Polycystic Ovarian Syndrome: Diagnosis, Preconceptional Management and Health Risks

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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

Infertility in Women

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
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
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

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

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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PCOS: Hyperandrogenism

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

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop, 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

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


Androgenic alopecia

- Most common form
- Diffuse thinning, more marked in frontal and parietal
- Higher levels of 5-a 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 RA 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, 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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  - PCO-like ovaries on transvaginal ultrasound

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
- 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

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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 2004;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; Oct60(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

PCOS - Obesity

- 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

PCOS Consensus Workshop, Hum Reprod 2008

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"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;
Wright CE et al., Int J Obes Relat Metab Disord 2004;
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);
Stamers 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!