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
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

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<tr>
<th>1999</th>
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<td>Revised AES Criteria</td>
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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

The Menstrual Cycle

[Diagram of the menstrual cycle with key hormones and stages]
**Diagnostic criteria of PCOS**

- Anovulation (lack of ovulation) documented by:
  - History
  - Menstrual cyclicity
  - Mølilmal 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
- Hypogonadotropic hypogonadism
- Premature ovarian failure

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

**Revised diagnostic criteria**

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

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

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
- Frontal hairline maintained with temporal recession
- Higher levels of 5-α reductase, more androgen receptors and lower cytochrome P450

B. Yildiz Best Practice&Research Clin Endoc&Metabolism 2006;20(2):167-76

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
  - OR
  - **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

ACOG Practice Bulletin PCOS 2009

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

Markers of Insulin Resistance

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

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;94:603-6
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

PCOS Consensus Workshop, Hum Reprod 2008

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
  - Hyperandrogenism
  - Insulin resistance
Health Risks of PCOS

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

ACOG Practice Bulletin PCOS 2009

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 Boomonsi 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

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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

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
FSH
LH
+
Estradiol
-

Clomiphene citrate ovulation induction Protocol

- Menses
- Ultrasound
- Timed intercourse
- β-HCG test

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%)

Kousta et al, Hum Reprod Update 1997

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

---

**Ovulation and pregnancy rates per treatment arm in PPCOS I. (Pregnancy in Polycystic Ovary Syndrome trial I)**

- Metformin live birth-rate 7.2% (15 of 208)
- Combination therapy 26.8% (56 of 209)

---

**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

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

Advanced Treatment Options
- Gonadotropins with IUI
- Laparoscopic surgery
- IVF
Oocyte (egg) Retrieval

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!