

PCOS Overview

- ◆ Definition
 - Ultrasound Findings
 - Hypothalamic-Pituitary-Ovarian Axis abnormalities
 - Insulin resistance
- ◆ Diagnosis
- ◆ Treatment Options
 - Fertility
 - Menstrual disturbances
 - Hirsutism

PCOS Objectives

- ◆ To provide an overview of current thinking and research
- ◆ To help you better understand this condition
- ◆ To allow you to be an active participant in your patients medical care

PCOS Definition

POLYCYST OVARY SYNDROME is a generic description for a broad spectrum of clinical and morphological findings in women with an endocrine dysfunction, specifically abnormal androgen production and metabolism.

PCOS Symptoms

Symptom	Percent
Obesity	~45
Hirsutism	~65
Virilization	~20
Cyclic Menses	~15
Abnormal menses	~30
Amenorrhea	~50
Dysmenorrhea	~20
Biphasic BBT	~15
Infertility	~75

Percent

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

PCOS Health Risks

- ◆ More likely to have hysterectomy Dahlgren E, et al: Fertil Steril 57:505, 1992
- ◆ Coronary heart disease risk factors significantly ↑ 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

PCOS

Sequelae

- ◆ 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
Birdsall MA, et al: Ann Intern Med 126:32, 1997
- ◆ PCOa present in 42% of CVD patients



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



PCOS

Findings

- | | | |
|--|---|---|
| <p>Physical</p> <ul style="list-style-type: none"> ◆ Obesity ◆ Hirsutism ◆ Acanthosis ◆ Abnormal menses ◆ Acne | <p>Biochemical</p> <ul style="list-style-type: none"> ◆ ↑ Androgen <ul style="list-style-type: none"> ■ Testosterone ■ DHEAS ■ Androstenedione ■ 17OH progesterone ◆ ↓ SHBG ◆ ↑ LH ◆ Insulin/Glucose ◆ ↑ PAI-1 ◆ ↑ Lipids | <p>Ultrasound</p> <ul style="list-style-type: none"> ◆ Necklace sign ◆ ↑ Ovarian volume ◆ Antral follicle count ◆ Doppler blood flow changes |
|--|---|---|



PCOS

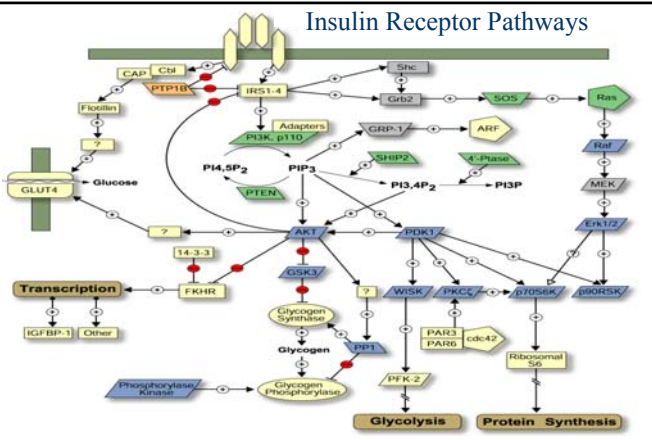
Insulin Connection

- ◆ 30% of obese PCOS women have ↓ glucose tolerance by their 30's
- ◆ Insulin-mediated glucose uptake is ↓ 35-40%
- ◆ ↓ glucose-stimulated insulin release (*↓ β-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



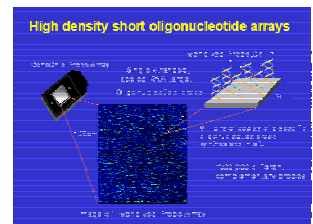
Insulin Receptor Pathways



Insulin Resistance Gene Chip

- ◆ 210 genes in metabolic pathways related to insulin resistance

- | | |
|-------------------------|---------------------------|
| • Signaling | • Glucose uptake |
| • Glucose oxidation | • Glucose storage |
| • Fat uptake | • Fat storage |
| • Fat oxidation | • Cytoskeletal components |
| • Transcription factors | |



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



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
- ◆ PCO appearance associated with testosterone, androstenedione and glucose clearance

Anders Y et al: *Contracept Fertil Sex* 23:415, 1995

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, metformin, thiazolidinediones
- ◆ Testosterone conversion → *5 α -reductase enzyme*
 - Finasteride
- ◆ Androgen receptor
 - Flutamide, spironolactone, CPA
- ◆ Hair Follicle
 - Vaniqa



PCOS

Exercise

- ◆ Peripheral muscle cells metabolize 80% of glucose
- ◆ Aerobic exercise
 - 3-4x/wk 20-30 min/session
 - Burns 100-200 kcal
 - 40% improvement in insulin sensitivity within 48 hrs.

DeFronzo RA, et al: *Diabetes* 36:1379, 1987; Segal KR, et al: *J Appl Physiol* 71:2502, 1991



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.”

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



The Diet Dilemma



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



PCOS *Dietary Recommendations*

- ♦ Focus on lowering dietary fat as a means for promoting negative energy balance has led to an underestimation of the potential role of dietary composition in promoting reductions in energy intake and weight loss

Roberts SB, et al: J Am Coll Nutr 21:140S, 2002

- ♦ 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 effect than low fat in obese children

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



PCOS *Dietary Sequelae*

- ♦ 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

Willett WC, et al: Am J Clin Nutr 75:492, 2002



PCOS *Dietary Recommendations*

- ♦ 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

- ♦ 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, 2003



PCOS *Dietary Recommendations*

- ♦ 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.

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



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



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 β-cell failure

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



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
- ♦ TZD (*thiazolidinedione*) ↓ FFA, TG, LDL-oxidation, PAI-1, ± BP
- ♦ Metformin & TZD may be combined
- ♦ Hypoglycemia results from diet and too little, not too much metformin or TZD
- ♦ ↓ insulin may improve menstrual cyclicity
 - ↓ endometrial cancer risk
 - ↓ androgens



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, black adults have 60% greater risk and Hispanic adults have 90% greater risk



PCOS *Fertility Treatment Options*

- ♦ Diet
- ♦ Exercise
- ♦ Insulin sensitizer
- ♦ Ovulation induction
 - Clomiphene/letrozole
 - Gonadotropins
 - GnRH-agonist/gonadotropins
- ♦ Ovarian drilling
- ♦ Assisted Reproductive Technology (IVF)



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%



PCOS

Injectable Gonadotropins

- ◆ Birth control pretreatment
- ◆ GnRH-agonist vs antagonist
- ◆ Low dose treatment (*multidose vials*)
- ◆ Low dose hCG



Avoiding Multiple Births and OHSS

- ◆ Follicular reduction
- ◆ Conversion to IVF
- ◆ Oocyte cryopreservation
- ◆ Cycle cancellation



Metformin

GRS Treatment Criteria

- ◆ 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



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

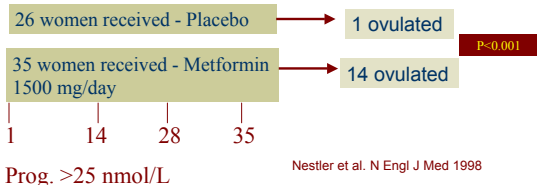
GRS Metformin Protocol

- ◆ Metformin 500 mg XR 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 tid or add Avandia/Actos (check ALT)
 - Letrozole/clomiphene
 - Ovarian drilling
 - Low dose injectables

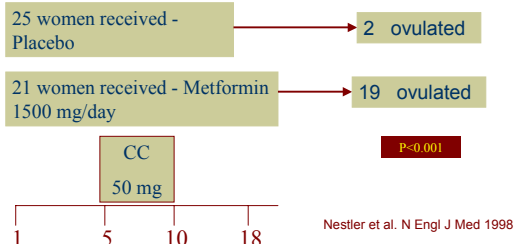


PCOS *Metformin & Ovulation*

61 PCOS women with BMI >28



Ovulation Induction *Metformin With Clomiphene*



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%) and pregnancy rates (63% vs 36%, NS)
 - Pregnancy in women who ovulated appeared higher in metformin patients (75% vs 44%, p=0.054)

Lavole 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

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 *Conclusion*

- “We know how to speak many falsehoods which resemble real things, but we know, when we will how to speak true things.”
- “Everything should be made as simple as possible, but not simpler.”

Hesiod

Albert Einstein