“Polycystic ovary syndrome (PCOS) is a condition of unexplained hyperandrogenic anovulation that most likely represents a heterogeneous disorder. Its etiology remains unknown, and treatment is largely symptom based and empirical. Recent findings suggest PCOS has substantial metabolic sequelae, including risk of diabetes and possibly cardiovascular disease, and that primary treatment should focus on metabolic sequelae.”

Number 41, December 2002
PCOS: Etiologies

• Aberrant GnRH secretion pattern; disrupted neurotransmitter patterns

• Increased ovarian androgen production, low SHBG, disrupt gonadotropin pattern

* Selective insulin resistance/compensatory hyperinsulinemia
What is insulin resistance in PCOS?

Insulin resistance in PCOS patients refers primarily to the impaired action of insulin on glucose transport and lipolysis in adipocytes, and possibly muscle, in the presence of normal insulin binding.

(Ciaraldi et al, 1995; Dunaif et al, 1995; Marsden et al, 1994; Ciraldi et al, 1997)
Approximately 90+% of PCOS patients can be considered to have insulin resistance and/or hyperinsulinemia, above and beyond that predicted by weight alone when assessed by the hyperinsulinemic euglycemic clamp (gold standard)
Diagnostic Criteria 2003
(ASRM & ESHRE)

• 2 of the following
  – Oligo or anovulation
  – Clinical and/or biochemical evidence of hyperandrogenism
  – Polycystic ovaries on ultrasound

• Does not include hyperinsulinemia, glucose intolerance

• Excludes other etiologies
PCOS: Differential Diagnosis

- Neoplasm: androgen secreting
- Nonclassical congenital adrenal hyperplasia
- Exogenous androgen intake
- Prolactinoma
- Thyroid disease
- Cushing’s syndrome
- Primary hypothalamic amenorrhea
- Primary ovarian failure
PCOS: Evaluation

- **History**: menstrual hx, onset/duration, hx weight gain, androgenic meds, family hx PCOS, DM, CAD

- **Physical**: hirsutism, acne, alopecia, balding, acanthosis, clitoral size, fat distribution
  - BMI (kg/m²); obese > 30
  - Waist:hip >0.72
PCOS: Evaluation
PCOS: Evaluation

In male pattern baldness, hair recedes in an "m" shape, the crown bald patch eventually meeting the top points to form a horseshoe shape.
PCOS: Evaluation
PCOS: Lab evaluation

- Cycle D3: FSH, LH, TSH, PRL, T, DHEAS, 17OHP, creatinine
- Oral GTT
  - Fasting glucose / insulin < 10
    - Normal < 110 mg/dl
    - Impaired 110-125 mg/dl
    - DM > 126 mg/dl
  - 75 gram oral glucose ingestion
- 2 Hour glucose / insulin < 55
  - Normal < 140 mg/dl
  - Impaired 140-199 mg/dl
  - DM (Type II) > 200 mg/dl
- Lipid profile
PCOS: Lab evaluation
Insulin Testing

• Single level vs avg x 3 q 10 minutes
  Fasting:
  10 normal
  10 – 14 mild resistance
  > 14 severe resistance

• Glucose : insulin
  < 4.5 normal
  sensitivity 95%
  specificity 84%
PCOS: Ultrasound evaluation

Polycystic ovaries

- 12 or more follicles 2-9mm / ovarian volume > 10 ml
PCOS: Overview

• Background and definition
• Evaluation and diagnosis
• Treatment
  – Not attempting to conceive
  – Attempting to conceive
Primary Treatment Goals

Prevention:

- Glucose intolerance / type II DM
- Cardiovascular disease
- Endometrial cancer
- Acne / hirsutism / alopecia / obesity
Prevalence of type 2 DM & IGT by WHO criteria in 254 PCOS women

NGT = Normal glucose tolerance
Type 2 DM = Type 2 Diabetes Mellitus

Legro et al, JCEM 84:165-169, 1999
First observations on heart disease risk and PCOS

- Study in Sweden on women who had a wedge resection of the ovary
- Followed up several decades later
- Higher prevalence for diabetes mellitus
- Increased risk of cardiac disease judged by lipids
- No hard clinical endpoints, i.e. heart attacks, strokes, deaths

Dhalgren et al 1992
Premature atherosclerosis and PCOS

• Case control study of PCOS and control subjects
• B mode ultrasonography of carotid intimal thickness
• PCOS 7.2% severe changes in carotid plaque vs 0.7% for controls
• Carotid intimal thickness was greater in women over 44 years with PCOS compared to controls
• Young women did not have the same problem

Talbott et al Ather Thromb Vasc Biol 2000
Menstrual irregularity and cardiovascular disease

- Nurses’ Health Study 83,000 women, 1.15 million years of follow up
- 1417 cases of heart attack, 838 stroke including 471 cases of ischemic stroke
- Compared to women with regular periods, those with very irregular periods had an increased risk of fatal or nonfatal stroke of 1.67 and 1.25 respectively
- Confounders such as BMI did not contribute to the difference

Solomon et al JCEM 2002
Long term management of PCOS patient not trying to conceive

ASRM/ACOG – Stress lifestyle modification:

- weight loss (low CHO diet)
- exercise (45 mins brisk walking 3x/wk)
- low fat diet

Try to minimize long term medical therapies
PCOS / Patient with insulin resistance

• Lifestyle modification
• Metformin ? How long ? What are long term effects
136 PCOS patients randomized to:

- Metformin
- or
- Simvastatin \( \times 3 \) months
- or

Combination

Insulin sensitivity improved the most with simvastatin alone (↓ in testosterone comparable in all 3 groups)

Banaszewska et al J. Clin Endocrinol. Metab. 2009; 94:493845
PCOS Patient with significant dyslipidemia

- Lifestyle modification
- Statin / abnormal gtt + metformin

Statins – require reliable contraception (progestin IUD)
PCOS Patient with oligo/anovulatory cycles

- Lifestyle modification
- OCP
- Abnl. gtt / metformin
- Abnl. gtt + dyslipidemia / metformin + statin

OCPs / Worsening glucose intolerance – es. Prediabetic or diabetic??
48 PCOS patients randomized to:

- DRP/20 EE (Yaz/Yasmin)
  or
- DRP/20 EE + Metformin 1500 mg/d x 6 months
  or
- DRP/20 EE + CPA

→ DRP/EE 20 improved insulin sensitivity with no deterioration in lipid profile
→ Metformin did not alter the results
→ CPA abolished the improved DRP/EE effect
PCOS Patient with acne, hirsutism, or alopecia

- Oral contraceptive
- Spironolactone (androgen receptor blocker)
- Flutamide (androgen receptor blocker – liver toxicity)
- Finasteride (inhibits $5\alpha$ reductase $T \rightarrow DHT$) (propecia – not effective in post menopausal women for alopecia)
- Minoxidil 2.5%
- Eflornithine Hydrochloride Vaniqa (ornithine decarboxylase inhibitor)

Medications OK with metformin / statins
PCOS: Overview

• Background and definition
• Evaluation and diagnosis
• **Treatment**
  – Not attempting to conceive
  – **Attempting to conceive**
PCOS: Fertility

- Weight loss
- Clomiphene citrate
- Aromatase inhibitors
- Glucophage
- Combination therapy
- Ovarian diathermy
- Injectable gonadotropins
- IVF
PCOS: Fertility

- **Weight loss**
  - Reduces obesity related hyperinsulinemia
  - Effect seen with 5% loss
  - Reduce LH, T
  - 6/12 conceived in one study
  - More responsive to OI treatment, insulin sensitizing agents
PCOS: Fertility

• 50 - 250 mg x 5 d
• Monitoring: uLH, U/S
• Side effects: vasomotor 20%, pain 5%, nausea 3%, visual sx / HA 1%
• Contraindicated: ovarian cyst, pregnancy
## PCOS: CC Success Rates

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Ovulation (%)</th>
<th>Conception (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>52.1</td>
<td>52.8</td>
</tr>
<tr>
<td>100</td>
<td>21.9</td>
<td>20.7</td>
</tr>
<tr>
<td>150</td>
<td>12.3</td>
<td>9.8</td>
</tr>
<tr>
<td>200</td>
<td>6.9</td>
<td>8.8</td>
</tr>
<tr>
<td>250</td>
<td>4.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>
PCOS: CC Cumulative Pregnancy Rates
Clomid Humor

ANOTHER MAGIC CLOMID MOMENT!
PCOS: Desires Pregnancy

Fertil Steril, 78:2; 280-285; 2002
PCOS: Fertility

Compare CC v AI
12 PCO & 10 oligo ovulators
All with prior inadequate CC response

• No ovulation
• Endometrium < 5mm

Letrozole, 2.5mg, days 3-7

• 75% ovulated with endometrium > 8mm – 3 pregnancies

Fertil Steril, 75:2; 305-309; 2001
PCOS: Fertility

- 500 mg BID x 2 wks, then 1000 mg BID
- Monitoring: uLH, U/S
- Contraindicated: renal impairment (Creat > 1.4), metabolic acidosis (DKA)
- Temp D/C during Xray w/ contrast IV
PCOS: Fertility
Biguanides – Insulin sensitizing agents

- RCT Metformin (1500mg) + CC in PCOS patients
- Nestler 1998 (n=61)
- Vandermolen 2001 (n=27)
- Kocak 2002 (n=56)

PCOS: Fertility

• Oral contraceptive suppression
  – Desogen x 2 months
  – CC, 100mg D5-9, after 3 day pill free interval
  – U/S monitor D12
  – Trigger ovulation @ 20mm follicle size

• N=38, 95 treatment cycles

• 82% pregnancy rate in first 3 treatments

Fertil Steril, 71:544-546; 1999
PCOS: Fertility

**Dexamethasone Co-therapy**

230 PCOS / CC resistant / Normal DHEAS

200 mg CC days 5-9

**Dex 2 mg d 5-14**
- Avg d 12 follicle 18 mm vs 14 mm
- Ovulation 80% vs 20%
- Pregnancy 41% vs 4.2%

Placebo

Fertil Steril, 78:5; 1001-1004; 2002
PCOS: Fertility

Ovarian Cautery

- First year: Ov 80%, PR 50%
- SAB 15%, Multiples 2%
- Metabolic effect uncertain
- Adhesions 29%
  - 2nd look no value
- 2nd line therapy
PCOS: Fertility

Gonadotropin therapy

• Products: rFSH, uFSH, FSH/LH

• Protocols
  – “Conventional”: 75 IU x 7d
  – “Fixed”: 150 IU x 14d
  – “Low Dose Step Up”: 75 IU x 7d, Inc by 37.5 IU Q7
  – “Step Down”: 225 IU x 2d, then 75 IU x 7d

• Monitor: Sono, Estradiol
PCOS: Fertility

- Low dose regimens appear superior
- 75% ovulation rate, 50% – 75% mono-follicular
- Per cycle 15% – 23%
- Cumulative PR 55% – 57%
PCOS: Fertility

• OHSS
  – Fixed 9 - 29%
  – Low dose 0 – 11%
  – Risk: high follicle number, E2 > 2500 pg/ml

• Miscarriage rate as high as 32%

• Multiple gestation
  – FSH OI – 20%
  – IVF_ET – 35%
PCOS: Desires Pregnancy

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THE GOOD NEWS, FOLKS, IS THAT YOU ARE PREGNANT WITH TWIN DAUGHTERS. THE BAD NEWS IS THAT YOUR TWINS ARE PREGNANT TOO.

PROBLEMS WITH FERTILITY DRUGS.