Polycystic Ovarian Syndrome: Diagnosis, Preconceptional Management and Health Risks

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May 6, 2016
Objectives

- To review how to make the diagnosis of Polycystic Ovarian Syndrome (PCOS) including evidence based testing
- To review the health risks and appropriate counseling for patients with PCOS
- To discuss recommended options for the treatment of infertility in PCOS patients
Infertility in Women

- 40% Tubal & Pelvic
- 40% Ovulatory
- 10% Unexplained
- 10% Less common disorders

Speroff 2011
Polycystic Ovarian Syndrome

- “…recognized as the most common endocrine disorder of reproductive-aged women around the world.”

- “Correct diagnosis of PCOS impacts on the likelihood of associated metabolic and cardiovascular risks and leads to appropriate intervention…”

Nestler et al., Fertil Steril, 2002; NF Goodman et al., Endoc Prac 2015
Diagnosing a syndrome: 2 of 3

- Oligoovulation or anovulation
- Hyperandrogenism (clinical or biological)
- PCO-like ovaries on transvaginal ultrasound

R Azziz et al. J Clin Endocrinol Metab 2006
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R Azziz et al. J Clin Endocrinol Metab 2006
The median menstrual cycle length is 28 days but ranges from 21 to 35 days.

Illingworth P. Endocrinology 2011; Chapter 129, 2341-2355
The Menstrual Cycle
Normal HPO axis

Hypothalamus → Pituitary → Ovary → Uterus → Menses

GnRH → FSH → LH → Estrogen → Progesterone

Adapted from Speroff and Fritz 2011
Diagnostic criteria of PCOS: Oligoovulation

- Anovulation/oligoovulation documented by:
  - History
  - Menstrual cyclicity
    - Oligomenorrhea = Cycle length >35 days
    - Cycle length slightly longer than normal (32 to 35 days) or slightly irregular (32 to 36 days)
  - Ovulation predictor kit
  - Basal body temperature
  - Day 21 Serum Progesterone levels
    - >3 ng/mL consistent with ovulation

Goodman et al., Endocrine Practice 2015;21(11):1291-8
Evaluation of oligo/amenorrhea

- History and physical exam
- Pregnancy test!
- Baseline (day 3 or random) Follicle Stimulating Hormone, Estradiol
- Thyroid stimulating hormone
- Prolactin
- Antimullerian Hormone
- +/- Pelvic ultrasound
Evaluation of oligo/amenorrhea

- LH/FSH ratio
  - Typically elevated in PCOS but NOT used as part of diagnostic criteria

Goodman et al., Endocrine Practice 2015;21(11):1291-8
Normal HPO axis

Hypothalamus

GnRH

Prolactin

GnRH

FSH

LH

Estrogen

Progesterone

Ovary

Pituitary

TRH

TSH

Menses

Adapted from Speroff and Fritz 2011
Antimullerian Hormone

- Member of TGF-β superfamily
- Synthesized by granulosa cells of small antral and preantral follicles
- Gonadotropin independent

La Marca, A. et al. Hum Reprod Update 2010 16:113-130
AMH secretion

- La Marca, A. et al. Hum Reprod Update 2010 16:113-130;
- doi:10.1093/humupd/dmp036
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R Azziz et al. J Clin Endocrinol Metab 2006
PCOS: Hyperandrogenism

- Clinical Assessment
  - Hirsutism
    - Primary clinical indicator
  - Acne
  - Alopecia (frontal balding)

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group,
Hum Reprod 2004
Hirsutism = excessive male pattern terminal hair growth

- Observed in 70-80% of patients with hyperandrogenism
- Hair density and hair growth vary among ethnic groups
- Androgens prolong anagen phase of body hair
- F-G score ≥ 6

JB O’Driscoll et al., Clin Endoc 1994;41(2):231-236
Modified Ferriman-Gallwey score

Bulent O. Yildiz, Best Practice & Research Clin Endoc & Metab
2006;20(2):167-76
Acne

- Androgens have major autocrine and paracrine effects in the development of acne

- *Most acne patients do not have androgen excess*

- If isolated, questionable if sufficient for diagnosis of hyperandrogenism

F Borgia, Acta Dermato-Venereologica 2004;84(3):201-4;
B Yildiz Best Practice & Research Clin Endoc & Metabolism 2006;20(2):167-76
Androgenic alopecia

- Most common form
- Diffuse thinning, more marked in frontal and parietal
- Higher levels of 5-α reductase, more androgen receptors and lower cytochrome P450

Evaluation of Hyperandrogenic anovulation

- Total testosterone
- Free testosterone or free androgen index
  - Increased in 60% of women with hyperandrogenic PCOS
  - Inaccurate and variable lab methods
  - Recommended by AES
    - Calculate free T based upon RIA or mass spectrometry and SHBG

# Evaluation of PCOS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen secreting neoplasm</td>
<td>Total Testosterone</td>
</tr>
<tr>
<td></td>
<td>DHEAS</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia (Late-onset)</td>
<td>Follicular phase 17-hydroxyprogesterone</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Salivary cortisol x 2 or 24 hour urinary free cortisol collection</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>TSH</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
<td>FSH/Estradiol</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>FSH/Estradiol/AMH</td>
</tr>
</tbody>
</table>

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R Azziz et al. J Clin Endocrinol Metab 2006
PCO-like ovary ultrasound

- Transvaginal ultrasound probe with a frequency of at least 8 Hz
  - Early follicular phase
- May substitute AMH > 4.5 ng/mL when no ovarian ultrasound is available

Dumesic et al., Endocrine Reviews 2015; 36(5):487-525;
Johnstone et al., J Clin Endocrinol Metab 2010;95(11):4965-4972
Goodman et al., Endocrine Practice 2015;21(11):1291-1298
Dewailly et al., Hum Reprod 2011;26:3123-9
- Enlarged ovarian volume (>10 ml)
- PCO ovarian morphology: at least 25 small follicles (2-9 mm) in each ovary
  - Associated with infertility if concurrent ovulatory disorder

Dumesic et al., Endocrine Reviews 2015; 36(5):487-525;
Johnstone et al., J Clin Endocrinol Metab 2010;95(11):4965-4972
Goodman et al., Endocrine Practice 2015;21(11):1291-1298
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Insulin resistance: A ‘unique predisposition’

- Results in hyperinsulinemia
- Plays an intrinsic role in the pathogenesis of PCOS.
- Obese women with PCOS are at increased risk for Metabolic Syndrome
  - impaired glucose tolerance (IGT; 31 to 35%)
  - type 2 diabetes mellitus (T2DM; 7.5 to 10%)

Goodman et al., Endocrine Practice 2015; Dec;21(12):1415-26
Dunaif A et al., JCEM 1987
ACOG Practice Bulletin #108, Obstetrics and Gynecology October 2009
Metabolic screening in PCOS

- Fasting glucose
- 75 g Oral glucose tolerance test with two-hour level
- Fasting lipid and lipoprotein level
- Hemoglobin A1C

Lipid abnormalities in PCOS

- Dyslipidemia common
- Higher non-HDL cholesterol
- Unclear if due to insulin resistance or androgen excess

Cardiovascular health in PCOS

- PCOS patients with higher coronary calcification scores (40% vs 20%)
  - Not explained by age or BMI
- Carotid intima media thickness greater in PCOS
  - Lean, overweight and obese individuals
- Higher aortic calcification in PCOS
- Inconclusive Evidence for increased CVD morbidity and mortality in women with PCOS

Talbott et al, JCEM 20014;89:5454-5461
Health Risks of PCOS

- Skin disorders
- Metabolic syndrome
- Nonalcoholic fatty liver disease
- Obesity related disorders
- Mood disturbances and depression
- Sleep disorders

ACOG Practice Bulletin PCOS 2009, reaffirmed 2015
Long Term Complications

- Diabetes - 3-7x risk
- Endometrial Hyperplasia or Cancer
- Hypertension
- Coronary artery disease
  - Lifelong metabolic dysfunction in PCOS exaggerates CVD risk

Health risks of PCOS

- Vitamin D deficiency is associated with multiple metabolic risk factors in PCOS women
- No evidence that vitamin D supplementation reduced or mitigated metabolic and hormonal dysregulations in PCOS

Hi et al., Metabolism 2011; Oct;60(10):1475-81
He et al., Nutrients. 2015 Jun 8;7(6):4555-77
Pregnancy risks in PCOS

- Miscarriage rates not increased independent of obesity
- Gestational diabetes (40-50%)
  - Fetal macrosomia
- Gestational hypertensive disorders (5%)
- Birth of SGA infants (10-15%)
- Preterm births
- Risks of multiples from infertility treatments

SM Veltman-Verhulst et al., Hum reprod 2010;25:3123-8
CM Boomsma et al., Hum Reprod Update 2006;12:673-83
Many of the effects of obesity are additive to the PCOS problems
- Associated with failure of infertility treatments
- Adversely affects reproduction
- Weight loss may improve metabolic abnormalities
“Of course you don’t look fat.”
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A.C.O.G. Committee Opinion on Obesity in Pregnancy

“Obstetricians should provide education about the possible complications and should encourage obese patients to undertake a weight reduction program, including diet, exercise and behavioral modification, before attempting pregnancy.”

ACOG Committee Opinion #549, January 2013
Lifestyle Modifications

- Weight loss recommended as first line therapy in obese women with PCOS seeking pregnancy
  - Weight loss (5%) is associated with improved ovulation rates in women with PCOS
- Incorporate exercise which tends to be lower
  - Improved long term weight loss maintenance

Tarlatzis et al., Fertil Steril 2008:89(3); Pasquali R et al., Hum Reprod Update 2003;9:359-72; Moran LJ et al., J Clin Endocrinol Metab 2003
Lifestyle Modifications

- No “optimal” diet
- Hypocaloric (1000-1500 kcal per day)
- Aim to achieve 5% weight loss
- ?Compliant
- ?Willing to wait

Tarlatzis et al., Fertil Steril 2008:89(3);
Stamets K et al., Fertil Steril. 2004 Mar;81(3):630-7
ACOG Practice Bulletin PCOS 2009, reaffirmed 2015
Other methods for weight loss

- Bariatric surgery
  - PCOS phenotype very frequent in morbidly obese women (Alvarez-Blasco et al., Arch Int Med 2006)
  - Disorder improves markedly after sustained weight loss following bariatric surgery (Escobar-Morreale et al., JCEM 2005)

- Pharmacologic agents
  - Few quality studies but promising results

PCOS Consensus Workshop, Hum Reprod 2008
Options for ovulation induction

- First line: Clomiphene citrate
  - Overall ovulation rates of 75-85%
  - Pregnancy rates of 20-40% (JCEM 1998, 1999)

- Second line: aromatase inhibitors (Letrozole)
- +/- Metformin
  - Best suited for patients with glucose intolerance

- Last resort: Injectable gonadotropins
  - IUI or IVF

ACOG Practice Bulletin PCOS 2009, reaffirmed 2015
PCOS Consensus Workshop, Hum Reprod 2008
Conclusions

- Accurately diagnosing PCOS is key
- Significant health and obstetric risks associated with PCOS
- Lifestyle modifications are a first step to improve fertility
- Several different fertility treatment options are available to patients

*Ultimately, we all share the goal of a healthy pregnancy !!!*
THANK YOU!