PCOS
Polycystic Ovarian Syndrome
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PCOS

Objectives

- To understand how PCOS interferes with fertility
- Treatment options to restore fertility
Insulin Resistance & Rush Hour

The doors are closing.
Take the next train, please.
PCOS

**Pregnancy Complications**

- **Spontaneous Abortions**
  - Increased in high BMI/PCOS patients
  
  Wang *et al.* Hum Reprod 16:2606; 2001

- **Impaired Glucose Tolerance**
  
  Turhan *et al.* Int J Gynaecol Obstet 81:163; 2003

- **Gestational Diabetes**
  
  Mikola *et al.* Hum Reprod 16:1537; 2001
  Bjercke *et al.* Gynecol Obstet Invest 54:94; 2002

- **Hypertension**
  
  Weerakiet *et al.* Gynecol Endocrinol 19:134; 2004

- **Small for Gestational Age**
  
  Sir-Petermann *et al.*, Hum Repro 20:2122; 2005
Muscle tissue is active tissue that burns calories and fat is inactive tissue that stores calories.

- You might use as many as 75 calories per day to support the energy needs of 1 lb of muscle tissue.
- You might use as few as 3 calories a day to support the energy needs of 1 lb of fat

Those trying to burn calories and lose body fat should increase muscle mass.
2-3 sets at 75% of max. weight load
Muscle failure ~ 50 seconds or 8-10 reps
2 min break between sets
7 day rest after working each area
Exercise large muscle groups first
Add 5 lbs if reps ↑ >5
Moderate to slow speed
- A longer period of muscle tension
- A higher level of muscle force
- A lower level of momentum
- A lower risk of tissue injury
Dynamic Variable Resistance changes throughout the movement range.
- Nautilus, HammerStrength
PCOS

Weight Loss

- Frequency of obesity in women with anovulation and PCO: 30%-75%

- Six month weight-loss program for overweight anovulatory women

  Results of the Treatment group:
  - Lost an average of 6.3 kg (13.9 lbs)
  - Decreased fasting insulin and testosterone levels
  - Increased SHBG concentrations
  - **92% resumed ovulation** (12/13)
  - **85% became pregnant** (11/13)

Ehrmann. NEJM 325:1223; 2005

Clark et al. Hum Reprod 10:2705; 1995
PCOS Nutritional Supplements

- **Myoinositol 1,000 mg bid**
  - *Pregnitude™ Ovasitol*

- **NAC 600mg bid**

- **Cinnamon 600 mg bid**

- **Fish Oil 1,000 mg/day:**
  - *NatureMade Burpless*

- **Maitake Mushroom Extract**

- **Chlorogenic Acid**

- **Advocare Carbease:** *white kidney bean extract, coffer bean extract*

- **Irwin Natural 3-in 1 Carb Blocker:**
  - *chromium piccolinate, Fish Oil, white kidney bean extract, cinnamon, lipase, protease, black pepper extract*

- **Garcinia Cambogia Ultra**
PCOS

**Dietary Recommendations**

- **Diets based on low-GI foods produced greater weight loss** than did equivalent diets based on high-GI foods.
  

- **Low GI diet more effective than low fat** in obese children
  

- The **glycemic index appears to be a better predictor** of the metabolic effects of a diet than the sugar content.
  

- **Substitute nonhydrogenated unsaturated fats for saturated and trans-fats**
  
  - ↑ omega-3 fatty acids from fish, fish oil supplements, or plant sources
  - ↑ fruits, vegetables, nuts, and whole grains
  - ↓ refined grain products.
  - Simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence.

Reproductive Factors

- Gonadotropin sensitivity
- Oocyte maturity
- Embryo development
- Delayed ovulation
- Implantation
- Proinflammatory state
- Miscarriage
PCOS Observations

- >75% anovulatory women
- ↑ LH pulsatility
  Taylor et al. J Clin Endocrinol Metab 82:2248; 1997
- 6-fold ↑ of primary growth follicles
  Webber et al. Lancet 362:1017; 2003
- Follicular arrest: impaired selection of dominant follicle
- Circulating markers of oxidative stress are abnormal independent of obesity
- ↑ AMH / ↑ antral follicles
  ↓ adiponectin
- ↑ CRP
- ↑ cytokines ? obesity
  — ↑ TNF-α, IL-6, IFNγ
- ↑ testosterone
  — ↓ HOXA-10
- Δ uterine & ovarian blood flow
- ↑ Sleep apnea
PCOS & TNF-α

- TNF-α ↑ in normal-weight women with PCOS
  Bivikli M, et al. Metab Syndr Relat Disord 4(2) 122, 2006

- Insulin resistance is associated with ↑TNF-α, 60% ↑ lipid accumulation in blastomeres, & 45% ↑ apoptosis
  Moley KH, et al. SGI abstract, 2008

- TNF-α inhibits FSH induced follicle growth, E2 production & hCG induced ovulation in mice follicles

- TNF-α induces apoptosis in bovine pre-implantation embryos

- Oocytes exposed to TNF-α during maturation developed fewer blastocysts & increased blastomere apoptosis >9 cell stage.

- Thiazolidinediones ↓ TNF-α

- Dan-Shao Hua Xian & Resveratrol (grapes, peanuts) ↑ transcription of PPAR-γ and ↓ TNF-α
  Aggarwal BB, et al. Cell Cycle, 7(8), 2008
  Cheng ML. Hepatobiliary Pancreas Dis Int. 7(2), 179, 2008
PCOS & Adiponectin

- Adiponectin produced by adipose tissue
  - Subcutaneous fat > visceral fat
- Adiponectin ↓ with ↑ BMI
- Improves insulin sensitivity
- ↑ human granulosa cell estrogen & progesterone production
- Improves oocyte maturation and embryo development
- ↓ AdipoR in women with implantation failure
- Adipokines could be a link between reproduction & energy metabolism partly explaining infertility related to obesity & PCOS.

Infertility Treatments

- Low glycemic diet, strength training, supplements, insulin sensitizers
- If BMI elevated, 5-10% weight loss
- Insulin sensitizer as single agent
- Supplements
  - NAC, Ovasitol, Cinnamon, Carb Blocker, Maitake Mushroom Chlorogenic Acid, Fish Oil, Low Dose Aspirin
- Letrozole or *clomiphene* ± Insulin sensitizer
- Gonadotropins + insulin sensitizer
  - Birth control pretreatment
  - GnRH-agonist vs antagonist
  - Low dose treatment
  - Low dose hCG
  - Follicular reduction + oocyte cryopreservation
- Ovarian surgery
- *IVM, IVF*
Letrozole vs Clomiphene for Infertility in PCOS

- 750 women received letrozole or clomiphene for 5 cycles
- Rotterdam PCOS criteria
- 18-40 years old
- Adequate sperm, ≥ 1 patent fallopian tube & nl uterine cavity

- Ovulation rate
  - 61.7% vs 48.3% of cycles
- Live births
  - 27.5% vs 19.1% L vs C
  - 44% more likely with L
- No significant difference in preg loss rate
- Twins 3.4% vs 7.4% NS
- Clomiphene ↑ hot flashes
- Letrozole ↑ fatigue & dizziness

Metformin

Who might benefit?

- 8 or fewer menses per year
- Hirsutism or elevated androgens
- Acanthosis nigricans
- History of gestational diabetes
- PCO appearing ovaries
- Family history of diabetes
- Fasting insulin over 10 miu/ml; 2 hour over 50 miu/ml
- Hypoglycemic response on 2hr IGTT
- Metabolic Syndrome
PCOS

**GRS Metformin Protocol**

- Metformin 500 mg qd wk 1; bid wk 2; tid wk 3; followed by metformin 850 mg bid
- Take with full glass of water/milk at middle of meal
- Monitor BBT’s, u-hCG if 16 day temp rise seen
- Re-evaluate @ 3 months
  - Additional time
  - Supplements: NAC, Cinnamon, Ovasitol, Carb blocker
  - Increased metformin to 1000mg bid
  - Add Actos
  - Letrozole/clomiphene
  - Ovarian drilling
  - Low dose injectables with oocyte cryopreservation
  - IVF
Metformin

Who Gets Pregnant?

- 93.7% had normal FBS
- 50% had insulin < 15 miu/ml
- 89% had normal testosterone levels

Lab tests don’t predict who gets pregnant!
61 PCOS women with BMI >28

26 women received - **Placebo**
- 1 ovulated

35 women received - **Metformin**
- 14 ovulated

1500 mg/day

Prog. >25 nmol/L

25 women received - **Placebo**

- 2 ovulated

21 women received - **Metformin**

- 19 ovulated

- 1500 mg/day

**CC**

- 50 mg

Metformin Improves Pregnancy Rates

- OGTT offered to women with obesity, AN, GDM, FHX or CC failure
- 51 had hyperinsulinemia
  - **Group 1: Metformin alone** (n=11), Met+CC (n=17),
  - **Group 2: CC alone** (n=23) for 7.5 months average
  - Ovulation (82% vs 78%)
  - Pregnancy rates (63% vs 36%, NS)
  - Pregnancy in women who ovulated appeared higher in metformin patients (75% vs 44%, p=0.054)

Pregnancies Following Metformin in PCOS

- Anovulatory patients (N=48) with PCOS
  - Metformin 500 mg b.i.d. 6 weeks, t.i.d. thereafter
  - Clomiphene added if anovulatory at 12 weeks
  - 31/48 (64.5%) resumed spontaneous menses
  - 16/31 (52%) conceived within the first six months
  - 3/16 (19%) had spontaneous abortions
  - 19/48 (40%) suffered gastrointestinal related side-effects, including diarrhea, abdominal cramping, and nausea

Glucophage XR vs Clomiphene

- 626 infertile women with the polycystic ovary syndrome

**Pregnancy rate**
- Clomiphene + placebo 22.5%
- Extended release metformin plus placebo 7.2%
- Clomiphene + metformin XR 26.8%

**Multiples** 6%, 0%, 3%

**Synergistic effect of diet and exercise ignored**

**Equivalency of Glucophage XR and metformin not proven**

Metformin Reduces Pregnancy Loss in PCOS

- Retrospective study of PCOS women who became pregnant
  - Group 1: received metformin during pregnancy (n=101)
  - Group 2: control (n=31)

- Early loss rate 12.9% vs 41.9% (p=0.001)
- Prior SPAB: 15.7% vs 58.3% (p=0.005)

PCOS

Ovarian Drilling

- Spontaneous ovulation
  - 60-95%

- Pregnancy
  - 60-85%
PCOS

Ovarian Drilling

**Advantages**
- High success rate
- Prolonged response
- Multiple births
- OHSS
- Dose, duration ovulation induction

**Disadvantages**
- Adhesion formation
  - Interceed not beneficial
- Requires surgery
- 1/3 require ovulation medications
- POF risk
- Less successful in smokers 25% vs 95%
Objective: To compare conventional IVF outcomes of PCOS and non-PCOS patients

Materials and Methods: Meta-analysis of nine studies
- 458 PCOS (n=793 cycles)
- 694 Control (n=1116 cycles)

Analysis Requirements:
- Non-male factor control matches
- 2003 PCOS criteria used
- Patients within a study on same ovarian protocol

PCOS & IVF META-ANALYSIS

Results:
- PCOS patients demonstrated a reduced chance of oocyte retrieval per started cycle
- Significantly more oocytes per retrieval in PCOS group

N/S Results:
- Chance of Embryo Transfer (ET) per oocyte retrieval
- Number of oocytes fertilized
- Clinical pregnancy rate per started cycle

Conclusions:
- Increased cancellation rate and lower fertilization rate, but more oocytes per retrieval with PCOS women using IVF
- Similar pregnancy and live birth rates were achieved

Patients are often hyperresponders.

- Reduced follicular vascularization in PCOS women
  
  - Hyperinsulinemia can result in higher E2/androstendione ratios and increased immature follicles.

A major concern is Ovarian Hyperstimulation Syndrome (OHSS).

How do you lower risk of OHSS?

- Insulin sensitizers
- Lower gonadotropin doses
- GnRH antagonist cycles
- Coasting vs low dose hCG
- Embryo cryo with ET in an unstimulated cycle
- Oocyte vitrification
- Hespan, Dostinex

Delvigne & Roszenberg Hum Reprod Update 8:559; 2002