PCOS: *Taking Control*

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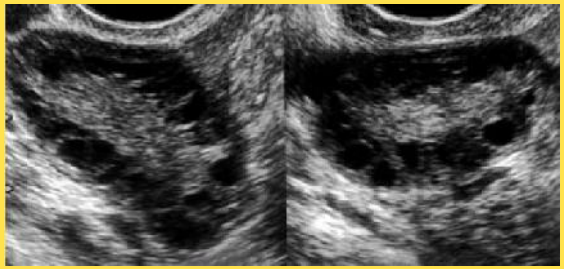

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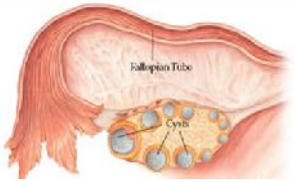
PCOS *Objectives*

- To understand that PCOS is a metabolic disorder with life-long health implications for the individual and family members
- To review contemporary evaluation and multidisciplinary management of PCOS

PCOS *Overview*



- Definition
- Symptom Presentation
- Diagnostic Criteria
- Pathophysiology
- Metabolic and Reproductive Complications
- Treatment Options

PCOS *History & Epidemiology*

- 1st described by Irving Stein and Michael Leventhal as a triad of amenorrhea, obesity and hirsutism (1935)
- The most common endocrine disorder in women of reproductive age ~ 2 - 8% of women

  Knochenhauer *et al*. J Clin Endocrinol Metab 83:3078; 1998
- Current suggested prevalence in the U.S.
  - Caucasian: 4.8%
  - African American: 8.0% — Azziz et al. J Clin Endo Meta 89:2745; 2004
  - Hispanic or Latino: 13% — Goodarzi et al. Fert Ster 84:766; 2005
  - 5-10% of women — Ehrmann. NEJM 325:1223; 2005

Definitions & Abbreviations

- PCO = Polycystic Ovary
- PCOD = Polycystic Ovarian Disease
- **PCOS = Polycystic Ovarian Syndrome**
- PCOA = Polycystic Appearing Ovary

POLYCYSTIC OVARIAN SYNDROME *is a description for a broad spectrum of clinical and physical findings in women with an endocrine dysfunction, specifically insulin resistance, metabolic syndrome or abnormal androgen production.*

POLYCYSTIC OVARIAN SYNDROME *is the most common endocrine abnormality in adult women, and is emerging as a common cause of menstrual disturbances in the adolescent population*

PCOS *Diagnostic Criteria*

Difficult to diagnosis

1. Changing criteria
2. Varying criteria over time

NIH-Sponsored 1990 Criteria (Both 1 and 2)

1. **Chronic anovulation *[irregular mestrual cycles]***
2. Clinical and/or biochemical signs of **hyperandrogenism** and exclusion of other etiologies. ***[elevated male hormones]***

Rotterdam ESRHE/ASRM- 2003 Criteria (2 out of 3)

1. **Oligo- or anovulation**
2. Clinical and/or biochemical signs of **hyperandrogenism**
3. **Polycystic appearing ovaries** and exclusion of other etiologies (CAH, androgen-secreting tumors, Cushing's syndrome)

NIH 2012 Conference ???

Adapted from Fert Steril 81:19; 2004

PCOS *Diagnostic Criteria*

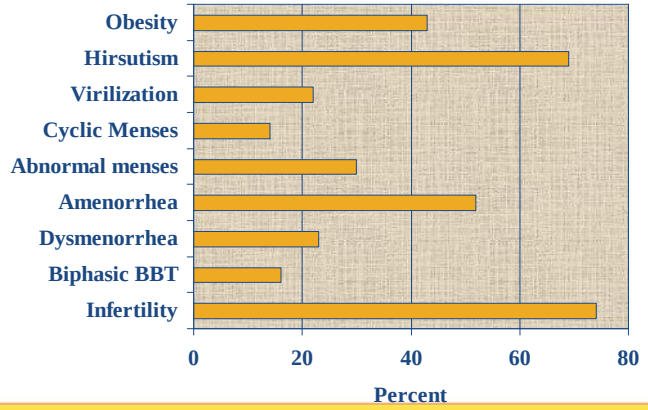
- At least one of the following:
  - —12 or more follicles measuring 2-9 mm in diameter
  - —Increased ovarian volume (>10 cm^3)
    - ➢ Omits follicle distribution or increased stromal volume
- 20% of normal menstruating women have PCO

ASRM Fact Sheet PCOS, 2005

- "Asymptomatic PCO" is not PCOS

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fert Steril 81:19; 2004

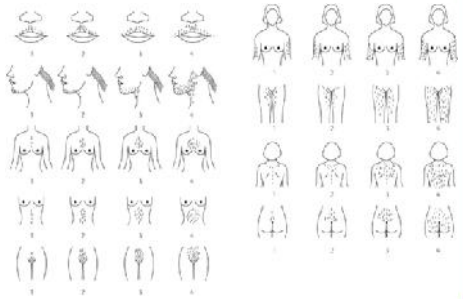
PCO…S *Presentation*



Goldzieher JW, et al: JCEM 22:325, 1962

PCOS *Presentation*

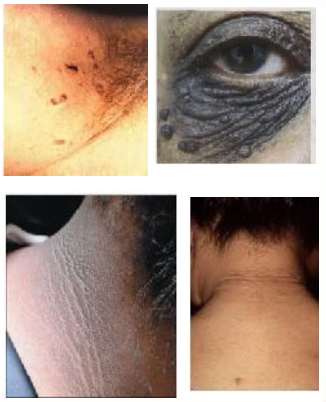
- Additional PCOS features may include:
  - Lipid abnormalities
  - Hypertension
  - Sleep apnea
  - **Acne**
  - **Hirsutism**
  - **Hair loss**
  - **Furunculitis**
  - **Acanthosis**
  - Premature puberty



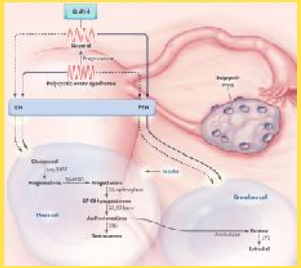
Azziz. Obstet Gynec 101:995; 2003

Acanthosis Nigricans

- **PCOS,** Insulin resistance, diabetes, cancer & obesity
- Prevalence
  - 7% of school children
  - 66% children > 200% ideal wt
  - AA 13%, Hisp 5%, Cauc 0.5%
  - HI OR 4 in children with AN
- **Associated with skin tags**



PCOS *Pathogenesis*



- **Primary disorder of gonadotropin secretion**
  - Excess LH
  - Androgen excess leads to follicular arrest
- **Ovarian and adrenal hyperandrogenism**
  - 20-30% demonstrate ↑ DHEAS
- **Primary disorder of insulin resistance**
  - Fasting & challenged hyperinsulinemia or Insulin:Glucose ratio
  - Dyssynchronus β-cell function
  - Insulin stimulates adrenal & ovarian androgen production

Ehrmann. NEJM 325:1223; 2005 Cristello *et al*. Gynec Endocrin 21:340; 2005

Insulin Action: *Androgen Enhancement*

- Synthesis and pulsatility of LH
- Adrenal sensitivity to ACTH
- Thecal sensitivity to LH
- Adrenal and ovarian 17α-hydroxylase/17,10-lyase activity
- IGFBP-1 levels

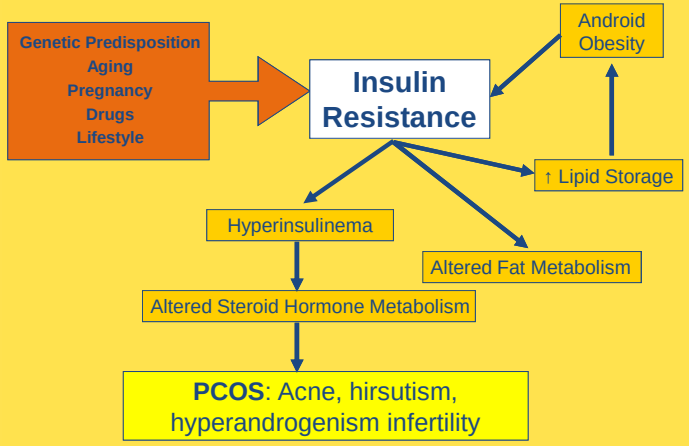
- Upregulation of ovarian IGF-1 receptors
- Ovarian enlargement and cyst development in synergy with LH and βhCG in animal studies
- Inhibition of hepatic SHBG synthesis

Adapted from Luque-Ramirez *et al*. Clinica Chimica Acta Epub 2005

PCOS *Insulin Connection*

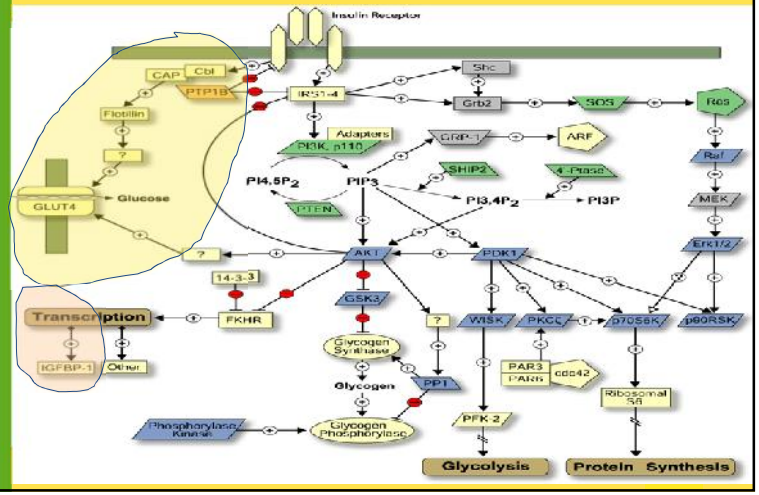
- 30% of obese PCOS women have ↓ glucose tolerance by their 30's
- Insulin-mediated glucose uptake is ↓ 35-40%
- ↓ glucose-stimulated insulin release *(↓ ß-cell function)*
- 50% of PCOS women demonstrate post-receptor defect
- ↑ insulin, steroidogenesis and LH release

Dunaif A, et al: J Clin Invest 96:801, 1995



Adapted from Cristello *et al*. Gynec Endocrin 21:340; 2005

Insulin Receptor Pathways



PCOS *FFA & Insulin Resistance*

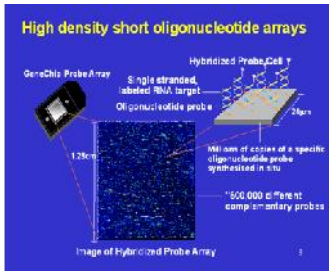
- ↑ FFA release from adipose tissue or failure of FFA using tissues to remove them normally, lead to ↑ TG
- ↑ delivery of FFA to muscle ↓ muscle glucose uptake and utilization
- IR correlates with intramuscular TG store
- Lipotoxicity: Intracellular TG linked to pancreatic ß-cell failure

Ziegler O, et al: Diabetes Metab 27:261, 2001

- Depakote (valproic acid) ↓ FFA utilization ì PCOS

Insulin Resistance Gene Chip

- 210 genes in metabolic pathways related to insulin resistance
  - Signaling
  - Glucose oxidation
  - Fat uptake
  - Fat oxidation
  - Transciption factors
  - Glucose uptake
  - Glucose storage
  - Fat storage
  - Cytoskeletal components



Walder K, et al: Ann NY Acad Sci 967:274, 2002

PCOS *IUGR antecedent*

- Fetal Origins
- Increased risk of hyperinsulinema, premature pubarche, and earlier signs of PCOS
  - —In children born with intrauterine growth retardation or post-term birth

    Ibanez *et al*. Clin Endocrinol (Oxf) 55:667; 2001
  - —In girls with pre-mature pubarche born with low birth weight (LBW), even non-obese

    Ibanez et al. J Pediatric 144:23; 2004

PCOS *Genetic Link?*

- Familial clustering of PCOS common
  - — 1st degree relatives of patients with PCOS may be at high risk for diabetes and glucose intolerance
  - — Mothers and sisters of PCOS patients have higher androgen levels than control subjects

    Yildiz *et al*. J Clin Endocrinol Metab 88:2031; 2003
  - — Male individuals who are first-degree relatives of patients with PCOS have a higher degree of dyslipidemia and insulin resistance

    Reis KS, et al: Rev Bras Ginecol Obstet 32(7): 334, 2010
- PCOS is a genetically determined ovarian disorder… symptoms are based on the interaction of genes and with the environment.

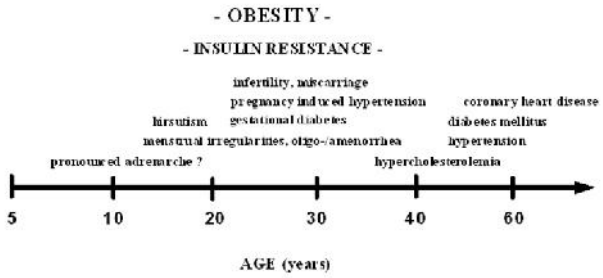
  Franks et al. Int J Androl 29:278; 2006

PCOS *Insulin-Related Genetic Variants*

Gene	Polymorphism	Phenotype
IGF-2	*Apa*I	PCOS
IGF-IR	Trinucleotide repeat	Increased fasting glucose and insulin resistance
PPAR-γ2	Pro12Ala	Body mass index
		Lower insulin resistance
		PCOS
		Obesity
		Lower insulin resistance and hirsutism score
Paraoxonase (PON-1)	-108C/T	PCOS
	Leu55Met	Obesity and insulin resistance
SORBS1	Thr228Ala	Obesity
Calpain-10	UCSNP-43,-19,-63	PCOS and insulin levels
	UCSNP-43,-45	Hirsutism score and idiopathic hirsutism
	UCSNP-44	PCOS
Adiponectin	45 T/G	Androstenedione
		PCOS
		Insulin resistance
	276 G/I	Obesity and insulin resistance
		Lower adiponectin levels

Adapted from Luque-Ramirez *et al*. Clinica Chimica Acta Epub 2005

PCOS *Sequelae*



PCOS *Sequelae*

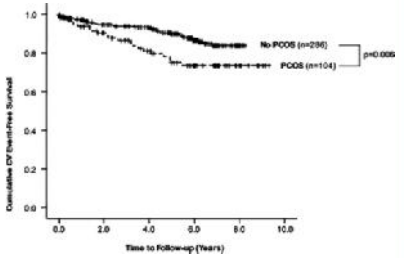
- Skin Disorders
- Non-Alcoholic Fatty Liver
- Type II Diabetes
- Cardiovascular Disease / Metabolic Syndrome
- Mood Disorders
- Gynecologic Cancers
- Sleep Apnea
- Infertility

PCOS *Health Risks*

- More likely to have hysterectomy
  Dahlgren E, et al: Fertil Steril 57:505, 1992
- ↑ Coronary heart disease risk factors
  - Talbott E, et al:Arterioscler Thromb Vasc Biol 15:821, 1995
- ↑ TC, LDL-C, & TG in IR & NIR
  Talbott E, et al: J Clin Epidemiol 51:415, 1998, Melrow D, et al: Hum Reprod 11:1848, 1996
- Blood pressure ↑ with insulin level and is ↑ in obese PCOS women
  Conway GS, et al: Clin Endocrinol 37:119.1992
- Relative risk of MI ↑ 7.4 times age matched controls
  Dahlgren E, et al: Acta Obstet Gynecol Scand 71:599, 1992
- ↑ Risk of diabetes associated death (3.6 O.R.)
  Pierpont T, et al: J Clin Epidemiol 51:581, 1998
- More extensive CVD on heart catheterization with PCOS
- PCOa present in 42% of CVD patients
  Birdsall MA, et al: Ann Intern Med 126:32, 1997

Hyperinsulinemia *CVD Risk Factors*

- Endothelium dysfunction
  (impaired NO vasodilation)
- Disorders of coagulation & fibrinolysis
  - ↑ Plasminogen activator inhibitor-1
  - ↓ Plasminogen activator activity
  - ↑ Fibrinogen levels
  - ↑ Activation of coagulation
- Hypertension
- Dyslipidemia

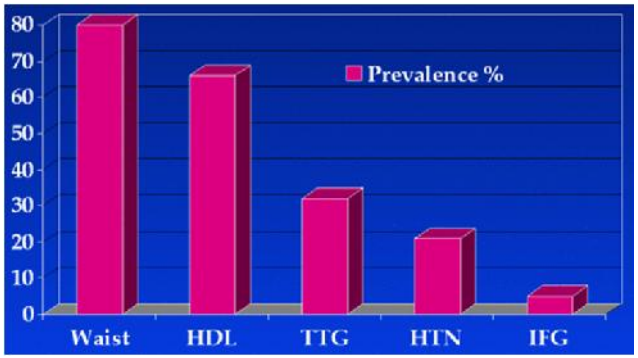


Pepine CJ, et al: J Clin Endocrinol Metab 93:1276, 2008

PCOS: *Metabolic Disorder*

- Insulin Resistance
  - High association with PCOS
    Dunaif. Endocr Rev 18:774; 1997
  - 10% have Type 2 Diabetes
  - 30-35% have Impaired Glucose Tolerance (IGT)
    Ehrmann et al. Diabetes Care 22:141; 1999
    Legro et al. J Clin Endocrinol Metab 84:2974; 1999
- Obesity
  - 50% of PCOS patients are obese
    Goldzieher & Young. Endocrinol Metab Clin North Am. 21:141; 1992
  - Amplifies biochemical and clinical abnormalities of PCOS
    Kiddy et al. Clin Endocrinol (Oxf) 32:213; 1990

Metabolic Syndrome



Ehrmann DA, et al: J Clin Endocrinol Metab 91:48. 2006

PCOS: *Mood Disorders*

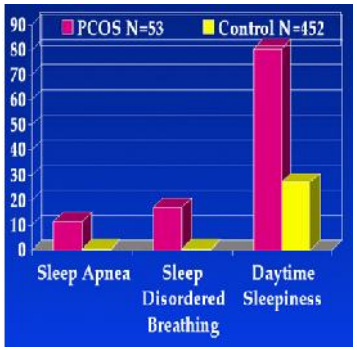
- Depression
  - Higher prevalence in PCOS patients, associated with higher BMI *(P=0.05)* and greater insulin resistance *(P=0.02)*
    Rasgon et al. J Affect Disord 74:299; 2003
  - Reduced quality of life and limited sexual satisfaction, most parameters not corrected by weight loss
    Elsenbruch et al. J Clin Endocrinol Metab 88:5801; 2003

PCOS: *Endometrial Cancer*

- Endometrial Cancer
  - Long-term follow-up of 786 PCOS women found an increased risk of endometrial cancer
    Wild *et al*. Hum Fertil (Camb) 3:101; 2000
  - PCO found in women <50 yrs of age with endometrial cancer, 62.5% vs 27.3% of controls (P=0.033)
    Pillay *et al*. Hum Reprod Epub 2005

PCOS *Sleep Apnea*

- Sleep Apnea
  - Increased Sleep Disordered Breathing (SDB) and daytime sleepiness in PCOS vs. controls



Vgontzas *et al*. Sleep Med Rev 9:211; 2005

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

PCOS *Infertility*

- >75% of women with anovulation infertility

  Franks *et al*. Int J Androl 29:278; 2006
- Increased LH pulse frequency and amplitude

  Taylor et al. J Clin Endocrinol Metab 82:2248; 1997
- Six-fold increase of primary growth follicles

  Webber et al. Lancet 362:1017; 2003
- Follicular arrest: impaired selection of dominant follicle

  Jonard & Dewailly. Hum Reprod Update 10:107; 2004

Different Diagnosis

Gynaecologists		Endocrinologists
172		138
Essential Diagnostic Criteria (P<0.001)		
61% PCO		81% Androgenization
59% Androgenization		70% Menstrual Irregularity
47% Menstrual Irregularity		
47% LH/FSH Ratio		
Diagnostic Evaluation (P<0.001)		
91%	Request Ovarian Ultrasound	44%
58%	Measure Adrenal Androgens	80%
34%	Measure Lipids	67%
First Line of Treatment		
Both used exercise and diet recommendations		
Infertility Treatment		
Clomiphene Citrate		Insulin Sensitizers

Cussons *et al*. Clin Endocrin (Oxf) 62:289; 2005

PCOS *Findings*

Physical
- Obesity
- Hirsutism
- Acanthosis
- Abnormal menses
- Acne

Biochemical
- ↑ Androgen
  - Testosterone
  - *DHEAS*
  - *17OH progesterone*
- ↓ *SHBG*
- ↑ Anti-mullerian hormone
- *↑ LH*
- 2 hr Insulin/Glucose Tolerance Test
- *↑ PAI-1*
- ↑ Lipids
- ↑ hs CRP

Ultrasound
- Necklace sign
- ↑ Ovarian volume
- Antral follicle count
- *Doppler blood flow changes*

PCOS *Ultrasound*

- 1078 reproductive age women screened by US
  - 183 (17%) demonstrated PCO appearance
    - 80% had irregular or absent cycles
    - 19.7% had regular cycles

    AndersY et al: Contacept Fertil Sex 23:415, 1995
- PCO appearance associated with testosterone, androstenedione and glucose clearance

  Najmabadi, et al: Fertil Steril 67:631, 1997, Dewally D, et al: Ann Ny Acad Sci 587:206, 1993

Androgen production, action & control

- Pituitary → *ACTH, LH*
  - GnRH-a, birthcontrol pills, progesterone
- Adrenal → *DHEAS, Androstendione, Testosterone*
  - Dexamethasone
- Ovary → *Androstendione, Testosterone*
  - Spironolactone+BCP, Drosperinone BCP, metformin, thiazolidinediones
- Testosterone conversion → *5α-reductase enzyme*
  - Finasteride
- Androgen receptor
  - Flutamide, spironolactone, CPA, Drosperinone BCP
- Hair Follicle
  - Vaniqa

Muscle & Insulin Resistance

- **Muscles clear 80% of glucose from circulation**
  - Utilized during endurance cardio > 60 – 70% target rate & resistance training over 70% of weight max
  - Stored as glycogen
- **Sugar intake 10x over past 100 years**
  - As glycogen storage ↑ muscles become more insulin resistant, insulin levels rise
  - Insulin = storage
    - Once glycogen storage maxed, FFA stored as TG
- **Loss of muscle mass leads to ↓ glucose clearance ↑ IR & ↑ TG producti**
- **RT leads to ↑ muscle mass, ↑ glucose clearance, ↓ IR & ↓TG productic**

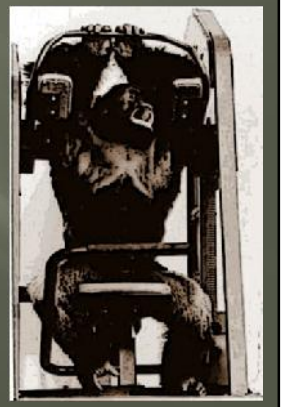
PCOS, Insulin Resistance, Muscle & Japanese Subway Rush Hours

Burning Calories

- **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 1lb 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.**

Strength Training Program

- 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%

  Ehrmann. NEJM 325:1223; 2005

- 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)

  Clark et al. Hum Reprod 10:2705; 1995

PCOS *Diet & Weight Loss*

- Hypocaloric diets ↓ insulin resistance
  - —10-20% protein, ~50% carbohydrates
  - —< 30% total fat, < 10% saturated fat

  ADA nutritional recommendations: Diabetes Care 20S:14, 1997
- Further improvement with 5-10kg weight reduction
- Two fold ↑ glucose disposal rate with 16% ↓ weight

  Niskanen L, et al: J Obes Relat Metab Disord 20:154, 1996

Role of Dietary Nutrients

- Interact with hormonal signals to govern the expression of genes encoding proteins involved in energy metabolism, cell differentiation, and cell growth
- Govern the tissue content and activity of different proteins by functioning as regulators of gene transcription, nuclear RNA processing, mRNA degradation, and mRNA translation, as well as functioning as posttranslational modifiers of proteins
- FFA have a very strong direct influence on the molecular events that govern gene expression

Clarke S, et al: Ann NY Acad Sci 967:283, 2002

Is obesity related to high fat diets?

"A substantial decline in the percentage of energy from fat during the last 2 decades has corresponded with a massive increase in the prevalence of obesity.

Diets high in fat do not appear to be the primary cause of the high prevalence of excess body fat in our society, and reductions in fat will not be a solution."

Willet WC, et al: Am J Med 113S:47S, 2002

PCOS *Dietary Sequalae*

- Diets with a high glycemic load and a low cereal fiber content increase risk of diabetes in women.

  Salmeron J, et al: JAMA 277:472, 1997
- Exacerbation of the proinflammatory process may be a mechanism whereby a high intake of rapidly digested and absorbed carbohydrates increases the risk of ischemic heart disease, especially in overweight women prone to insulin resistance

  Willet WC, et al: Am J Clin Nutr 75:492 2002
- Improvements in menstrual cyclicity were associated with greater decreases in insulin resistance and fasting insulin.

  Norman RJ, et al: J Clin Endocrinol Metab 88:812 2003

PCOS *Dietary Recommendations*

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

  Brand-Miller JC, et al: Am J Clin Nutr 76:281,2002

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

  Spieth LE, et al: Arch Ped Adol, 154:947, 2000

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

  Jenkins DJ, et al: Curr Opin Clin Nutr Metab Care 6:165, 20

- 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.

  Willet WC, et al: JAMA 288:2569, 2002

PCOS *Dietary Recommendations*

- Avoid High Fructose Corn Syrup Sweeteners
  - ↓ appetite suppression ↓ Gherelin secretion
  - Calories stored as triglycerides and fat
  - Hepatoxicity similar to alcohol
- Potential Benefit
  - D-chiro inositol
  - DHA/Fish Oils Essential Fatty Acid Supplementation
  - Antioxidants
  - Resveratrol

PCOS *Dietary Goals*

- Consume more foods
  - rich in complex carbohydrates
  - monounsaturated fat
  - fiber
  - with a ↓ ratio of omega-6 to omega-3 fatty acids
- Reduce
  - Total caloric intake
  - Saturated fat
  - Cholesterol

Sugar, The Bitter Truth

Dr. Robert Lustig, UCSF

Diabetes Epidemic

- Diabetes afflicts 16 million Americans
  - —20% of those age 20 or older
  - —95% type II
- Prevalence tripled last 30 years
- Risk ↑ 5 times with BMI > 30
- Compared to whites, African-American adults have 60% greater risk and Hispanic adults have 90% greater risk

Diabetes Prevention Program

- 3,234 people with impaired GTT followed 3 years
  - —BMI 34
- Low fat diet and exercise (150 minutes/wk)
  - —58% reduction of diabetes risk (71% for 60 & older)
  - —Loss of 5-7% of body weight (15 pounds)
- Metformin 850 mg twice daily
  - —31% reduction of diabetes risk
  - —Loss of 5% of body weight

PCOS *Medical Therapy Benefits*

- Metformin: ↓ appetite, BP, PAI-1, plasma lipids
- Actos & Avandia *(thiazolidinediones pioglitasone, rosiglitazone):* ↓ FFA, TG, LDL-oxidation, PAI-1, ± BP
- Metformin & TZD: may be combined
- Byetta (exenatide): incretin GLP1 mimetic, or Januvia (sitaglipitin) DPP4 inhibitor: ↓TG, BP, appetite & weight, ↑ HDL
- Hypoglycemia results from diet and too little, not too much metformin or TZD
- ↓ insulin may improve menstrual cyclicity
  - — ↓ endometrial cancer risk
  - — ↓ androgens

Infertility Treatments

- If BMI elevated, 5% weight loss
- Insulin sensitizer as single agent
- Insulin sensitizer + clomiphene or letrozole
- Gonadotropins + insulin sensitizer
  - — Birth control pretreatment
  - — GnRH-agonist vs antagonist
  - — Low dose treatment *(multidose vials)*
  - — Low dose hCG
  - — Follicular reduction + oocyte cryopreservation
- Ovarian surgery
- IVM
- IVF

Kim *et al.* Fertil Steril 73:1097, 2000

PCOS *Ovarian Drilling*

- Spontaneous ovulation
  - 60-95%
- Pregnancy
  - 60-85%

PCOS *Ovarian Drilling*

Advantages	*Disadvantages*
• High success rate	• Adhesion formation
• Prolonged response	— Interceed not beneficial
• Multiple births	• Requires surgery
• OHSS	• 1/3 require ovulation medications
• Dose, duration ovulation induction	• POF risk
	• Less successful in smokers 25% vs 95%

Metformin *Who will 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
  - Increased metformin to 850mg tid or 1000mg bid
  - Add Avandia/Actos (check ALT) or Byetta injections or Januvia
  - 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

Labtests don't predict who gets pregnant!

PCOS *Metformin & Ovulation*

61 PCOS women with BMI >28

26 women received - Placebo → 1 ovulated

P<0.001

35 women received - Metformin 1500 mg/day → 14 ovulated

1 14 28 35

Prog. >25 nmol/L

Nestler et al. N Engl J Med 1998

PCOS *Metformin & Clomiphene*

25 women received - Placebo → 2 ovulated

21 women received - Metformin 1500 mg/day → 19 ovulated

P<0.001

CC 50 mg

1 5 10 18

Nestler et al. N Engl J Med 1998

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)

Lavoie HB, et al. Abstract P2-426 Endocrine Society, 2001

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

Heard MJ, et al: Abstract 140, Society of Gynecologic Investigation, 2001

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

Legro etal: N Engl J Med. 2007 Feb 8;356(6):551-66.

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)

Jakubowicz DJ, et al: abstract P2-427, Endocrine Society, 2001

PCOS & IVF META-ANALYSIS

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

Heijnen *et al*. Human Reprod Update 12:13; 2006

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

Heijnen *et al*. Human Reprod Update 12:13; 2006

ICSI Clinical Study: *Esinler et al.*

Objective: To determine the ET & ICSI outcomes of PCOS patients

Materials and Methods: Case-control study at an IVF Center; Ankara, Turkey

- 99 PCOS (n=109 cycles)
- 58 PCO (n=58 cycles)
- 210 Control (n=232 cycles)

Intervention: Controlled Ovarian Hyperstimulation (COH) & ICSI

Measurements: Oocyte number, fertilization rate, embryo quality, clinical pregnancy rate, implantation rate and OHSS

Esinler *et al*. Fert Steril 84:932; 2005

Embryological and Pregnancy Data

Variable	PCOS	PCO-only	Control	*P* Value
No. of oocyte-cumulus complexes	15.5 ± 7.3	15.3 ± 6.4	11.7 ± 6.1	<.01
No. of metaphase oocytes	13.4 ± 7.1	13.1 ± 5.6	10.3 ± 5.8	<.01
Metaphase II oocytes/total oocytes (%)	87	86	87	NS
2-pronucleated/metaphase II oocytes (%)	72	67	70	NS
No. of 2-pronucleated oocytes	10.1 ± 5.4	9.1 ± 5.2	7.2 ± 4.4	<.01
No. of transferred grade 1 embryos	1.1 ± 0.1	1.0 ± 0.2	0.7 ± 0.1	<.05
No. of transferred grade 1 embryos/no. of embryos transferred (%)	33.3	34.2	24.6	<.05
No. of transferred grade 2 embryos	2.0 ± 0.1	2.1 ± 0.3	2.2 ± 0.1	NS
No. of embryos transferred	3.2 ± 1.1	3.2 ± 1.3	3.0 ± 1.2	NS
No. of cycles with embryo freezing (n,%)	39 (35.8)	14 (24.1)	64 (28.1)	NS
Clinical pregnancy rate/embryo transfer (%)	66.0	59.6	44.3	<.05
Implantation rate (%)	28.8	24.3	23.1	NS
Multiple pregnancy rate (%)	48	48	41	NS
Twin (%)	39	44	34	NS
Triplet (%)	9	4	7	NS
Miscarriage rate (n,%)	6 (11.8)	3 (33.3)	14 (14.1)	<.05
No of OHSS requiring hospitalization (n,%)	4 (3.7)	1 (1.7)	3 (1.3)	NS

Adapted from Esinler *et al*. Fert Steril 84:932; 2005

PCOS *Stimulated Cycles*

- Patients are often hyperresponders
  - Reduced follicular vascularization in PCOS women
    Jarvela *et al*. Fert Steril 82:1358; 2004
  - Hyperinsulinema can result in higher E2/androstendione ratios and increased immature follicles
    Fulghesu *et al*. J Clin Endocrinol Metab 82:644; 1997
- A major concern is Ovarian Hyperstimulation Syndrome (OHSS)
- How do you lower risk of OHSS?
  - Lower gonadotropin doses
  - 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

PCOS Nutritional Supplements

- **Myoinositol 4,000 mg/day**: *Pregnitude™*
- **Fish Oil 1,000 mg/day:** *NatureMade Burpless*
- **Irwin Natural 3-in 1 Carb Blocker**: *chromium piccolinate, Fish Oil, white kidney bean extract, cinnamon, lipase, protease, black pepper extract*
- **Cinnamon**
- **Advocare Carbease:** *white kidney bean extract, coffer bean extract*
- **Maitake Mushroom Extract**
- **Garcinia Cambogia Ultra**

PCOS & TNF-~

- 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 induces apoptosis in bovine pre-implantation embryos
  Hansen PJ, et al. Reproduction 133(6) 1129, 2007
- Oocytes exposed to TNF-α during maturation developed fewer blastocysts & increased blastomere apoptosis >9 cell stage.
  Hansen PJ, et al. Am J Reprod Immunol, 50(5) 380, 2003
- Thiazolidinediones ↓ TNF-α
  McVeigh GE, et al. Br J Pharmacol, 153(4), 2008
- 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 Hepatobilliary Pancreeat Dis Int. 7(2), 179, 2008

Conclusions

- PCOS is a multifaceted condition requiring a multidisciplinary approach
  - —Varying presentations
  - —Dermatologic sequalae
  - —Long-term consequences
    - Genetic and pre-natal implications
    - Metabolic Syndrome
    - Reproductive Complications
- Infertility
  - —Common endocrinopathy in pre-menopausal women, causing menstrual irregularities and hirsutism
  - —Multiple treatments available with potentially successful outcomes

PCOS *Conclusion*

- "We know how to speak many falsehoods which resemble real things, but we know, when we will how to speak true things."

  Hesiod

- "Everything should be made as simple as possible, but not simpler."

  Albert Einstein