivery

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Green-top Guideline No. 33 November 2014

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Metabolic syndrome

In general, the diagnosis of metabolic syndrome requires three of the following five clinical characteristics:

- Increased **waist circumference** (population specific, >88 cm in the United States)
- Increased **blood pressure** (≥130 mm Hg systolic; ≥85 mm Hg diastolic)
- Increased **triglycerides** (≥150 mg/dL)
- Decreased **HDL-cholesterol** (<50 mg/dL)
- Increased **fasting glucose** (≥100 mg/dL) or previously established diabetes mellitus
Metabolic Syndrome Therapy

1. Treat underlying causes: weight reduction, diet, exercise
   - Bariatric medical and surgical options
2. Treat underlying cardiovascular risk factors:
   - Antihypertensives
   - Oral hypoglycemics
   - Statins
PCOS and Infertility

❖ 70-90% of anovulatory disorder
❖ 50% will have primary infertility and 25% secondary infertility
When do you consider Metformin as 1st line treatment for PCOS?

A. Patient with sign of Insulin resistance
B. Patient with impaired glucose tolerance
C. Patient who failed ovulation induction with oral agents such as Clomophine Citrate
D. Patients with morbid obesity or BMI more than 35
Therapeutic Options: PCOS

1. **Lifestyle changes:**
   - Weight reduction, exercise, behavior modification

2. **Medical therapy:**
   - Ovulation induction for anovulation
   - Insulin sensitizers for insulin resistance

3. **Surgical therapy:**
   - For anovulation
Therapeutic Options: PCOS

Lifestyle Management

• Combined approaches are most successful
• Goal is to achieve 5% reduction in body weight
  – Diet (low glycemic index)
  – Exercise
  – Pharmacologic treatment
  – Bariatric surgery
Medical Therapy: PCOS

**Anovulation: Desiring pregnancy**

- Induction of ovulation:
  - Clomiphene, gonadotropins
  - Insulin sensitizers
  - *Aromatase Inhibitors (Letrozole 2.5-7.5 mg/d x 5)*
  - (FDA Pregnancy category D)
Medical Therapy: PCOS

**IGT or DM2**

- Agents for insulin sensitization

Metformin 500-2000 mg/d

[Other agents are available but have higher potential for side effects and adverse risks]
CC vs MFN vs CC+MFN: What’s Best?

Reproductive Medicine Network Study *NEJM* 2007: Feb 8

- RCT: CC vs MFN vs CC+MFN (626 infertile women/PCOS) x 6 mos.

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>MFN*</th>
<th>CC+MFN</th>
<th>(p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live-birth rate (%)</td>
<td>22.5</td>
<td>7.2*</td>
<td>26.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Ovulation rate</td>
<td>76.1</td>
<td>55.3*</td>
<td>83.3</td>
<td></td>
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<tr>
<td>Mean # of Ov./ Pt.</td>
<td>2.22 ±1.87</td>
<td>1.4 ±1.72</td>
<td>2.8 ±2.0*</td>
<td>0.001</td>
</tr>
<tr>
<td>Multiple Preg. Rate</td>
<td>6.0</td>
<td>0.0</td>
<td>3.1</td>
<td></td>
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</table>

- No difference in pregnancy loss rates
- MFN: Positive effects on BMI, T & HSBG, and insulin/IR
- In all groups; a BMI <30 had a higher live-birth rate (vs >30)

**Conclusion:** CC is superior to Metformin
Medical Therapy: PCOS

Infertility Treatment
Clomiphene Citrate: SOGC (1-A)
For ovulation induction in PCOS
  - 50 to 150 mg / day for 5 days
  - Multiple gestation rate 8-10%
  - 80% ovulatory, 40% pregnant
  - Monitoring: [May not be necessary]
  - Max treatment 6 ovulatory cycles
Guidelines for **Metformin** Use in PCOS

[Not as a first line therapy]

**Indications:**
- PCOS with Type 2 DM or glucose intolerance
- CC-resistant anovulation
- HAIR-AN, severe hyperandrogenism + Insulin Resistance
- Failed weight loss and exercise
Medical Therapy: PCOS

RCT of *Letrozole* vs *CC* in PCOS

• Double blind, multicenter trial
• 750 women with up to 5 treatment cycles

CC vs Letrozole

Live Birth rate 19.1% vs 27.5%*

Ovulation rate 48.3% vs 61.7%*

*P<0.05

NEJM 2014;371:1119-29
“CLOMIPHENE Failure/Resistance”

- **Definition:** (1) Failure to induce ovulation  
  (2) Failure to conceive

- **Further evaluation:**  
  (1) Serum FSH if no ovulation  
  (2) Hyperinsulinemia/IR  
  (3) Hyperandrogenemia

- **Therapeutic options:**  
  (1) Gonadotropin Rx  
  (2) Insulin sensitizers for PCOS  
  (3) Ovarian diathermy for PCOS

- Clomiphene response; the higher the BMI, the lower the ovulation rates in PCOS women

Douchi et al, Acta Ob Gyn Scan 2004;83:838
Laparoscopic Ovarian Drilling (LOD)
Effects of Ovarian Electrocautery: PCOS

Retrospective study:

10 -20 years following electrocautery for PCOS

1. Ovulation: > 78% of normal weight women, 50-65% of women (BMI > 25)

2. Significant decrease in Testosterone, Minimal change in DHEAS

3. Increase in SHBG

1. Live birth rates: 34% vs. 38%
2. Significantly lower rates of multiple gestation, ovarian hyperstimulation with LOD
3. No data about long term risks of LOD on ovarian function
4. Role for both? Better response to CC or gonadotropin Rx after diathermy

Optimize OI

ASRM Prize Paper 2014

Effects of preconception intervention on the PCOS phenotype, ovulation, and live birth rates: a multi-center, multi-phase RCT


<table>
<thead>
<tr>
<th></th>
<th>Ovulation rates %</th>
<th>Live BR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCP</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Diet/Exercise/Behav mod</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>Both strategies*</td>
<td>67</td>
<td>26</td>
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</table>
Hirsutism and Hyperandrogenism

Grading Hirsutism:

**Ferriman-Gallwey Score**

1. Nine Regions Graded on 0 – 4 scale
2. Upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arm, and thigh
3. Sum of grades on nine anatomical sites: Max.score 36
   • Upper limit of normal scores: Ethnic differences

Ferriman D & Gallwey JD, JCEM 1961
Hirsutism Score 8 - 15 = mild hirsutism

5% of black/white reproducing age women

Ferriman D, Gallwey JD JCEM 1961; 21:1440-7
Hirsutism and Hyperandrogenism

Differential Dx: Hyperandrogenism

Non-Classic Congenital Adrenal Hyperplasia:
  • 1-5% of all hyperandrogenic women

Androgen-secreting tumors [ovarian or adrenal]:
  – 0.2% of all hyperandrogenic women
  – But over half are malignant
  – Incidentally discovered adrenal masses need further evaluation

Martin KA et al JCEM 2008; 93:1105
When do you refer PCOS patient to GREI?

A. Always
B. Only if they wish to conceive
C. If they are infertile
D. Failed 1st line treatment
E. Severe PCOS
When to refer PCOS patient to GREI

❖ Infertility
❖ Abnormal uterine bleeding
❖ Severe PCOS
❖ Failed 1st line treatment
Management summary
Menstrual irregularities

Life style
OCP
Progestin
Hormonal IUD

Hyperandrogenism

Life style
OCP

Infertility

R/O other causes
OI
LOD

Pregnancy complication

Preconception counselling
GDM screening
PCOS Clinical Guidelines

References
13. John T. Queenan, Jr., MD
19. Bayram N, van Wely M, Kaaijk EM, Bossuyt PM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation
Thank you