Polycystic Ovary Syndrome: What Every Dermatologist Needs to Know

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Conflict of Interest Statement

I have no relevant financial disclosures

I will discuss “off-label” use of medication
Objectives

1. Cutaneous manifestations of PCOS

2. PCOS clinical features, workup, diagnosis and management
Why discuss PCOS?
Recognizing the Female Patient with Hyperandrogenism

- Acne refractory to standard therapies, especially isotretinoin
- Moderate to severe acne
  - 19-34% have PCOS
- Adult onset/exacerbation of acne
- Irregular menses/premenstrual acne flares
- Acne on lower face and neck
- Seborrhea
- Hirsutism
Differential Diagnosis of Hyperandrogenism

- Polycystic ovary syndrome (90%)
  Prevalence 5%-18% depending on population, diagnostic criteria
- Hyperprolactinemia (2.3%)
- Congenital adrenal hyperplasia (1.3%)
- Tumors of the ovary or adrenal gland (<0.5%)
- Cushing’s syndrome
- Androgenic medications (danazol, anabolic steroids, androgenic progestins, progesterone-releasing IUD)

Glintborg & Andersen, Gynecol Endocrinol 2010;26:281-96
Polycystic Ovary Syndrome

**Definition**
- Endocrine metabolic syndrome originally described by Stein and Leventhal in 1935 identifying women with amenorrhea and polycystic ovaries
  
  Belosi et al., Hum Reprod 2006;12:3108-3115
- Heterogeneous disorder
- Definition and diagnostic criteria are controversial
Polycystic Ovary Syndrome

Definition

2 out of 3 criteria necessary for diagnosis:

1. Oligo- or anovulation (<8 menses/yr)
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries and exclusion of other etiologies (CAH, androgen-secreting tumors, Cushing’s syndrome)

2003 Rotterdam PCOS consensus
Fertil Steril 2004;81;19-25
## Polycystic Ovary Syndrome

### Clinical Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PCOS</td>
<td>61%</td>
<td>Irregular menses, Polycystic ovaries, Hyperandrogenemia, Hyperinsulinemia</td>
</tr>
<tr>
<td>Hyperandrogenism and chronic anovulation</td>
<td>7%</td>
<td>Irregular menses, Normal ovaries, Hyperandrogenemia, Hyperinsulinemia</td>
</tr>
<tr>
<td>Ovulatory PCOS</td>
<td>16%</td>
<td>Normal menses, Polycystic ovaries, Hyperandrogenemia, Hyperinsulinemia</td>
</tr>
<tr>
<td>Mild PCOS</td>
<td>16%</td>
<td>Irregular menses, Polycystic ovaries, Mildly raised androgen concentrations, Normal insulin concentrations</td>
</tr>
</tbody>
</table>

*Norman et al., Lancet 2007;370:685-697*
Polycystic Ovary Syndrome
Risk Factors

• Strong link with insulin resistance and glucose intolerance
• Risk factors for PCOS:
  – Obesity and/or insulin resistance
  – Type 1, Type 2 and gestational diabetes
  – Oligo-ovulatory infertility
  – Low birth weight
  – Premature adrenarche
  – First-degree relative with PCOS
• Higher rates of metabolic syndrome, hypertension, and dyslipidemia in first degree relatives

Laboratory Workup for Diagnosis of PCOS

PCOS is a diagnosis of exclusion
Laboratory workup to rule out other diagnoses as clinically indicated when irregular menses are present:

- Testosterone/DHEAS/Free T/Androstenedione/SHBG: Androgen secreting tumor
- Prolactin: Hyperprolactinemia
- FSH: Premature ovarian failure
- LH testing to r/o gonadotropin deficiency
- 17-OH progesterone: Congenital adrenal hyperplasia
- 24-hour urine free cortisol: Cushing’s syndrome
- Transvaginal Ultrasound
- TSH, HCG
Laboratory Findings in PCOS

Testosterone
- Elevated in 60-80% of PCOS
- Levels > 200 ng/dl suggestive of ovarian or adrenal tumor

DHEAS
- Elevated in about 25% of PCOS
- Levels 400-800 ug/dL suggest CAH
- Levels > 800 ug/dL suggest adrenal tumor
Hormonal Acne Laboratory Workup: Bottom Line

- When irregular menses or other signs of PCOS present:
  - Testosterone
  - SHBG
  - Free Testosterone
  - DHEAS
  - Prolactin
  - +/- Transvaginal U/S
Clinical Features of PCOS

- Hyperandrogenism
- Menstrual Irregularity
- Metabolic
Clinical Features of PCOS
Hyperandrogenism

Cutaneous signs:

- Hirsutism in 60-70%
- Trunkal hirsutism predictive of PCOS
  (Schmidt et. al JAMA Dermatol 2016)
- Inflammatory acne of the lower face and neck in 30%
- Seborrhea
- Bitemporal or female pattern alopecia
  (not diagnostic for hyperandrogenism as a solitary finding)
Cross-sectional analysis health system database
22,990 pts. with HS
Prevalence of PCOS in HS was 9.0%, vs. 2.9% in patients without HS (p<.0001).
Chance of HS patients having PCOS was 2.14 [95% CI 2.04-2.24] times that of non-HS patients
Similar association as to diabetes, obesity
Screen HS patients with androgen excess for PCOS
Clinical Features of PCOS
Menstrual irregularity

- Amenorrhea or oligomenorrhea
- Infertility in 74%
- Higher risk of pregnancy complications
  - Gestational diabetes, miscarriage
- Dysfunctional uterine bleeding with increased risk for endometrial carcinoma exacerbated by obesity, insulin resistance

Giudice LC, JCEM 2006;20:235-44
Clinical Features of PCOS
Metabolic

- 30-75% of women with PCOS are obese
- 33% of non-diabetic women with PCOS have the metabolic syndrome by age 40, 20% by age 20
- 10% have type II diabetes by age 40
- Women with PCOS have higher rates of insulin resistance compared to weight-matched controls
- Test all PCOS women with 2-hr OGTT, lipid profile--HbA1c testing less sensitive
- 1.5 fold risk for VTE, 3.7-fold with OCPS

Ford ES et al., JAMA 2002;287:356-59
Veiling Magnussen et al., Fertil Steril 2011 96:1275-80
Goodman NF et. Al, 2015 Endocrine Practice
<table>
<thead>
<tr>
<th>Cutaneous Finding</th>
<th>Key Distribution</th>
<th>Systemic Association</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>Face (forehead)</td>
<td>None</td>
<td>Increased prevalence among patients who meet PCOS diagnosis but no significant difference in distribution or lesional counts, not associated with biochemical hyperandrogenism, not a reliable marker of hyperandrogenism in PCOS</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Truncal is most specific (chest, abdomen, or back), less specific are chin and thigh, nonspecific are upper lip and upper arm</td>
<td>Elevated free testosterone level, increased insulin resistance, increased BMI, dyslipidemia (HDL-C, triglycerides)</td>
<td>Excellent marker for PCOS and warrants selective endocrine and metabolic diagnostic evaluation, requires a comprehensive skin examination</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Axillae</td>
<td>Elevated free testosterone level, increased insulin resistance, increased glucose intolerance, increased BMI, dyslipidemia (total cholesterol, LDL-C, HDL-C, or triglycerides)</td>
<td>Excellent marker for PCOS and warrants selective endocrine and metabolic diagnostic evaluation, requires a comprehensive skin examination</td>
</tr>
<tr>
<td>Androgenic alopecia</td>
<td>Scalp</td>
<td>Lower prevalence of polycystic ovaries, associated with clinical but not biochemical hyperandrogenism</td>
<td>Not a reliable marker for PCOS</td>
</tr>
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Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCOS, polycystic ovary syndrome.
Clinical Features of PCOS
Cardiovascular Disease: Risk Uncertain

• Systematic review and meta-analysis of five observational controlled studies found a RR of 1.5 for coronary heart disease or stroke among women with PCOS adjusted for BMI.

• Only prospective cohort/control study to date showed no increased risk in a lean PCOS population

Schmidt et.al JClin Endocrinol Metab 2011; 96:3794-3803
Obstructive Sleep Apnea

- 5-30-fold higher risk for OSA in PCOS
- Higher rates of DM in PCOS women with OSA
- Treatment with CPAP improves insulin sensitivity, decreases sympathetic output and decreases diastolic blood pressure

Nitche and Ehrmann, Best Pract&Rsch Clin Endocrin Metab 2010;24:717-30
Mokhlesi et al., Fertil Steril 2012 Jan 18 (Epub ahead of print)
Tasali et al. J Clin Endocrinol Metab 2011;96:365-74
Nonalcoholic Fatty Liver Disease (NAFLD)

- Higher rates in women with PCOS compared to age and weight-matched controls
- Can progress to NASH, cirrhosis, and hepatocellular carcinoma

Women with PCOS have higher rates of:
- Depression
- Anxiety
- Body dissatisfaction
- Eating disorders
- Sexual and relational functioning
- Decreased health-related quality-of-life
- Hirsutism and obesity biggest factors
Pathophysiology of PCOS

Genetics

• The etiology of PCOS remains unknown but appears to be a complex multigenic disorder
• 25-50% have family h/o PCOS and DM
• Candidate genes regulating insulin resistance and androgen production include Cytochrome P450c17, Cytochrome P450c11a and Insulin receptor substrate 1
• Animal studies and effect of congenital virilizing tumors support role of in utero and neonatal androgen exposure

Goodman et al, Endocrine Practice 2015
Pathophysiology of PCOS

1. Abnormal gonadotropin secretion
2. Hyperinsulinemia
3. Abnormal intra-ovarian androgen signalling
Insulin Resistance

Visceral Fat

Insulin
PCOS Physiology and the Skin: What Dermatologists Need to Know

Androgens
Hormonal acne—a local phenomenon

- Severity of acne and hirsutism does NOT correlate with serum androgen levels

- Laboratory abnormalities/work-up not needed to initiate hormonal therapy
Treatment of PCOS

• Weight loss
• Oral contraceptives
• Anti-androgen medications
  - cyproterone acetate, spironolactone, drospirenone
• Insulin-sensitizing agents
  - metformin
Treatment of PCOS

- Weight loss
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Weight Loss

• >5-10% improves ovulation, fertility, metabolic profile, androgen levels, acne and hirsutism
• No specific diet recommended
• Metformin improves weight loss when combined with lifestyle changes

Glintborg & Andersen, Gynecol Endocrinol 2010;26:281-96
Metformin

• Antihyperglycemic agent that reduces hepatic glucose production and reduces insulin resistance in muscle and fat.

• Improves clinical pregnancy and ovulation rates but not live births whether used alone or with clomiphene.

• Decreases miscarriage, gestational diabetes, HTN.

• Indicated in PCOS patients with infertility, glucose intolerance or hyperinsulinemia.

Summary

• Dermatologists are in a unique position to identify patients with hyperandrogenism and PCOS.
• PCOS is a multisystem disorder with potentially serious physical and mental health manifestations.
• It is important to recognize the patient with PCOS for appropriate management and prevention of systemic disease.
Thank you!!!

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