POLYCYSTIC OVARY SYNDROME (PCOS)

New Perspectives

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At the conclusion of this presentation, participants should be able to:

- Appreciate the spectrum of clinical presentations of PCOS
- Appreciate the breadth of health implications of PCOS
- Initiate a diagnostic workup & rule out conditions that mimic PCOS
- Individualize risk assessment and tailor management strategies
- Become familiar with emerging concepts in the field
PCOS Demographics

- **Prevalence:**
  - 5-10% of premenopausal women
- Geographical and racial disparity?
- Obese versus lean phenotype
Clinical Presentation

- **Ovulatory Disturbance**
  - Oligomenorrhea
  - Amenorrhea
  - Meno-metrorrhagia

- **Hyperandrogenism**
  - Hirsutism
  - Acne
  - Alopecia

- **PCO**

- **Diagnosis of Exclusion**

- Premature adrenarche
- Early onset puberty
- Fertility
  - Infertility
  - Subfertility
Common Symptoms of PCOS (n=263)

Mean age: 28.6 (SD 6) years
Mean BMI 33 (SD 9) kg/m²
Scalp Hair Thinning (SHT) – a common symptom of PCOS

Women with PCOS (N=263)
- SHT 27%

General population
- SHT 6%

Ikhena D et al. ASRM 2013 Annual Meeting
**Endocrine**
- Hyperandrogenemia
  - Ovarian
  - Adrenal
    - Androgen Metabolites
- Altered FSH:LH ratio
- Prolactin excess?

**Metabolic**
- Hyperinsulinemia
- Abnormal glucose homeostasis
- Dyslipidemia
  - Low HDL
  - Elevated TG
- Pro-inflammatory
- Hyper-homocysteinemia?
Causative Mechanisms... still unclear

- **Hypothalamic dysfunction**
  - GnRH pulsatility

- **Pituitary dysfunction**
  - Altered FSH:LH
  - Altered LH pulsatility
  - Hyperprolactinemia

- **Adrenal dysfunction**
  - Excess adrenal androgens

- **Ovarian dysfunction**
  - Theca cell
    - Excess ovarian androgens
  - Granulosa cell
    - Elevated AMH

- **Metabolic underpinnings**
  - Insulin resistance

- **Genetic disorder**
  - Heritability

- **Epigenetic disorder**
  - IUGR/SGA
  - Maternal obesity
  - GDM
# PCOS Diagnostic Classifications

<table>
<thead>
<tr>
<th>Symptoms/ Signs</th>
<th>NIH 1990</th>
<th>Rotterdam 2003</th>
<th>AES 2006</th>
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<tbody>
<tr>
<td>Oligomenorrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperandrogenism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>Hyperandrogenemia</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>PCO on US&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>+/-</td>
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**Diagnostic Criteria**

- **Ovarian volume > 10ml and/or > 12 follicles < 9mm in size in at least one ovary**

<table>
<thead>
<tr>
<th></th>
<th>Oligomenorrhea plus androgen excess</th>
<th>Any two of the above criteria</th>
<th>Ovulation related concerns plus androgen excess</th>
</tr>
</thead>
</table>

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<sup>a</sup> 8 or less menses per year  
<sup>b</sup> Acne or hirsuitism or androgenic alopecia  
<sup>c</sup> Ovarian volume > 10ml and/or > 12 follicles < 9mm in size in at least one ovary

Health Concerns

- **Infertility**
  - Multiples
  - OHSS
  - Miscarriage
  - Complications of pregnancy
    - GDM
    - Macrosomia
- **Risk for Progeny**

- **Gynecological**
  - DUB
  - Endometrial pathology
  - CVD
  - Stroke
  - Diabetes
  - Depression
  - Cancer
  - All cause mortality
Evaluation

- **Clinical**
  - History
  - Exam
    - BMI/WC/NC
    - Objective hirsutism
    - Severity & distribution of acne/hair loss
    - Hallmarks of IR?
      - Acanthosis nigricans
      - Skin tags
  - Pelvic ultrasound
    - PCO
    - Endometrial echo

- **Rule out...**
  - Thyroid disorder
  - Hyperprolactinemia
  - Late onset CAH
  - Cushing Syndrome
  - Androgen secreting tumor

- **Assess risks**
  - Diabetes/ CVD
  - Depression
  - Endometrial cancer
  - Pregnancy related
Subjective Quantification of Hair Excess Using FG Score

- Ferramin Gallway Score
- Objective
- Subjective
- p=0.041
- n=96

- r=0.79; p<0.0001
- Ferramin Gallway Score (Objective Assessment)

- p=0.041
- Subjective
- Objective
>12 non-growing follicles <9mm in a single ovary
Ovarian volume >10mm³

Ovarian stromal density relates to degree of insulin resistance and hyperandrogenemia
Investigations

- Pelvic US
- Androgens
  - Total/Free T
  - DHEAS
    - Androstenedione
    - 3αAG
  - FSH/LH/E2
  - Prolactin
  - TSH
  - 17OH Progesterone
    - 17OH Pregnenolone

- AMH
- Fasting Lipids
- OGTT (75 gm)
- 25OH Vitamin D

- Miscellaneous
  - 24 hr. UFC
  - C-Reactive Protein
  - Homocysteine
  - Endometrial biopsy
Glycemic Status of Women with PCOS (n=197)

- Normal: 84%
- IFG: 8%
- IGT: 7%
- DM: 1%

Mean age: 26 ± 6 years
Mean BMI: 34 ± 9 kg/m²

Pal L. Unpublished
The Dx of metabolic syndrome requires 3 of the following 5 clinical characteristics

1. Increased waist circumference
2. Increased blood pressure ($\geq 130\text{mmHg systolic}$, $\geq 85\text{ mm Hg diastolic}$)
3. Increased triglycerides (dyslipidemia)
4. Decreased HDL-cholesterol ($<50\text{mg/dl}$)
5. Increased fasting glucose ($\geq 100\text{ mg/dl}$) or previously established diabetes mellitus
OGTT Response in Women with PCOS c/o Scalp Hair Thinning (SHT)

Women with PCOS who acknowledge SHT are significantly more likely to manifest IGT or DM on OGTT compared to those without this
Homocysteine, Insulin Resistance & Hyperandrogenemia

Elevated Homocysteine in Women with Hyperandrogenemia

- Normal Total Testosterone (<=45ng/dl)
- Elevated Total Testosterone (>45ng/dl)

Lower Homocysteine levels were associated with Normal Total Testosterone (<=45ng/dl) compared to Elevated Total Testosterone (>45ng/dl).

Two tailed p=0.024

Higher homocysteine levels with worsening insulin resistance

- Worse
- GIR
- Better

Fasting Glucose: Insulin Ratio (log transformed)

r = -0.41, p=0.004

Lathief et al. et al. AEPCOS annual meeting, 2011
Progressive decline in pancreatic β cell reserve
Glucose intolerance
DM T2

Chronic low grade inflammation

- ↑ C-reactive protein
- ↑ interleukin-6
- ↑ leucocyte count

Inflammatory markers

- ↑ plasminogen activator inhibitor Type 1 (PAI-1)
- ↑ Principal Inhibitor of tissue plasminogen (+PA)
- ↑ Urokinase

Inhibiting Fibrinolysis

a. Obesity → aggravate the underlying insulin resistance
b. Rate of progression from glucose intolerance to DM is ↑ up to 10% in PCOS women.
c. Risk of DMT2 is ↑ 3-7 fold in women with PCOS
N.B. Metformin ↓ levels of c-reaction protein, & soluble vascular cellular adhesions molecules (sVCAM), *(Alleviate chronic inflammation)*
Vitamin D Deficiency & PCOS?

- Obesity
- Dyslipidemia
- Insulin resistance
- Pro-inflammatory milieu
- Diabetes and CVD
- Breast cancer
- Depression
Vitamin D Status of Women with PCOS

Vitamin D level in women enrolled in PPCOS1 (n=540) & NHANES 2003-6 (n=1280)

Significantly Reduced serum 25OHD : BMI ratio in PPCOS1 compared to general US population

Pal L et al. ASRM 2012
Reproductive Relevance of Vitamin D Status in PCOS?

Hypothesis

- Higher serum 25OHD levels will relate to an increased likelihood of fertility treatment success in women with PCOS
  - Improved ovulatory response
  - Improved live birth
Improved Androgen Profile with Vitamin D & Ca Rx.

Serum total testosterone (ng/ml)

Androstenedione (ng/ml)

Two tailed p=0.036

Two tailed p= 0.090; one tailed p=0.045

Vitamin D Status Predicts Ovulatory Response in CC & M users

Reduced Likelihood for ovulatory response in women with serum 25OHD<20ng/ml

OR: 0.58, 95% CI 0.39-0.86, p=0.006

Pal L et al. ASRM 2012
Cardioprotective Implications of Vitamin D for Women With PCOS
Vitamin D Deficiency & Depressive Symptoms in PCOS

Correlation b/w PHQ score & Serum 25OHD
Exaggerated relationship in population deficient in vitamin D

Moore A et al. ASRM 2011
Vitamin D deficiency is highly prevalent

Importance of Vitamin D for health is established

Improved fertility treatment success is noted in women with normal vitamin D status

Maternal vitamin D status has implications for fetal & neonatal wellbeing

Goal of supplementation should be to achieve normalization of vitamin D status through combination of supplements and lifestyle.
Symptom Specific Approach

Hyperandrogenism
- OCP
- Anti-androgen Rx
  - AR blocker
  - 5α reductase inhibitor
- Ornithine decarboxylase inhibitor
- Insulin sensitizers
- Statins
- Glucocorticoids
- Vitamin D
- Myoinositol
- Depilatory strategies

Menstrual issues
- Combined hormonal contraceptives (CHC)
  - Oral
  - Vaginal
  - Transdermal
- Progestin only
  - Oral
  - IM
  - IUD
  - Subcutaneous
Choice of CHC - Considerations

- Contraceptive needs?
- Degree & nature of hyperandrogenism
- Risk profile
  - Migraines?
  - Hypertriglyceridemia?
  - Gall stones?
- Dose of EE
- Route of EE
  - Oral/TV/TD
- Compliance?

Progestin

- Androgenic potential
- Anti-androgenic
- Risk profile
  - Metabolic
  - Mood/ affect
- Route
  - Oral/IM/SQ/IUD
PCOS Related Infertility

Rule out other contributors

Ovulation Induction
- Clomid
- Aromatase Inhibitors (Letrozole)-PPCOSII
- Gonadotropins
- Ovarian Drilling
- Ovarian Wedge resection?

IVF
- GnRH antagonist
- GnRH agonist trigger
  - Metformin

IVM Adjunct
- Insulin sensitizer
- Psychological support
- Vitamin D
- Myo-inositol
Endometrial Risk Reduction

- Combined Hormonal Contraceptive
- Progestin alone
  - Regimen
  - Route
  - Dose
- Metformin ?
- Endometrial surveillance
CVD & DM Risk Reduction Strategies

- Insulin Sensitizers
  - Incretins
    - GLP-1
    - DPP-4 Inhibitors
- Bariatric Surgery
- Vitamin D?
- Lipid Lowering
- Lifestyle
Management Summary

- Remember - PCOS is a diagnosis of exclusion
- Prioritize Mx goals
- Quantify risks
  - Endometrial
  - DM
  - CVD
  - Depression
  - Infertility
- Initiate preventive strategies
- **Optimize lifestyle**
  - Diet
  - Physical activity
- Choice & Rx urgency should be dictated by patient’s needs & prioritized goals
PCOS is a polygenic disorder likely involving the interaction of numerous genomic variants and the influence of environmental factors. Candidate genes include all the molecules that participate in the affected metabolic & reproductive pathways.
Conclusion:

We clearly are in a new era in our understanding & management of women with PCOS.
Conclusion:

In the past, we treated the specific problems of **infertility**, **dysfunctional uterine bleeding**, and **hirsutism** effectively.
We now have the opportunity, indeed the obligation, to offer interventions that can help prevent or reverse some of the metabolic consequences of the disorder that have an important impact on overall health and on the quality & quantity of life.
Take Home Points:

- PCOS is COMMON
- PCOS is A HETEROGENEOUS disorder
- Diagnosis has LONG TERM health implications for the patient & her progeny
- A HOLISTIC approach to PCOS management should include attention to overt symptoms as well as covert risks.