Polycystic Ovarian Syndrome: Preconceptional Management and Health Risks

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PCOS: changing women’s health paradigm

Metabolic disease

Reproductive disorders

(young age)
- menstrual disorders
- hirsutism
- contraception
- sexual health
- infertility

(older age)
- pregnancy complications
- quality of life
- type 2 diabetes
- cardiovascular disease
- cancer risk?

Multi-disciplinary approaches
- pediatrics
- dermatology
- gynecology
- endocrinology
- diabetology
- cardiology
- geriatri

BCJM Fauser et al., Fertility and Sterility 2012 Volume 97 (1): 28 - 38.e25
Objectives

- To review the definitions of PCOS and associated phenotypes
- To discuss diagnosis and treatment of insulin resistance
- To discuss the health risks associated with PCOS in later life and pregnancy
- To review the most effective methods of ovulation induction to achieve live birth in PCOS patients
Infertility in Women

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

Speroff 2011
Polycystic Ovarian Syndrome

- Most common cause of female infertility in the United States
- Affects 20% infertile population
- Affects 6-10% of women of childbearing age (3.5-5.0 million women in U.S.)
- How to define??

Nestler et al., Fertil Steril, 2002
PCOS Definition

1999 - NIH criteria
- Oligoovulation
- Hyperandrogenism

2003 - Rotterdam criteria
2/3:
- Oligoovulation
- Hyperandrogenism
- PCO like ovaries

2006 - Revised AES Criteria
- Hyperandrogenism and
- Oligoovulation or
- PCO like ovaries
Revised diagnostic criteria

- Hyperandrogenism (male pattern hormones)
- Either
  - Oligomenorrhea or amenorrhea
  - OR
  - PCO like ovaries by ultrasound

R Azziz et al. J Clin Endocrinol Metab 2006
Revised diagnostic criteria

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R Azziz et al. J Clin Endocrinol Metab 2006
The Menstrual Cycle
Diagnostic criteria of PCOS

- Anovulation (lack of ovulation) documented by:
  - History
    - Menstrual cyclicity
    - Moliminal symptoms
    - Ovulation predictor kit
    - Basal body temperature
  - Day 21 Serum Progesterone levels
    - >3 ng/dL consistent with ovulation
Polycystic Ovarian Syndrome:
Exclude other causes

- Adult onset Congenital Adrenal Hyperplasia
  - Basal morning follicular 17-OHP (Azziz et al., Fertil Steril 1999)
- Hyperprolactinemia
- Androgen-secreting neoplasms
- Thyroid dysfunction
- Cushing’s syndrome
- Hypogonadotrophic hypogonadism
- Premature ovarian failure

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group,
Hum Reprod 2004
Revised diagnostic criteria

- **Hyperandrogenism**
- Either
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R Azziz et al. J Clin Endocrinol Metab 2006
PCOS: Hyperandrogenic anovulation

Clinical Assessment

- Hirsutism = excessive male pattern terminal hair growth
  - Primary clinical indicator (JCEM 1999)
- Acne
- Alopecia (frontal balding)

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, Hum Reprod 2004
Hirsutism

- 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

Androgenic alopecia

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

PCOS: Hyperandrogenic anovulation

- Total testosterone to exclude other causes
- Free testosterone or free androgen index
  - Inaccurate and variable lab methods
  - Recommended by AES
    - Calculate free T based upon RIA or mass spectrometry and SHBG

Revised diagnostic criteria

- Hyperandrogenism
- Either
  - Oligomenorrhea or amenorrhea
  - **PCO like ovaries by ultrasound**

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

‘A presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (>10mL)’
(Balen et al, Hum Reprod Update 2003)
PCO like ovaries

- 20% of women will have PCO on sonogram
  - Not associated with infertility unless combined with ovulation disorder (Fertil Steril 80:966)
Etiologies PCOS

- Genetic contribution
- No specific environmental substance
- Insulin resistance
- Obesity
Polycystic Ovarian Syndrome: Insulin resistance

- Not included in diagnostic criteria
- Results in **hyperinsulinemia** (elevated insulin)
- **Insulin sensitivity decreased by 35-40%**
  - Independent of obesity
  - Exacerbated by obesity
- 10-30% PCOS pts are lean

Dunaif A et al., JCEM 1987
PCOS and Glucose Intolerance

Dunaif A & Thomas A, 2001
Markers of Insulin Resistance

- BMI > 27 kg/m²
- Waist-to-hip ratio > 0.85
- Waist > 100 cm
- Acanthosis nigricans
  - Velvety smooth patches
- Numerous achrochordons

Barbieri, 2000
Metabolic screening in PCOS

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

ACOG Practice Bulletin, 2009
Testing for Insulin Resistance

- **Fasting glucose:**
  - Normal <100 mg/dL
  - Impaired 101-125 mg/dL
  - DM ≥126 mg/dL

- **Two hour 75g glucose tolerance test:**
  - Normal < 140 mg/dL
  - Impaired 140-199 mg/dL
  - DM ≥ 200 mg/dL

- **Hgb A1c** - expensive, not recommended for screening

Speroff, 2011; ACOG Practice Bulletin, PCOS 2009
Management of IGT and T2D in PCOS

- No large scale studies
- Diet and lifestyle
- Metformin
- Preliminary studies of bariatric surgery in reversing metabolic and endocrine abnormalities are promising

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 Insulin resistance have more subclinical vascular disease
  - Adjusted for age and BMI
    - Coronary Angiography

- Evidence for increased CVD morbidity and mortality in women with PCOS remains inconclusive

D Wiltgen et al., Fertil Steril 2010;94:2493-6
PCOS - Obesity

- 35-60% of PCOS
- Many of the effects of obesity are additive to the PCOS problems
  - Associated with failure of infertility treatments
- Adversely affects reproduction
Obesity and PCOS

- More upper body fat distribution
  - Greater abdominal or visceral adiposity associated with greater insulin resistance
  - Associated with lower SHBG
- Possible functional differences in PCOS adipose tissue
PCOS and Metabolic Syndrome

- Constellation of CVD risk factors
- **Classic NIH-criteria PCOS** at higher risk
  - Hyperandrogensim
  - Insulin resistance
Health Risks of PCOS

- Skin disorders
- Metabolic syndrome
- Nonalcoholic fatty liver disease
- Obesity related disorders
- Mood disturbances and depression
Long Term Complications

- Diabetes - 3-7x risk
- Endometrial Hyperplasia or Cancer
- Hyperlipidemia
- Hypertension
- Coronary artery disease
  - Atherosclerotic CVD in postmenopausal women is associated with PCOS-like features
  - Lifelong metabolic dysfunction in PCOS exaggerates CVD risk

Risks in pregnancy in PCOS

- 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
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
"Whoa—way too much information!"
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Treatments for ovulation induction in PCOS

- Weight loss recommended as first line therapy in obese women with PCOS seeking pregnancy
- Weight loss is associated with improved ovulation rates in women with PCOS

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
Which Diet is best for PCOS?

- Little agreement on “optimal” diet
  - High protein-low COH-low fat hypocaloric
  - High COH- low fat hypocaloric
- Hypocaloric (1000-1500 kcal per day)
- Aim to achieve 5% weight loss

Tarlatzis et al., Fertil Steril 2008:89(3);
Stamets K et al., Fertil Steril. 2004 Mar;81(3):630-7
Exercise in PCOS

- Baseline activity may be lower in PCOS patients
- Regular exercise important component of weight loss programs
  - Associated with better long-term weight loss maintenance
- Always consider physical limitations

Weight Loss in Anovulation

- Recommend lifestyle modification first
- ?Compliant
- ?Willing to wait
- 10-30% PCOS pts are lean
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
Clomiphene citrate

- First line of treatment in PCOS for ovulation induction
- Low cost
- Patient-friendly oral route
- Relatively few adverse effects
- Abundant clinical data regarding safety

Consensus on infertility related to Polycystic Ovarian Syndrome, Fertil Steril 2008;89(3):505-22
Clomiphene citrate ovulation induction Protocol

Menses

CC x 5 days

Day 2-5

Timed intercourse

ß-HCG test

Ultrasound

Day of ovulation or hCG
Clomiphene Citrate in PCOS

- Overall ovulation rates of 75-85%
- Pregnancy rates of 30-40% (JCEM 1998, 1999)
- 70% will ovulate at 50-100 mg
- If resistant to 150 mg, 10-15% ovulation rate with higher doses
  - FDA recommends 750 mg/treatment cycle (Dickey et al., Hum Reprod 1996)

Kocak et al., Fertil Steril 2002
Negatives of Clomiphene Citrate

- Anti-estrogenic effect
  - Endometrial lining
  - Cervical mucus
- 4-10% incidence multiple pregnancy
- Low risk of OHSS (<<1%)
Clomiphene Citrate in PCOS

- Age predictive of likelihood of success

- Poor responders to Clomiphene Citrate
  - More likely to be insulin resistant
  - More likely to be obese
  - More likely to be hyperandrogenic

Kocak et al., Fertil Steril 2002; Consensus on infertility related to PCOS, Fertil Steril 2008
Aromatase inhibitors

- Smaller studies suggest their treatment results are comparable to CC
- Lower multiples rates due to monofollicular ovulation induction

Mechanism of Metformin

- Oral biguanide hyperglycemic agent
- Enhances glucose uptake/activates glucose transporters
- Decreases hepatic glucose production
- Reduces hyperinsulinemia
- Improved insulin sensitivity
- Does not increase insulin levels
Reproductive impact of polycystic ovary syndrome.
Metformin and PCOS Live birth rates

- Clomiphene Citrate live birth-rate 22.5% (47 of 209 subjects)
- Metformin group 7.2% (15 of 208)
- Combination therapy 26.8% (56 of 209) in the combination-therapy group
- CC superior to metformin, although with multiple birth rate

Legro et al., NEJM 2007
Metformin and PCOS

- Improvement in ovulation rates comparable to weight loss alone (Tang et al., Hum Reprod 2006)
- Should not be used as first line agent
- Advantage of adding Metformin to CC
- Best suited for use in women with glucose intolerance

PCOS Consensus Workshop, Hum Reprod 2008
Advanced Treatment Options

- Gonadotropins with IUI
- Laparoscopic surgery
- IVF
Gonadotropins-Intrauterine insemination
Gonadotropins-Intrauterine insemination

- Slow increase in FSH over a threshold dose
- Goal of monofollicular recruitment
- Risk of cancellation
Advanced Treatment Options

- Gonadotropins with IUI
- Laparoscopic surgery
- IVF
Operative laparoscopy
Ovarian drilling
Laparoscopic Ovarian Surgery

- Second line option with questionable benefit
- Avoids risk of stimulation
- In 50% adjuvant therapy will be required

Risks

- Surgery
- Adhesions
- Rarely premature ovarian failure

PCOS Consensus Workshop, Hum Reprod 2008
Advanced Treatment Options

- Gonadotropins with IUI
- Laparoscopic surgery
- IVF
Using ultrasound to view the ovary, the physician inserts the needle through the wall of the vagina into the ovary and removes the egg for use in IVF or GIFT.
In vitro fertilization (IVF)
Infertility Treatments in PCOS

- Preconceptional counseling important
  - Weight reduction
  - Exercise
  - Smoking
  - Alcohol consumption
Infertility Treatments in PCOS

- First line treatment for ovulation induction is Clomiphene citrate
- Second line treatment
  - Gonadotropins –IUI
  - Laparoscopic ovarian drilling in select patients
- Third line treatment is IVF

Consensus on infertility treatments related to PCOS, Fertility and Sterility 2008
Figure 1  Schematic representation of the change in emphasis from early age reproductive disorders to long-term metabolic and cardiovascular health.

BCJM Fauser et al., Fertility and Sterility Volume 97, Issue 1 2012 28 - 38.e25
THANK YOU!