Forty-first Annual
Postgraduate Program

November 8, 2008
San Francisco, CA

Impact of Metabolic Syndrome on Polycystic Ovary Syndrome

Course 7

Developed in
Cooperation with the
Androgen Excess
Special Interest Group

Sponsored by the
American Society for
Reproductive Medicine

Course 7: November 8, 2008

Impact of Metabolic Syndrome on Polycystic Ovary Syndrome

Dear Postgraduate Course Participant:

For the first time, this year you will be asked to complete a post-course quiz on the content of the course. Upon completion of the quiz, which is identical to the pre-course quiz, you will be directed automatically to a course evaluation. You are asked to complete the quiz and the evaluation. This year, the quiz is for informational purposes only and will not be used to determine your CME credits. CME credits will be based only on the lectures you attend and evaluate.
For your information, the quiz is printed at the back of this syllabus volume.

You will receive an email directing you to log-in, complete the post-course quiz and course evaluation, and claim your CME/CE Credits and/or ACOG Cognates. In order to claim ACOG Cognates, you will be required to provide your 10 digit ACOG Membership Number.

The email link to report is unique to you. Please DO NOT forward the link. Any difficulties, please email *pfenton@asrm.org*

Deadline for reporting credits: December 10, 2008.

Continuing Medical Education

Continuing medical education is a lifelong learning modality to enable physicians to remain current with medical advances. The goal of ASRM is to sponsor educational activities that provide learners with the tools needed to practice the best medicine and provide the best, most current care to patients.

As an accredited CME provider, ASRM adheres to the Essentials and policies of the Accreditation Council for Continuing Medical Education (ACCME). CME activities now must first, address specific, documented, clinically important gaps in physician knowledge, competence or performance; second, be documented to be effective at increasing physician knowledge, skill or performance; and third, conform to the ACCME Standards for Commercial Support.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Developed in Cooperation with the

ANDROGEN EXCESS SPECIAL INTEREST GROUP
AND THE ANDROGEN EXCESS SOCIETY
ANNUAL MEETING POSTGRADUATE COURSE
SAN FRANCISCO, CA
November 8, 2008

"IMPACT OF METABOLIC SYNDROME ON POLYCYSTIC OVARY SYNDROME"

Chair: **Frank González, M.D.**
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All speakers at the 2008 ASRM Annual Meeting and Postgraduate Courses were required to complete a disclosure form. These disclosures were reviewed and potential conflicts of interest resolved by the Subcommittee on Standards of Commercial Support of the Continuing Medical Education Committee. The faculty has revealed the following information as potential conflicts of interest:

Frank González, M.D.: Nothing to disclose

Jean-Patrice Baillargeon, M.D., M.Sc. : GSK : Consultant, Speaker

Enrico Carmina, M.D.: Nothing to disclose

This activity may include discussion of off-label or otherwise non-FDA approved uses of drugs or devices.

Accreditation statement:
The American Society for Reproductive Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation statement:
The American Society for Reproductive Medicine designates this educational activity for a maximum of 6.5 *AMA PRA Category 1Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

American College of Obstetricians and Gynecologists (ACOG)
The American College of Obstetricians and Gynecologists has assigned 7 cognate credits to this activity.

***

Please turn off/mute cell phones and pagers during the postgraduate course and all Annual Meeting sessions.

Thank you.

IMPACT OF METABOLIC SYNDROME ON POLYCYSTIC OVARY SYNDROME

NEEDS ASSESSMENT AND COURSE DESCRIPTION

Polycystic ovary syndrome (PCOS) no longer is merely a disorder of ovulatory dysfunction. One in 15 women worldwide suffers from PCOS, with a significant number of these women carrying the concomitant diagnosis of metabolic syndrome. Many physicians do not appreciate the association between PCOS and metabolic syndrome. Therefore, it is critical for practitioners in reproductive medicine, including reproductive endocrinologists, general obstetrician-gynecologists and family practitioners, to familiarize themselves with this association and the clinical manifestations of metabolic dysfunction in order to improve the long-term health of women with PCOS.

This course will review the latest concepts and management strategies related to metabolic syndrome when associated with PCOS. An exploration into the current diagnostic criteria, prevalence and association of metabolic syndrome as it relates to PCOS will be conducted. The faculty will utilize the most current evidence supporting the association between these two disorders in order to promote early diagnosis and treatment of the components of metabolic syndrome that most negatively impact the health of women with PCOS. This course will provide the participant the foundation for making these critical diagnoses in the office and for determining appropriate, often multidisciplinary treatment plans.

LEARNING OBJECTIVES

At the conclusion of this course, participants should be able to:

1. Describe the components of metabolic syndrome and how it is associated with PCOS.
2. Develop sound multidisciplinary treatment plans for patients with PCOS and concomitant metabolic syndrome.
3. Recommend when surgical intervention versus medical management is appropriate therapy.

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"IMPACT OF METABOLIC SYNDROME ON POLYCYSTIC OVARY SYNDROME"

Frank González, M.D., Chair

Saturday, November 8, 2008

08:15 – 08:30	Course Introduction and Orientation **Frank González, M.D.**
08:30 – 09:05	Overview of Metabolic Syndrome: Diagnosis and Prevalence in Polycystic Ovary Syndrome **Frank González, M.D.**
09:05 – 09:15	Questions and Answers
09:15 – 09:50	Type 2 Diabetes Mellitus and Polycystic Ovary Syndrome **Jean-Patrice Baillargeon, M.D., M.Sc.**
09:50 – 10:00	Questions and Answers
10:00 – 10:30	Break
10:30 – 11:05	Dyslipidemia and Cardiovascular Disease in Polycystic Ovary Syndrome **Jean-Patrice Baillargeon, M.D., M.Sc.**
11:05 – 11:15	Questions and Answers
11:15 – 11:50	Obesity as a Component and Contributor to Metabolic Syndrome in Polycystic Ovary Syndrome **Enrico Carmina, M.D.**
11:50 – 12:00	Questions and Answers
12:00 – 13:00	Lunch
13:00 – 13:45	Inflammation and Its Relation to Insulin Resistance and Atherogenesis in Polycystic Ovary Syndrome **Frank González, M.D.**
13:45 – 14:00	Questions and Answers

Saturday, November 8, 2008 (continued)

14:00 – 14:45	Lifestyle Modification: Prescription #1 for Managing Metabolic Syndrome in Polycystic Ovary Syndrome **Enrico Carmina, M.D.**
14:45 – 15:00	Questions and Answers
15:00 – 15:30	Break
15:30 – 16:05	Medical Management of Metabolic Syndrome in Polycystic Ovary Syndrome **Jean-Patrice Baillargeon, M.D., M.Sc.**
16:05 – 16:15	Questions and Answers
16:15 – 16:50	Surgical Management of Obesity to Ameliorate Metabolic Syndrome in Polycystic Ovary Syndrome **Frank González, M.D.**
16:50 – 17:00	Questions and Answers

OVERVIEW OF METABOLIC SYNDROME: DIAGNOSIS AND PREVALENC IN POLYCYSTIC OVARY SYNDROME

Frank González, M.D.
Department of Obstetrics and Gynecology
College of Medicine, Mayo Clinic
Rochester, MN

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Diagnose metabolic syndrome in women with PCOS.
2. Describe the increased prevalence of metabolic syndrome in women with PCOS, particularly in the U.S., due to increased body weight.
3. Describe the impact of inflammation and the utility of measuring C-reactive protein to determine the presence of metabolic syndrome in women with PCOS.

Overview of Metabolic Syndrome: Diagnosis and Prevalence in Polycystic Ovary Syndrome

Frank González, M.D.
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
College of Medicine, Mayo Clinic
Rochester, MN

MAYO CLINIC

Learning Objectives

At the conclusion of this presentation, participants should be able to:

1. Diagnose metabolic syndrome in women with PCOS
2. Describe the increased prevalence of metabolic syndrome in women with PCOS, particularly in the U.S., due to increased body weight
3. Describe the impact of inflammation and the utility of measuring C-reactive protein to determine the presence of metabolic syndrome in women PCOS

Disclosure

Frank González, M.D.

No Disclosures

Polycystic Ovary Syndrome

Definition:

- Common hyperandrogenic endocrine abnormality of unknown etiology
- Strong familial aggregation suggests a genetic basis for the disorder
- Environmental factors such as modern dietary patterns and a sedentary lifestyle *that promote* ***obesity*** can initiate or exacerbate the signs and symptoms of the disorder

Polycystic Ovary Syndrome

Prevalence:

- As many as 10% of premenopausal women are afflicted regardless of ethnicity
- It is the most common cause of female infertility

Polycystic Ovary Syndrome

Diagnostic Criteria (2 of the following 3)*

- Hyperandrogenism – either skin manifestations of androgen excess - or - hyperandrogenemia
- Chronic anovulation
- Polycystic ovarian morphology on ultrasound

- AND -

- Exclusion of phenotypically similar androgen excess disorders

*2003 Rotterdam Consensus Conference

Insulin Resistance in PCOS

- Insulin resistance is a common feature, affecting 70% of women with PCOS
- The compensatory hyperinsulinemia is considered to be a cause of the hyperandrogenism and anovulation
- Obesity, a promoter of insulin resistance, is evident in ~52%-64% of affected individuals

Insulin Resistance in PCOS

- Insulin resistance is ***greatest*** in the obese, regardless of whether PCOS is present
- Insulin resistance has also been documented in lean women with PCOS
- Hyperinsulinemia in the obese is ***both*** fasting and postprandial
- Only postprandial hyperinsulinemia is evident in lean women with PCOS

1996 - Morales et al. J Clin Endocrinol Metab 81:2854

Metabolic Syndrome and PCOS

- Insulin resistance is often associated with a constellation of cardiovascular risk factors referred to as metabolic syndrome
- Definition of metabolic syndrome based on the National Cholesterol Education Program Adult Treatment Panel III – presence of at least 3 of the following 5 conditions:
  - Abdominal obesity (waist circumference >88 cm)
  - Serum triglycerides ≥150 mg/dl
  - Serum high density lipoprotein-C < 50 mg/dl
  - Blood pressure ≥130/>85 mm Hg
  - Fasting glucose level ≥110 mg/dl

2001 – NCEP ATP III JAMA 285:2486

Metabolic Syndrome and PCOS

- Individuals with metabolic syndrome have a significantly higher risk of coronary artery disease and all-cause mortality, even in the absence of baseline cardiovascular disease or type 2 diabetes
- Prevalence of metabolic syndrome
  - 23% in the general female population
  - As high as 47% in women with PCOS
- Women with PCOS have an 11-fold increased risk of metabolic syndrome compared to age-matched contemporary controls

2002 – Ford et al. JAMA 287:356
2005 – Dokras et al. Obstet Gynecol 106:131

Metabolic Syndrome and PCOS

- Young women with PCOS (< age 30) also have a high prevalence of metabolic syndrome (24%) compared to age-matched controls (0%) and women in the NHANES study (6.7%)
- Truncal obesity is the most common component of the metabolic syndrome in women with PCOS

2005 – Dokras et al. Obstet Gynecol 106:131
2006 – Ehrmann et al. J Clin Endocrinol Metab 91:48

Metabolic Syndrome and PCOS

In a retrospective study of 106 women with PCOS

- 43% met the criteria for metabolic syndrome (n=46)
- Acanthosis nigricans was more frequent in women with PCOS with metabolic syndrome
- Free testosterone but not total testosterone was higher in women with PCOS with the metabolic syndrome
- Sex hormone-binding globulin was lower in women with PCOS with the metabolic syndrome
- In essence, women with PCOS with metabolic syndrome had features reflecting more severe insulin resistance

2004 – Apridonidze et al. J Clin Endocrinol Metab 90:1929

Metabolic Syndrome and PCOS

- In a prospective study of 282 Sicilian women of reproductive age with PCOS compared to 85 ovulatory controls
  - Prevalence of metabolic syndrome in women with PCOS was only 8.2%, compared to 2.4% in controls
  - Lower body weight in Sicilian women with PCOS (mean BMI 27 kg/m^2) most likely accounted for the lower prevalence of metabolic syndrome, compared to American women with the disorder

2006 – Carmina et al. Eur J Endocrinol 154:141

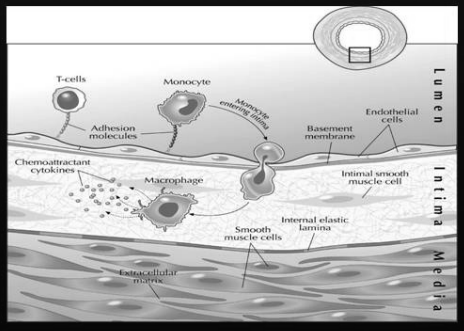
Metabolic Syndrome and Inflammation

- Metabolic syndrome is a major risk factor for cardiovascular disease
- Atherosclerosis is the progenitor of cardiovascular disease
- Molecular mechanisms related to inflammation are responsible for the development of atherosclerosis

2002 – Libby et al. Nature 142:868

Metabolic Syndrome and Inflammation

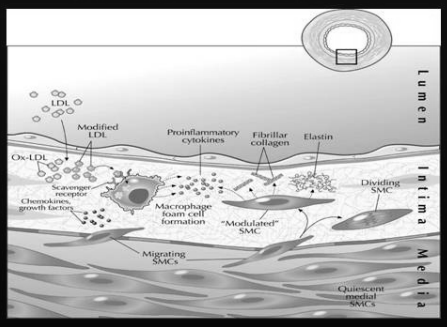
Formation of a nascent atherosclerotic lesion



2006 - Libby et al. J Am Coll Cardiol 48:A33

Metabolic Syndrome and Inflammation

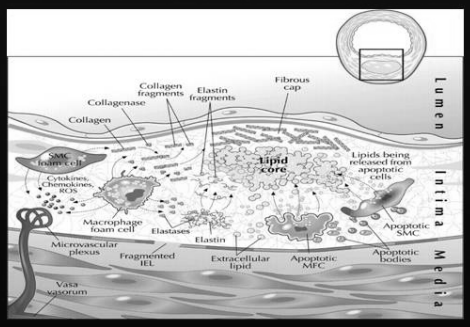
Formation of the fibrofatty plaque



2006 - Libby et al. J Am Coll Cardiol 48:A33

Metabolic Syndrome and Inflammation

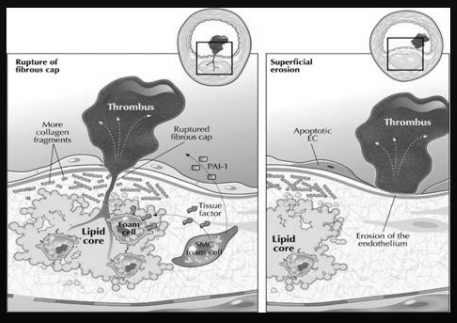
Maturation of the atherosclerotic plaque



2006 - Libby et al. J Am Coll Cardiol 48:A33

Metabolic Syndrome and Inflammation

Thrombotic complications of atherosclerosis



2006 - Libby et al. J Am Coll Cardiol 48:A33

Metabolic Syndrome and Inflammation

- C-reactive protein (CRP) is a major predictor of atherosclerosis and cardiovascular disease in asymptomatic individuals
- CRP may also play a functional role by promoting the uptake of lipids into foamy macrophages within atherosclerotic plaques
- Measurement of plasma CRP levels has been proposed as a criterion for defining the metabolic syndrome

2000 – Ridker et al. N Engl J Med 342:836
2001 – Zwaka et al. Circulation 103:1194

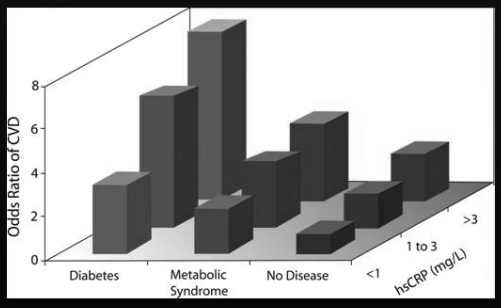
Metabolic Syndrome and Inflammation

- CRP levels were measured in a cohort of 14,719 apparently healthy women followed for 8 years
- 24% of the cohort had metabolic syndrome based on ATP III criteria
- A CRP level >3 mg/L was found to be equally predictive of a cardiovascular event compared to the ATP III criteria

2003 – Ridker et al. Circulation 107:391

Metabolic Syndrome and Inflammation

Odds ratios of cardiovascular disease in diabetic patients with metabolic syndrome in relation to CRP levels



2006 - Libby et al. J Am Coll Cardiol 48:A33

CRP Levels in PCOS

In a prospective study of 116 women with PCOS compared to 94 ovulatory controls

- CRP levels were increased in women with PCOS (5.5 mg/L) compared to controls (2.0 mg/L)
- CRP levels were positively correlated with BMI in women with PCOS ($r = 58$; $p < 0.05$)

2004 – Boulman et al. J Clin Endocrinol Metab 89:2160

Conclusion

- Abnormal parameters in body habitus, blood pressure, fasting lipids and glycemic status define the metabolic syndrome in women, independent of PCOS
- The prevalence of metabolic syndrome in women with PCOS in the U.S. is 2-fold higher compared to the general population
- The prevalence of metabolic syndrome in women with PCOS in Sicily is much lower compared to the U.S. due to their lower body weight, most likely related to a healthier lifestyle
- Inflammation is a promoter of cardiovascular disease
- Elevated CRP level is a marker of cardiovascular disease that also defines metabolic syndrome in women with PCOS

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12. Ridker PM, Buring JE, Cook, NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003: 107:391-7.
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14. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages; implications for atherosclerosis. Circulation 2001; 103:1194-7.

NOTES

NOTES

TYPE 2 DIABETES MELLITUS AND POLYCYSTIC OVARY SYNDROME

Jean-Patrice Baillargeon, M.D., M.Sc.
Department of Internal Medicine
University of Sherbrooke
Sherbrooke, Quebec
Canada

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the risks for type 2 diabetes in PCOS.
2. Compare the accuracy of the various methods to screen for type 2 diabetes.
3. Discuss the implications of the diagnosis of type 2 diabetes in the management of PCOS.

Type 2 Diabetes Mellitus and Polycystic Ovary Syndrome

Jean-Patrice Baillargeon, M.D.,M.Sc.
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Sherbrooke, Quebec
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DISCLOSURE

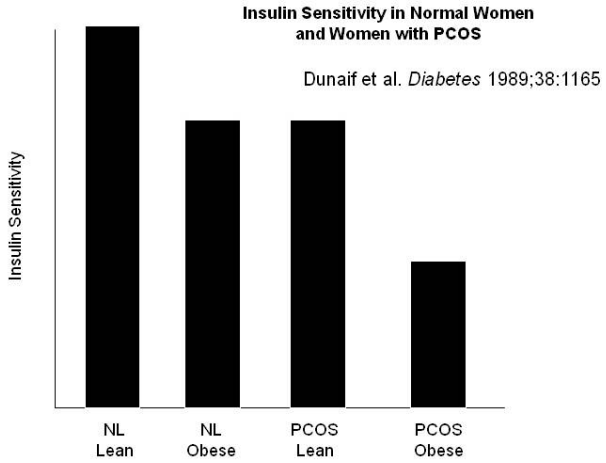
Jean-Patrice Baillargeon, M.D., M.Sc.

Received honoraria for conferences from:

Glaxo Smith Kline and Abbott Pharmaceuticals

Insulin Resistance and PCOS

- Hyperinsulinemic insulin resistance is an almost universal feature of women with PCOS
- PCOS is usually associated with an intrinsic form of insulin resistance in addition to the insulin resistance due to obesity
- Hyperinsulinemic insulin resistance occurs in both obese and nonobese women with PCOS



Insulin Resistance in Women With PCOS

Insulin sensitivity decreases

↓

Insulin release and circulating insulin increase proportionately

↓

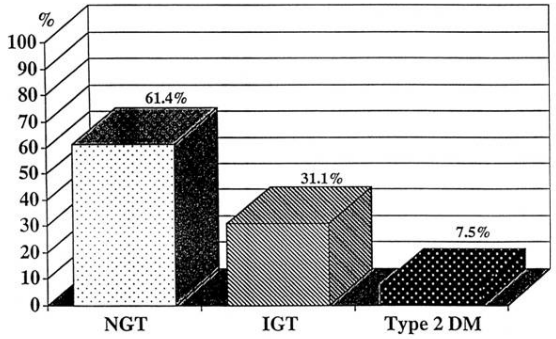
Normal glucose tolerance

↓

COMPENSATORY HYPERINSULINEMIC INSULIN RESISTANCE

Prevalence and Incidence of Glucose Intolerance in PCOS

Glucose Tolerance (by OGTT)
in 254 Women with PCOS 14-44 Years Old



Legro RS et al. *J Clin Endocrinol Metab* 1999;84:165

PCOS and Type 2 Diabetes

- **Cohort studies of women with PCOS in the U.S.**
  - **Prevalence of impaired glucose tolerance (31-35%) & type 2 diabetes (7.5-10.0%) is higher in women with PCOS compared to the general population (1.6% & 2.2% per NHANES III study)**
    Ehrmann DA, et al. *Diabetes Care 1999;22:141 & JCEM 1999; 84:165*
  - **Prevalence of impaired glucose tolerance (30%) & type 2 diabetes (7.4%) is also high in adolescents with PCOS**
    Palmert MR, et al. *J Clin Endocrinol Metab 2002;87:1017*
- **Prevalence of type 2 diabetes in perimenopausal women with a history of PCOS is 4-fold higher compared to controls (32% vs. 8%)**
  Cibula D, et al. *Hum Reprod* 2000;15:785

PCOS and Type 2 Diabetes

- **Australian women with PCOS followed for 6.2 yrs:**
  - **2.2 % annual conversion rate from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) or type 2 diabetes (DM2)**
  - **8.7% annual conversion rate from IGT to DM2**

Norman RJ, et al. *Hum Reprod* 2001;16:1995

- **A prospective controlled study:**
  - **71 PCOS patients and 23 controls followed for 2-3 yrs**
  - **In women with PCOS at baseline, 37% had IGT and 10% had DM2**
    - **16% conversion/year from NGT to IGT**
    - **2% conversion/year from IGT to DM2**
    - **2-fold increase compared to controls**

Ehrmann DA, et al. *J Clin Endocrinol Metab* 2005;90:3236

PCOS and Type 2 Diabetes

- **Larger prospective controlled study:**
  - **149 PCOS patients & 166 controls followed for 8 years**
  - **Diagnosis of DM2 was made by fasting glucose levels or reported history**
  - **Among 242 white women, aged 40-59 yrs:**
    - **6.5 increase in relative risk when adjusted for age**
    - **4.0 increase in relative risk when also adjusted for BMI**
    - **25-36% population-attributable risk based on a 6-10% prevalence of PCOS in the general population**

Talbott EO, et al. *J Women's Health* 2007;16:191

PCOS and Type 2 Diabetes

- **Nurses' Health Study II (NHSII):**
  - **101,073 women followed for 8 years**
  - **Conversion rate to DM2 was ≈ 2-fold higher in oligomenorrheic women, independent of weight**

Solomon CG, et al. *JAMA* 2001;286:2421

PCOS and Type 2 Diabetes

1/3-1/2 of obese women with PCOS develop IGT or DM2 by the age of 30

At any one time:

- >3 million women with PCOS will have IGT
- >1 million women with PCOS will have DM2

Prevalence of PCOS in Type 2 Diabetes

- 25-28% of premenopausal women with DM2 have PCOS, which is frequently undiagnosed

Conn JJ, et al. *Clin Endocrinol* 2000;52:81
Peppard HR, et al. *Diabetes Care* 2001;24:1050

- 82% of premenopausal women with DM2 have anatomic evidence of polycystic ovaries

Conn JJ, et al. *Clin Endocrinol* 2000;52:81

PCOS and Gestational Diabetes

- **Large population-based study:**
  - **1,542 PCOS patients and 84,882 controls**
  - **Prevalence of gestational diabetes (GDM):**
    - **14.3% in women with PCOS compared to 5.9% in controls**
    - **2.4-fold increased odds of having GDM in women with PCOS, independent of age, race/ethnicity and multiple gestation**

Lo JC, et al. *Diabetes Care* 2006;29:1915

- **Confirmed the results of a previous meta-analysis that revealed a 2.9-fold increased odds of having GDM in women with PCOS**

Boomsma CM, et al. *Hum Reprod Update* 2006;12:673

Screening for Glucose Intolerance in PCOS:

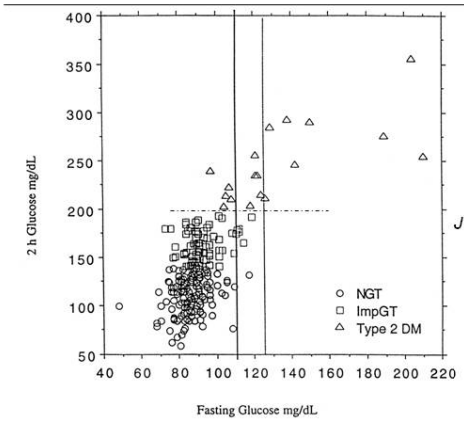
What's the Best Test?

ADA Recommendations

- **Screening for DM2 in asymptomatic individuals under the age of 45 should be performed if they:**
  - Are overweight (BMI > 25 kg/m^2)
  - Have additional risk factors, including PCOS
- **Measurement of a fasting glucose level is the recommended screening test**
- **Performance of an oral glucose tolerance test (OGTT) may be considered in patients with impaired fasting glucose (IFG), defined as a fasting glucose level ≥ 100 mg/dl**

Diabetes Care 2007;30:S4

Scattergram of Fasting and 2 Hour OGTT Glucose Levels in 254 Women with PCOS



Legro RS et al.
J Clin Endocrinol Metab
1999; 84:165

Abnormal Glucose Tolerance Screening in PCOS

Population-based study:

- **OGTT administered to 105 consecutive women with PCOS referred to an academic reproductive endocrine clinic**
- **Prevalence of abnormal glucose tolerance was 28%**
  - **23% had IGT and 5% had DM2**
  - **Mean age of 28 years (range 14-47 years)**
  - **Mean BMI of 35.5 kg/m^2 (range 19.0-54.8 kg/m^2)**
- **If ADA recommendations were to be followed, 1 out of every 7 women with PCOS would have a missed diagnosis of abnormal glucose tolerance!**

Baillargeon JP et al. Can Med Ass J 2007;176:933

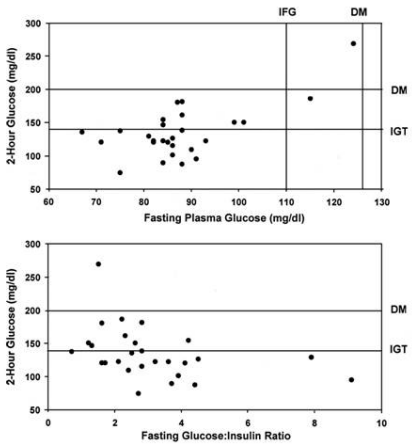
Performance of 2-hour glucose tolerance test compared with fasting glucose in PCOS

Baillargeon JP et al. *Can Med Ass J* 2007;176:933

2-h glucose test result ≥ 140 mg/dL

Fasting test result ≥ 100 mg/dL	Yes	No	Totals	
Yes	14	1	15	PPV: 14/15 = 93.3%
No	15	75	90	NPV: 75/90 = 83.3%
Totals:	29	76	*n* = 105	
	Sensitivity = 14/29 = 48.3%	Specificity = 75/76 = 98.7%		

Glucose Tolerance in Adolescents with PCOS



Palmert MR et al. *J Clin Endocrinol Metab* 2002; 87:1017

Screening Recommendations

- Measure glucose 2 hours after oral ingestion of a 75 gram glucose beverage†
  - IGT: 140-199 mg/dl
  - DM2: ≥ 200 mg/dl
- Perform regardless of BMI* -or- on all who are obese, but only those who are lean with other risk factors†
- Fasting serum glucose levels, insulin levels and hemoglobin A1c are NOT HELPFUL!

*ACOG, *Obstet Gynecol* 2002;100:1389
Salley KE, et al. AE and PCOS Society, *J Clin Endocrinol Metab* 2007;92:4546
†Revised 2003 consensus ASRM & ESHRE, *Fertil Steril* 2004;81:19

Screening Recommendations

Follow-up of women with PCOS for detection of abnormal glucose tolerance based on expert opinions (not evidence based)*

- Rescreen patients with NGT at least every 2 years or earlier if additional risk factors exist
- Screen patients with IGT annually for the development of DM2

**AE and PCOS Society*, Salley KE, et al. *JCEM* 2007;92:4546

Screening Recommendations During Pregnancy

- Women with PCOS are at high risk for developing GDM
- Screening for GDM upon confirmation pregnancy is warranted in women with PCOS
  - A one-step approach with an OGTT is favored
  - Diagnosis of GDM is made following a 100g OGTT when ≥ 2 glucose values exceed the following:
    - Fasting: 95 mg/dl
    - 1 hour: 180 mg/dl
    - 2 hour: 155 mg/dl
    - 3 hour: 140 mg/dl
- If the OGTT is normal, repeat between 24 and 28 weeks gestatation

Diabetes Care 2007;30:S4

Screening for Glucose Intolerance in PCOS:

Why is it important?

Women with PCOS Seeking Fertility

- Screening is important because many women with antenatal IGT also have the definition of GDM when pregnancy occurs
- Women with antenatal IGT or DM2 should:
  - Receive dietary advice and instruction for self-monitoring blood glucose (SMBG) during the 1st pregnancy visit
  - Receive insulin therapy after 1-2 weeks if diet fails to maintain SMBG in normal ranges (fasting < 105 mg/dl or 2-hour <130 mg/dl)

Diabetes Care 2004;27:S88

Management of PCOS

- Screening is important because it changes clinical management of PCOS symptoms
- In women with PCOS who have IGT or DM2, improvement of insulin sensitivity by lifestyle modification or medical therapy can effectively:
  - Prevent DM2 in patients with IGT
  - Prevent DM2 complications, mainly cardiovascular disease
- Making the diagnosis of IGT or DM2 is a convincing argument for a patient to begin lifestyle modification, the first-line treatment for PCOS

Newly Diagnosed DM2 in Women with PCOS

- **Screening is important because it changes clinical management of the patient**
- **Women with PCOS who are newly diagnosed with DM2 should:**
  - **Receive advice regarding lifestyle modification specific to diabetes**
  - **Be instructed on SMBG**
  - **Receive metformin (or another insulin sensitizer) with the goal of achieving a hemoglobin A1c <6%**
  - **Initiate more stringent control of lipids and blood pressure**
  - **Be monitored annually for lipid status, microalbuminuria, distal polyneuropathy and ophthalmologic alterations**

Diabetes Care 2004;27:S88

CONCLUSION

Summary & Key Points

- **Glucose intolerance is highly prevalent in PCOS, even at young age**
- **Conversion to IGT is increased in PCOS**
- **Screening for glucose intolerance requires an OGTT**
- **Optimal frequency for screening has not been determined**
- **Diagnosing DM2 has an important impact on the management of PCOS and requires specific follow up**

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NOTES

DYSLIPIDEMIA AND CARDIOVASCULAR DISEASE IN POLYCYSTIC OVARY SYNDROME

Jean-Patrice Baillargeon, M.D., M.Sc.
Department of Internal Medicine
University of Sherbrooke
Sherbrooke, Quebec
Canada

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the occurrence of dyslipidemia and other risk factors for cardiovascular disease in PCOS.
2. Discuss the risk of cardiovascular disease in women with PCOS.
3. Perform a suitable evaluation and implement appropriate follow-up for cardiovascular risk in women with PCOS.

Dyslipidemia and Cardiovascular Disease in Polycystic Ovary Syndrome

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DISCLOSURE

Jean-Patrice Baillargeon, M.D., M.Sc.

Received honoraria for conferences from:

Glaxo Smith Kline and Abbott Pharmaceuticals

Dyslipidemia in PCOS

Lipids in 244 Women with PCOS Compared to 244 Age-matched Controls

Variable	Cases (n = 244)	Controls (n = 244)
Age	35.3 ± 7.4	36.7 ± 7.7
Body mass index (kg/m^2)	29.9 ± 7.95	26.6 ± 6.77[a]
Waist-hip ratio	0.83 ± 0.13	0.76 ± 0.07[a]
Total cholesterol (mg/dL)	195.8 ± 32.95	185.7 ± 36.34[a]
HDL-T (mg/dL)	51.2 ± 14.74	56.1 ± 14.43[a]
HDL-2 (mg/dL)	8.4 ± 6.5	11.4 ± 7.78[a]
LDL-C (mg/dL)	119.9 ± 31.8	112 ± 32.6[a]
Insulin (μU/L)	23.3 ± 17.8	13.6 ± 8.7[a]
Triglycerides (mg/dL)	123.6 ± 88.7	87.3 ± 63.1[a]
Average systolic blood pressure (mm Hg)	113.5 ± 14.7	110.3 ± 13.1[a]
Diastolic blood pressure (mm Hg)	72.7 ± 10.5	70.8 ± 8.3[b]

[a]P < 0.01.
[b]P < .05.

Talbott E et al. *J Clin Epidemiol* 1998; 51:415

Lipids in Italian Overweight Women with PCOS Compared to Age- and BMI-matched Controls

	PCOS (n = 200)	Controls (n = 100)	P-value*
Fasting glucose (mg/dl)	95.3 ± 8.8	93.8. ± 8.6	0.16
Fasting insulin (μU/ml)	20.7 ± 4	12.6 ± 2.1	<0.001
HOMA	4.8 ± 1.1	2.91 ± 0.6	<0.001
AUC_{INS}	16 420 ± 950	4850 ± 1210	<0.001
AUC_{GLU}	12 310 ± 3580	11 720 ± 2950	0.15
AUC_{GLU}/AUC_{INS} ratio	0.7 ± 0.4	2.4 ± 0.7	<0.001
TC (mg/dl)	191.1 ± 17.4	170 ± 22.5	<0.001
LDL-C (md/dl)	117.2 ± 18.4	94.0 ± 17.9	<0.001
HDL-C (mg/dl)	42.2 ± 7.1	47.1 ± 8.6	<0.001
TG (mg/dl)	158.6 ± 33.9	144.3 ± 21.3	<0.001

Cascella T et al. *Hum Reprod* 2008; 23:153

Lipids in Women with Physician-diagnosed PCOS Compared to Age-matched Controls

A large registery study from Kaiser Permanente of Northern California

Characteristic	PCOS (n = 11,035)	No PCOS (n = 55,175)	*P* value
Cardiovascular risk factor			
Diabetes mellitus	988 (9.0)	1,136 (1.9)	<0.001
Diagnosed hypertension	1,341 (12.2)	2,693 (4.9)	<0.001
Diagnosed hypertension and/or elevated blood pressure	2,939 (26.6)	6,466 (11.7)	<0.001
Diagnosed dyslipidemia or LDL ≥ 160 mg/dl (4.14 mmol/liter)[a]	1,610 (14.6)	3,253 (5.9)	<0.001
HDL cholesterol < 40 mg/dl (1.04 mmol/liter)[b]	2,500 (22.7)	4,125 (7.5)	<0.001
Triglyceride >200 mg/dL (2.26 mmol/liter)[c]	1,769 (16.0)	2,570 (4.7)	<0.001

Lo JC et al. *J Clin Endocrinol Metab* 2006; 91:1357

Lipids in 195 Women with PCOS Compared to 62 Ethnically Matched Controls

Nonobese patients

Measurement (units)	Nonobese		
	Polycystic Ovary Syndrome (n = 42) Mean ± SD	Control Women (n = 27)	*P* Value (Adjusted for age)
Fasting insulin (μU/mL)	12 ± 4(*n* = 39)	11 ± 6(*n* = 23)	0.52
Fasting glucose (mg/dL)	83 ± 8	82 ± 5	0.87
Total cholesterol (mg/dL)	181 ± 34	156 ± 39	< 0.001
LDL-C (mg/dL)	115 ± 32	88 ± 26 (*n* = 26)	< 0.001
HDL-C (mg/dL)	45 ± 11	43 ± 9	0.99
Triglyceride (mg/dL)	103 ± 58	105 ± 74	0.99

Legro RS et al. *Am J Med* 2001; 111:607

Lipids in 195 Women with PCOS Compared to 62 Ethnically Matched Controls

Obese patients

Measurement (units)	Obese		
	Polycystic Ovary Syndrome (n = 153) Mean ± SD	Control (n = 35)	*P* Value (Adjusted for age)
Fasting insulin (μU/mL)	27 ± 16(*n* = 150)	17 ± 9(*n* = 25)	0.001
Fasting glucose (mg/dL)	89 ± 11.3	87 ± 8	0.44
Total cholesterol (mg/dL)	199 ± 39	174 ± 25	< 0.001
LDL-C (mg/dL)	130 ± 32 (*n* = 144)	117 ± 23 (n = 34)	0.006
HDL-C (mg/dL)	35 ± 10 (*n* = 152)	31 ± 14	0.002
Triglyceride (mg/dL)	194 ± 219	140 ± 88	0.04

Legro RS et al. *Am J Med* 2001; 111:607

Other Risk Factors of Cardiovascular Disease in PCOS

Blood Pressure in 244 Women with PCOS Compared to 244 Age-matched Controls

Variable	Cases (n = 244)	Controls (n = 244)
Age	35.3 ± 7.4	36.7 ± 7.7
Body mass index (kg/m^2)	29.9 ± 7.95	26.6 ± 6.77[a]
Waist-hip ratio	0.83 ± 0.13	0.76 ± 0.07[a]
Total cholesterol (mg/dL)	195.8 ± 32.95	185.7 ± 36.34[a]
HDL-T (mg/dL)	51.2 ± 14.74	56.1 ± 14.43[a]
HDL-2 (mg/dL)	8.4 ± 6.5	11.4 ± 7.78[a]
LDL-C (mg/dL)	119.9 ± 31.8	112 ± 32.6[a]
Insulin (μU/L)	23.3 ± 17.8	13.6 ± 8.7[a]
Triglycerides (mg/dL)	123.6 ± 88.7	87.3 ± 63.1[a]
Average systolic blood pressure (mm Hg)	113.5 ± 14.7	110.3 ± 13.1[a]
Diastolic blood pressure (mm Hg)	72.7 ± 10.5	70.8 ± 8.3[b]

[a] $P < 0.01$.
[b] $P < .05$.

Talbott E et al. *J Clin Epidemiol* 1998; 51:415

Diabetes & Hypertension in Women with Physician-diagnosed PCOS Compared to Age-matched Controls

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Cardiovascular risk factor			
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Lo JC et al. *J Clin Endocrinol Metab* 2006; 91:1357

Other Cardiovascular Risk Factors in PCOS

- Hypercoagulability
  - Increased PAI-1 and tPA, even in nonobese women with PCOS

Sampson M, et al *Clin Endocrinol* 1996; 45:623

- Pro-inflammatory state
  - Increased hsCRP, even in nonobese women with PCO

Bahceci M, at al *Horm Res* 2004; 62:283
Boulman N, et al *JCEM* 2004; 89:2160

- Endothelial dysfunction
  - Decreased flow-mediated vessel dilatating, even in young, nonobese women with PCOS

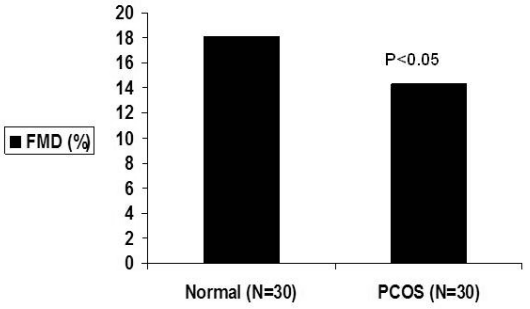
Cascella T, et al *Hum Reprod* 2008; 23:153
Orio F, et al. *JCEM* 2004; 89:4588 & Talbott EO, et al *JCEM* 2004; 89:5592

Other Cardiovascular Risk Factors in Italian Overweight Women with PCOS Compared to Age- and BMI-matched Controls

	PCOS ($n = 200$)	Controls ($n = 100$)	P-value*
Heart rate (beats/min)	77.8 ± 4.8	76.9 ± 4.5	0.11
SBP (mmHg)	118 ± 9	117 ± 8	0.35
DBP (mmHg)	80 ± 4.8	79 ± 4.6	0.08
IMT (mm)	0.46 ± 0.16	0.38 ± 0.09	<0.001
FMD (%)	13.7 + 2.3	17.8 + 2.2	<0.001
CRP (mg/l)	1.9 ± 0.8	0.8 ± 0.4	<0.001
WBC count (cell/mm^3)	7350 ± 380	5260 ± 230	<0.001
PAI-1 (IU/ml)	2.6 + 0.7	1.7 + 0.6	<0.001
Visceral fat (mm)	31.4 + 7.3	28.0 ± 6.1	<0.001

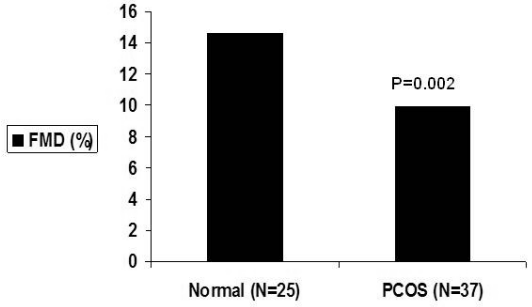
Cascella T et al. *Hum Reprod* 2008; 23:153

Flow-Mediated Dilation in Young (mean 22 yrs), Lean (mean BMI, 22 kg/m^2) Women with PCOS



Orio F et al. *J Clin Endocrinol Metab* 2004; 89:4588

Corroborated by Another Study (mean 23 yrs of Age and BMI 24 kg/m^2)



Tarkun I et al. *J Clin Endocrinol Metab* 2004; 89:5592

PCOS and Surrogate Markers of Established Cardiovascular Disease

Abnormal Markers of Established Cardiovascular Disease in PCOS

- **Coronary artery disease**
  - ↑ Coronary artery calcification
    - Young (<35 yrs of age) or nonobese women with PCOS

Shroff R, et al. *J Clin Endocrinol Metab* 2007; 92:4609
Talbott EO, et al. *J Clin Endocrinol Metab* 2004; 89:5454

- **Peripheral artery disease**
  - ↑ Carotid and femoral intima-media thickness (IMT)
    - Young (<35 yrs of age) or nonobese women with PCOS
  - ↑ Aortic calcifications
    - Nonobese women with PCOS

Cascella T, et al. *Hum Reprod* 2008; 23:153
Lakhani K, et al. *Atherosclerosis* 2004; 175:353
Vural B, et al. *Hum Reprod* 2005; 20:2409

IMT in Young (mean, 25 yrs), Overweight (mean, BMI 29 kg/m^2) Women with PCOS

	PCOS ($n = 200$)	Controls ($n = 100$)	P-value*
Heart rate (beats/min)	77.8 ± 4.8	76.9 ± 4.5	0.11
SBP (mmHg)	118 ± 9	117 ± 8	0.35
DBP (mmHg)	80 ± 4.8	79 ± 4.6	0.08
IMT (mm)	0.46 ± 0.16	0.38 ± 0.09	<0.001
FMD (%)	13.7 ± 2.3	17.8 ± 2.2	<0.001
CRP (mg/l)	1.9 ± 0.8	0.8 ± 0.4	<0.001
WBC count (cell/mm^3)	7350 ± 380	5260 ± 230	<0.001
PAI-1 (IU/ml)	2.6 ± 0.7	1.7 ± 0.6	<0.001
Visceral fat (mm)	31.4 ± 7.3	28.0 ± 6.1	<0.001

Cascella T et al. *Hum Reprod* 2008; 23:153

Independent Predictors of Increased IMT in Young, Overweight Women with PCOS

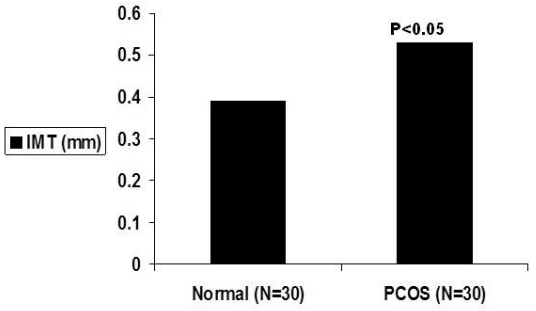
Table VI. Final model of multiple linear regression analysis of IMT as dependent variable in PCOS patients.

	Unstandardized coefficient (SE)	Standardized coefficient	P-value
VF	0.003 (0.001)	0.424	<0.001
FMD	0.009 (0.003)	0.238	0.002
CRP	0.062 (0.008)	0.663	<0.001
Constant	0.167		

Multiple linear regression analysis (stepwise method).
VF, visceral fat; FMD, flow-mediated dilation; CRP, C-reactive protein.

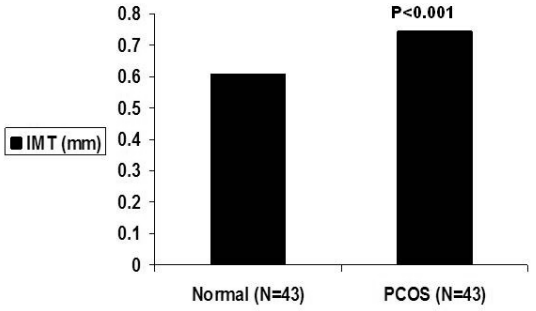
Cascella T et al. *Hum Reprod* 2008; 23:153

IMT in Young (mean, 22 yrs), Lean (mean BMI, 22 kg/m^2) Women with PCOS



Orio F et al. *J Clin Endocrinol Metab* 2004; 89:4588

Corroborated by Another Study (mean, 21 yrs and BMI 23 kg/m^2)



Vural B et al. *Hum Reprod* 2005; 20:2409

PCOS and Prevalence of Clinical Cardiovascular Disease

Prevalence of Coronary Artery Disease in Perimenopausal Women with PCOS

Table V. Prevalence of coronary artery disease (CAD), non-insulin diabetes mellitus (NIDDM) and hypertension in the PCOS and control groups

	PCOS $n = 28$		Controls $n = 752$		P-value
	Number	%	Number	%	
Coronary artery disease	6	21	38	5	$P < 0.001$
NIDDM	9	32	60	8	$P < 0.001$
Arterial hypertension	14	50	290	39	NS

NS = not significant.

Cibula D et al., *Hum Reprod* 2000; 15:785

Nurse Health Study Coronary Heart Disease

82,439 women without coronary heart disease (~34 yrs of at age at follow-up)

TABLE 2. RRs for CHD as a function of menstrual cycle regularity at ages 20–35 yr

	Menstrual cycle regularity ages 20–35 yr			
	Regular	Usually regular	Usually irregular	Very irregular
Total CHD				
No. of cases	810	327	184	96
Person-yr	715,293	264,924	126,406	49,292
Age-adjusted RR (95% CI)	1.0	1.02 (0.90–1.16)	1.25 (1.07–1.47)	1.67 (1.35–2.06)
Multivariate[a] RR (95% CI)	1.0	1.02 (0.89–1.16)	1.22 (1.04–1.44)	1.53 (1.24–1.90)
Fatal CHD				
No. of cases	248	117	52	36
Age-adjusted RR (95% CI)	1.0	1.17 (0.94–1.46)	1.16 (0.86–1.56)	2.04 (1.44–2.89)
Multivariate[a] RR (95% CI)	1.0	1.12 (0.90–1.40)	1.11 (0.82–1.50)	1.88 (1.32–2.67)

Solomon CG et al., *J Clin Endocrinol Metab* 2002; 87:2013

Screening and Follow-up for Cardiovascular Risk in Women with PCOS

Screening for Cardiovascular Risk Factors in PCOS

- **In all women with PCOS, including those who are young or nonobese:**
  - Measure waist circumference – a reflection of visceral adiposity
  - Measure blood pressure
  - Perform a complete fasting lipid profile and a 2-hour, 75 gram OGTT
  - Determine if the results are within the cut-off values for the metabolic syndrome
- **Standard recommendations for the routine assessment of cardiovascular disease are lacking – the decision to evaluate is based on symptoms**

Follow-up for Cardiovascular Risk Factors in PCOS

- Repeat blood pressure and fasting lipid profile annually
- Encourage your patients to be physically active!
  - A good functional capacity, without cardiac or lower limb symptoms, suggests the presence of healthy arterial beds
- Suggestions for prevention of cardiovascular disease will be discussed in my next lecture

CONCLUSION

Summary & Key Points

- Dyslipidemia in PCOS is characterized by ↓ HDL and ↑ TG, as well as ↑ LDL
- Other cardiovascular risk factors aggregate in PCOS
- Surrogate markers of cardiovascular disease are ↑ in women with PCOS, including those who are young or nonobese
- A few studies suggest an increased risk for clinical cardiovascular events in PCOS, which remains to be confirmed
- Existing evidence supports prompt screening and aggressive management if cardiovascular risk factors are present in women with PCOS

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NOTES

NOTES

OBESITY AS A COMPONENT AND CONTRIBUTOR TO METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

Enrico Carmina, M.D.
Department of Clinical Medicine
University of Palermo
Palermo, Italy

LEARNING OBJECTIVES
At the conclusion of this presentation, participants should be able to:

1. Describe the role of obesity in the development of metabolic syndrome in PCOS.
2. Describe the methods to assess abdominal obesity.
3. List the differences between patients with PCOS and weight-matched controls in terms of abdominal obesity.

OBESITY AS A COMPONENT AND CONTRIBUTOR TO METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

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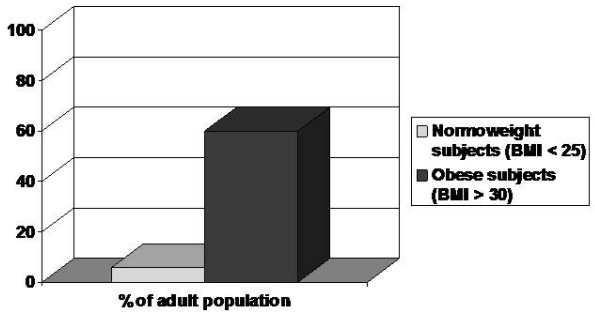
DISCLOSURE

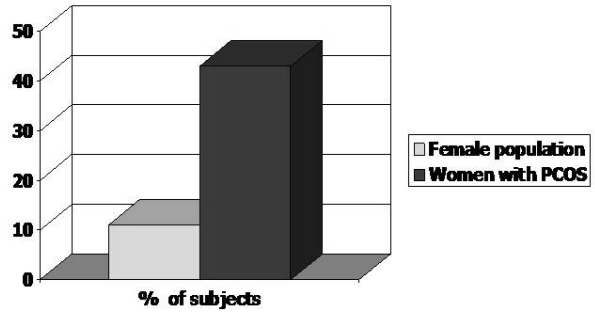
Enrico Carmina, M.D.

No disclosures

INFLUENCE OF OBESITY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE USA



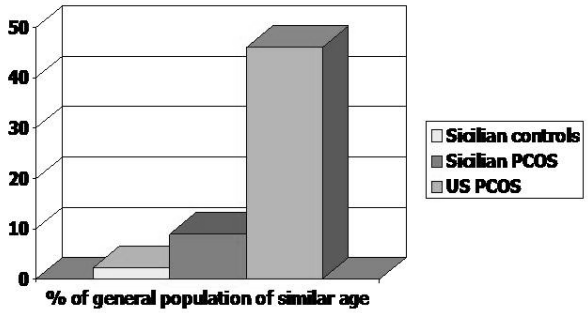
PREVALENCE OF METABOLIC SYNDROME IN THE USA DURING THIRD and FOURTH DECADE OF LIFE



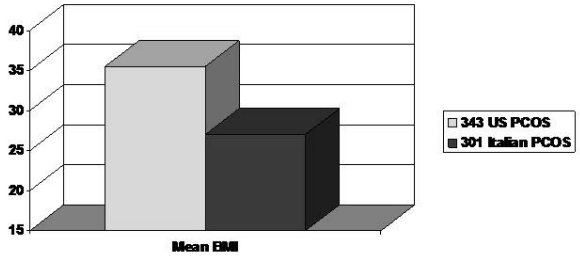
OBESITY AND METABOLIC SYNDROME

- In the general population, prevalence of metabolic syndrome is strictly related to the prevalence of obesity.
- Due to the high prevalence of obesity and insulin resistance in PCOS, the prevalence of metabolic syndrome in PCOS is 4-6 times higher than in the general population of similar age

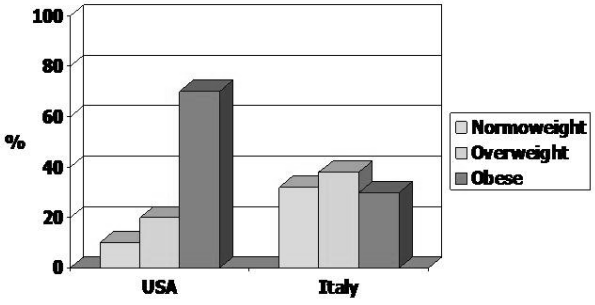
PREVALENCE OF METABOLIC SYNDROME IN SICILIAN AND U.S. WOMEN WITH PCOS



BODY WEIGHT IS LOWER IN ITALIAN WOMEN WITH PCOS THAN IN U.S. WOMEN WITH THE DISORDER



BODY WEIGHT DISTRIBUTION IN WOMEN WITH PCOS



PREVALENCE OF METABOLIC SYNDROME IN DIFFERENT POPULATIONS WITH PCOS

- Metabolic syndrome is more common in U.S. women with PCOS than in Sicilian women with PCOS
- Differences in body weight (but also in diet) determine these differences

SUBGROUPS OF OBESE SUBJECTS

Metabolically Healthy Obese (MHO)

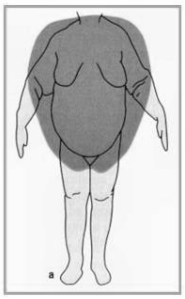
Low Visceral Fat
High BMI
High Fat mass
High Insulin Sensitivity
High HDL
Low Triglycerides

"At Risk" Obese

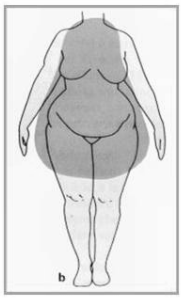
High Visceral Fat
High BMI
High Fat mass
Low Insulin Sensitivity
Low HDL
High Triglycerides

FAT DISTRIBUTION

android
centripetal



gynecoid
peripheral



DIFFERENCES IN METABOLIC AND CARDIOVASCULAR RISK DETERMINED BY FAT REGIONS

FAT AREA	RISK
VISCERAL FAT	HIGH
SUBCUTANEOUS ABDOMINAL FAT	MEDIUM
SUBCUTANEOUS LEG FAT	LOW

ABDOMINAL OBESITY AND METABOLIC SYNDROME IN PCOS

- Only abdominal obesity is related to metabolic syndrome
- BMI and total fat mass are not as reflective of metabolic syndrome compared to the amount of abdominal fat

ABDOMINAL OBESITY

Different methods may be used to demonstrate the presence of abdominal obesity:

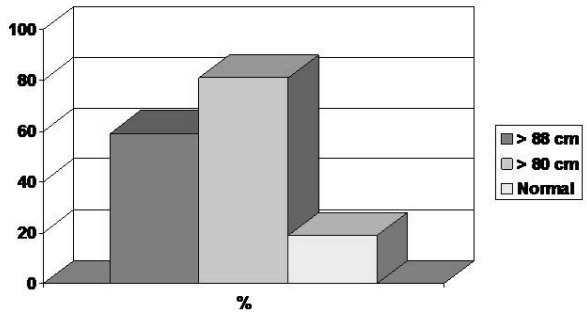
1. Measurement of waist circumference
2. CT or MRI scan
3. Abdominal ultrasounds
4. DEXA

CRITERIA FOR THE DIAGNOSIS OF METABOLIC SYNDROME IN THE FEMALE POPULATION

Risk factor	Defining level
Waist circumference	➢> 88 cm
HDL-cholesterol	➢< 50 mg/dl
Triglycerides	➢≥ 150 mg/dl
Blood pressure	➢≥ 130/>85 mm Hg
Fasting glucose	➢≥ 110 mg/dl

The syndrome is present if an individual has any three of the following five criteria
National Cholesterol Education Program Adult Treatment Panel III (JAMA 2001)

WAIST CIRCUMFERENCE IN PCOS



CT SCAN FOR EVALUATION OF ABDOMINAL OBESITY

ADVANTAGES

- The best method for determining the different abdominal fat areas
- Permits assessment of total subcutaneous abdominal fat (including posterior)
- Distinguishes between superficial and profound subcutaneous abdominal fat
- Permits assessment of visceral (omental and retroperitoneal) abdominal fat

CT SCAN FOR EVALUATION OF ABDOMINAL OBESITY

DISADVANTAGES

1. Expensive and suitable only for small research studies
2. Does not permit the assessment of total body fat
3. Does not permit the evaluation of fat distribution

ULTRASOUNDS FOR EVALUATION OF ABDOMINAL OBESITY

ADVANTAGES

1. Permits the assessment of abdominal subcutaneous and visceral fat
2. Inexpensive, easy and safe to perform

ULTRASOUND FOR EVALUATION OF FAT DISTRIBUTION

DISADVANTAGES

1. Does not assess different subcutaneous abdominal area
2. Does not assess posterior subcutaneous abdominal fat (and retroperitoneal fat)
3. Calculates quantity of abdominal fat measuring the distances of fixed points (possibility of mistakes)
4. Does not permit calculation of fat distribution
5. Operator dependent

DEXA FOR EVALUATION OF FAT DISTRIBUTION

ADVANTAGES

1. Easy and safe method
2. Permits the assessment of total fat quantity
3. Permits the assessment of total abdominal fat
4. Permits the assessment of fat in many different regions (including legs)
5. Permits calculation of fat distribution

DEXA FOR EVALUATION OF FAT DISTRIBUTION

DISADVANTAGES

1. Does not distinguish between visceral and subcutaneous abdominal fat
2. Does not distinguish between superficial and profound abdominal fat
3. The software has to be modified because it is prepared to measure truncal fat (and other tissues)

FAT QUANTITY AND DISTRIBUTION BY DEXA IN A NORMAL WOMAN (BMI 21.4 kg/m^2)

DXA Results Summary:

Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	133.33	1291.7	1627.3	1760.6	3052.3	42.3
R Arm	140.42	1112.2	1818.9	1959.4	3071.6	36.2
Trunk	444.89	4239.9	19133.7	19578.6	23818.5	17.8
L Leg	377.45	4236.0	6429.8	6807.2	11043.2	38.4
R Leg	381.49	4218.2	6770.4	7151.9	11370.1	37.1
Subtotal	1477.57	15098.0	35780.1	37257.7	52355.7	28.8
Head	508.38	816.9	2834.8	3343.2	4160.1	19.6
Total	**1985.95**	**15915.0**	**38614.9**	**40600.8**	**56515.8**	**28.2**

Sub-Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
R1	50.05	288.2	2000.6	2050.7	2338.9	12.3
R2	1.26	237.3	1925.1	1926.4	2163.6	11.0
R3	65.21	415.7	736.5	801.7	1217.4	34.1
Net	**116.53**	**907.4**	**4346.6**	**4463.1**	**5370.5**	**16.9**

FAT EVALUATION BY DEXA

	Mean	Upper normal limit
TRUNCAL FAT (g)	5200	8000
% OF TOTAL FAT	31.4	38.0
CENTRAL ABDOMINAL FAT (g)	300	520

FAT QUANTITY AND DISTRIBUTION IN AN OVERWEIGHT WOMAN WITH PCOS (BMI 28.3)

DXA Results Summary:

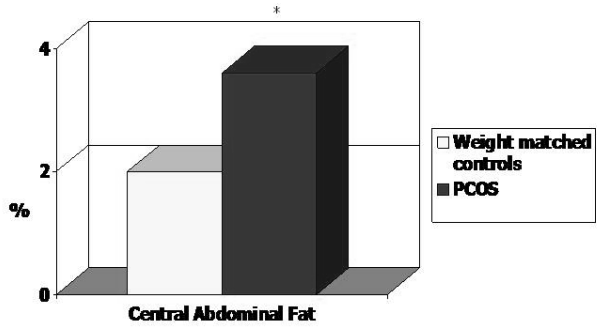
Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	139.58	4184.1	3178.8	3318.4	7502.5	55.8
R Arm	183.55	4593.0	3546.2	3729.7	8322.8	55.2
Trunk	335.74	10688.7	17134.0	17469.7	28158.4	38.0
L Leg	415.88	5502.3	9085.8	9501.6	15004.0	36.7
R Leg	434.90	5529.2	9688.6	10123.5	15652.7	35.3
Subtotal	1509.63	30497.4	42633.4	44143.0	74640.4	40.9
Head	453.20	1141.4	3830.3	4283.5	5425.0	21.0
Total	**1962.83**	**31638.8**	**46463.7**	**48426.5**	**80065.4**	**39.5**

FAT QUANTITY AND DISTRIBUTION IN AN OBESE WOMAN WITH PCOS (BMI 33.3)

DXA Results Summary:

Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	114.35	1616.9	1635.7	1750.0	3366.9	48.0
R Arm	107.80	1447.8	1288.4	1396.2	2844.0	50.9
Trunk	800.30	21999.8	26879.9	27680.2	49680.1	44.3
L Leg	442.50	9430.7	8113.1	8555.6	17986.2	52.4
R Leg	447.21	9057.5	8422.8	8870.0	17927.5	50.5
Subtotal	1912.16	43552.7	46339.8	48252.0	91804.6	47.4
Head	407.95	943.7	3213.2	3621.1	4564.8	20.7
Total	**2320.11**	**44496.4**	**49553.0**	**51873.1**	**96369.5**	**46.2**
Sub-Region	**BMC (g)**	**Fat (g)**	**Lean (g)**	**Lean+BMC (g)**	**Total Mass (g)**	**% Fat**
R1	67.09	1296.7	2722.6	2789.7	4086.4	31.7
R2	9.98	860.9	2974.5	2984.5	3845.3	22.4
R3	92.14	1157.0	1035.1	1127.2	2284.2	50.7
Net	**168.57**	**3191.5**	**6372.2**	**6540.8**	**9732.3**	**32.8**

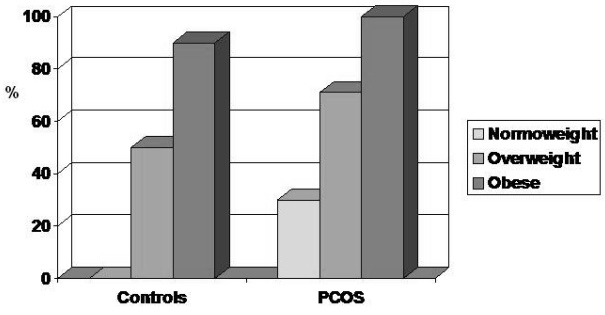
FAT DISTRIBUTION IN PCOS



FAT DISTRIBUTION IN PCOS

- Women with PCOS have increased abdominal fat
- Weight matched controls may have a lower quantity of abdominal fat in spite of having similar body mass index

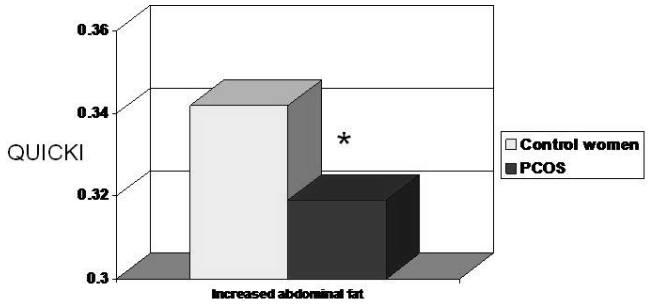
PREVALENCE OF ABDOMINAL OBESITY IN CONTROLS AND IN WOMEN WITH PCOS



ABDOMINAL OBESITY IN PCOS

- In PCOS, abdominal obesity is present in:
  - 90-100% of obese patients
  - 60-70% of overweight patients
  - 30% of normoweight patients

ABDOMINAL FAT AND INSULIN RESISTANCE IN PCOS



CONCLUSIONS

Women with PCOS have a higher prevalence of metabolic syndrome compared to the general population, due to:

- Increased prevalence of abdominal obesity
- Greater insulin resistance

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NOTES

INFLAMMATION AND ITS RELATION TO INSULIN RESISTANCE AND ATHEROGENESIS IN POLYCYSTIC OVARY SYNDROME

Frank González, M.D.
Department of Obstetrics and Gynecology
College of Medicine, Mayo Clinic
Rochester, MN

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the molecular pathways related to the proinflammatory state in PCOS.
2. Discuss the relationship of hyperglycemia-induced inflammation with insulin resistance and atherogenesis in PCOS.
3. Describe how abdominal adiposity is a perpetuator of inflammation and the resultant features of metabolic syndrome in women with PCOS.

Inflammation and Its Relation to Insulin Resistance and Atherogenesis in Polycystic Ovary Syndrome

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Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
College of Medicine, Mayo Clinic
Rochester, MN

MAYO CLINIC

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Disclosure

Frank González, M.D.

No Disclosures

Insulin Resistance in PCOS

- Insulin resistance is evident in traditionally responsive tissues (i.e., liver, muscle and adipose)
- In contrast, the ovary and the adrenal are exquisitely *insulin sensitive*
- The compensatory hyperinsulinemia of insulin resistance *stimulates* ovarian and adrenal androgen production along with arrest of follicular development

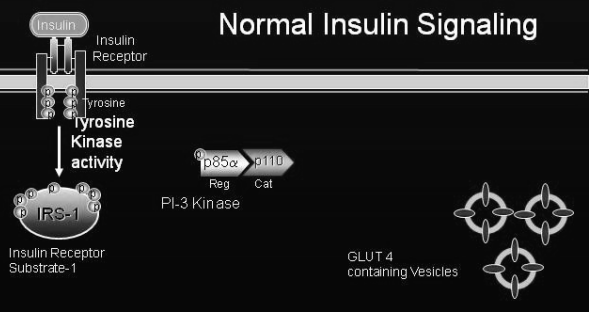
Insulin Resistance in PCOS

- The insulin receptor is genetically and functionally normal in PCOS
- Insulin resistance in PCOS is caused by a *post-receptor defect* in insulin signaling
- The insulin signaling defect culminates in inefficient glucose transport
- TNFα is a strong candidate for mediating insulin resistance in PCOS

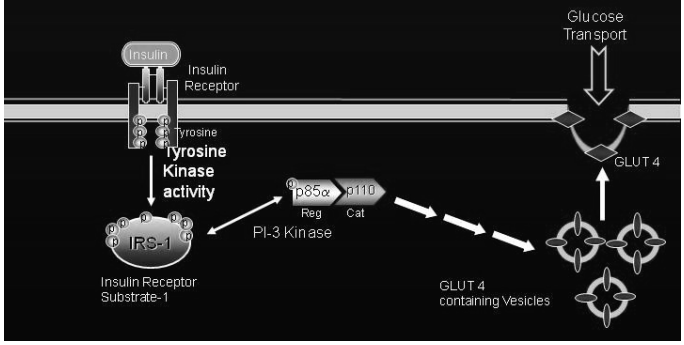
1992 - Ciaraldi et al. *J Clinical Endocrinol Metab* 73:577

1993 - Rosenbaum et al. *Am J Physiol* 264:E197

- Insulin binding activates the insulin receptor by tyrosine autophosphorylation
- Insulin receptor activation induces tyrosine phosphorylation of a family of proteins beginning with IRS-1 and eventually PI-3 Kinase

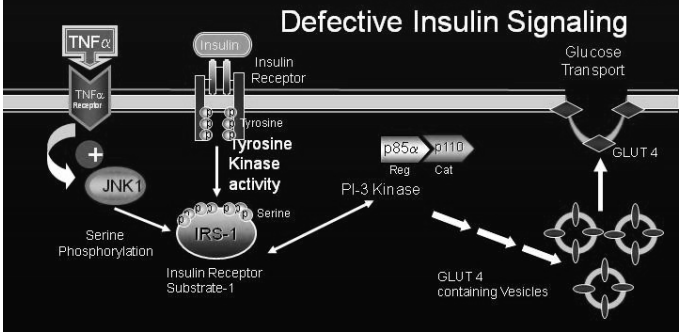


- IRS-1 serves as a docking site for PI-3 kinase
- The protein phosphorylation cascade culminates in GLUT 4 mobilization to facilitate glucose transport across the cell membrane



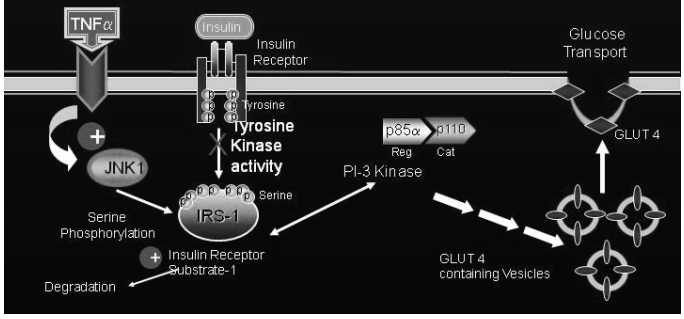
- TNFα binds to a cell membrane receptor
- JNK 1, a serine kinase is activated
- Serine residues in IRS-1 are preferentially phosphorylated over those of tyrosine

2002 - Hirosumi et al. *Nature* 420:333



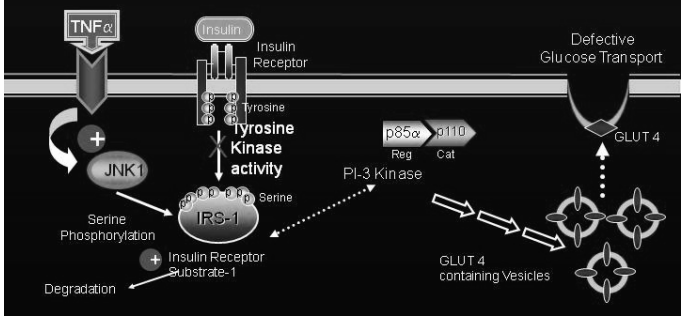
Increased serine phosphorylation causes:
- Uncoupling of the interaction between IRS-1 and the insulin receptor
- Increase in IRS-1 degradation

2001 - Rui et al. *J Clin Invest* 107:181
2003 - Greene et al. *Biochem* 41:7082



Decreased IRS-1 function causes:

- Truncation of the insulin signaling cascade
- Attenuated GLUT 4 mobilization



Inflammation in PCOS

- TNFα is a proinflammatory cytokine produced by circulating mononuclear cells (MNC)
- TNFα is a known molecular mediator of insulin resistance
- In PCOS, carbohydrate ingestion may trigger an inflammatory response, causing TNFα release from MNC to perpetuate insulin resistance

Inflammation in PCOS

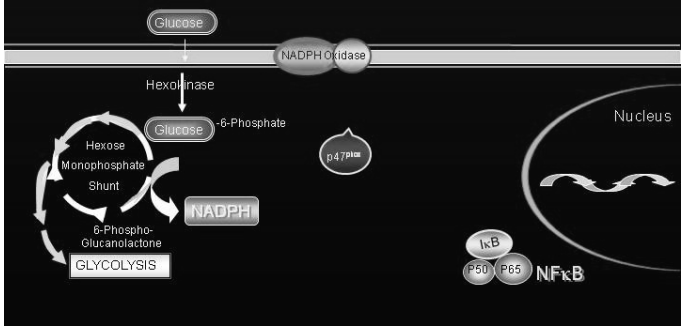
- Hyperglycemia is **proinflammatory** due to its ability to induce NADPH oxidase activity in MNC that leads to ROS generation

  2000 - Mohanty et al. *J Clin Endocrinol Metab* 85:2970
- The resultant oxidative stress activates NFκB, causing its dissociation from IκB, and subsequent nuclear translocation

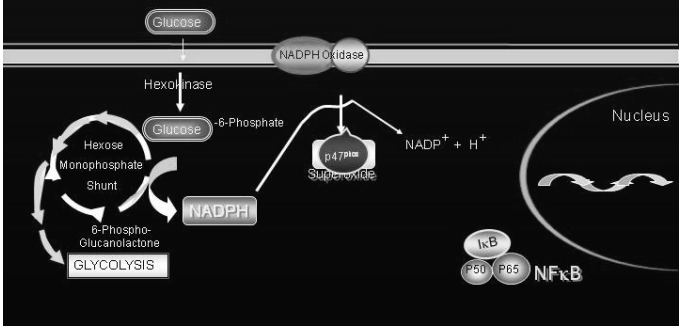
  2001 - Dandona et al. *J Clin Endocrinol Metab* 86:3257
- Activated intranuclear NFκB promotes TNFα gene transcription

  2002 - Evans et al. *Endoc Rev* 23:599

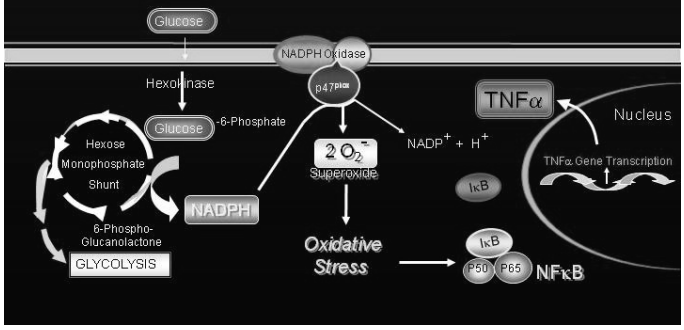
- Circulating glucose is utilized by MNC for glycolysis
- Some glucose is diverted to the hexose monophosphate shunt to generate NADPH



- Translocation of $p47^{phox}$ from the cytosol to the cell membrane activates NADPH oxidase
- NADPH is oxidized by NADPH oxidase which generates superoxide



- Superoxide-induced oxidative stress activates NFκB, resulting in its dissociation from IκB
- Activated NFκB translocates to the nucleus to promote TNFα gene transcription

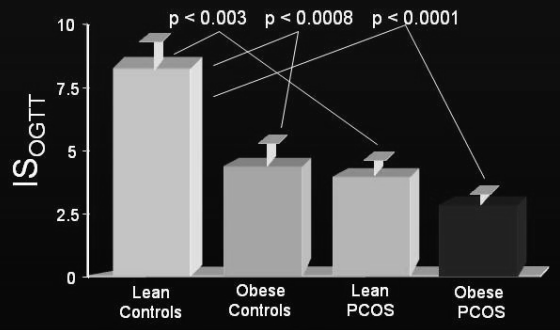


Inflammation in PCOS

Polycystic ovary syndrome (PCOS) is a proinflammatory state as evidenced by:

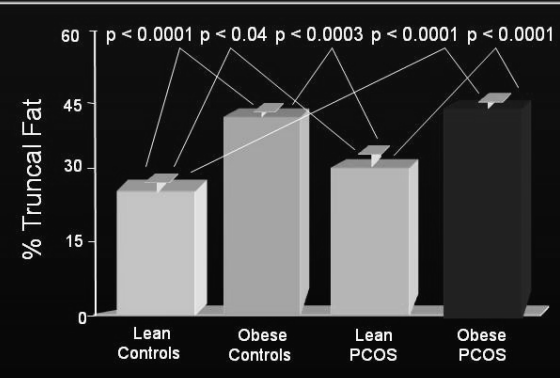
- ↑ TNFα levels independent of obesity
  1999 - González et al. *Metabolism* 48:437
- ↑ Reactive oxygen species-induced oxidative stress and ↑ NFκB activation independent of obesity
  2006 - González et al. *J Clin Endocrinol Metab* 91:336
  2006 - González et al. *J Clin Endocrinol Metab* 91:1508
- ↑ TNFα release from circulating mononuclear cells (MNC)
  2006 - González et al. *J Endocrinol* 183:581

Insulin Sensitivity



2005 - González et al. *J Clin Endocrinol Metab* 90:5336

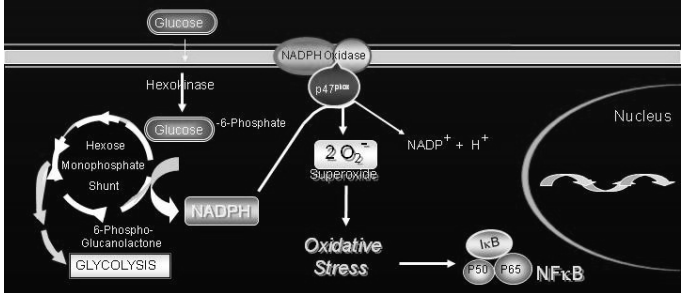
Abdominal Adiposity



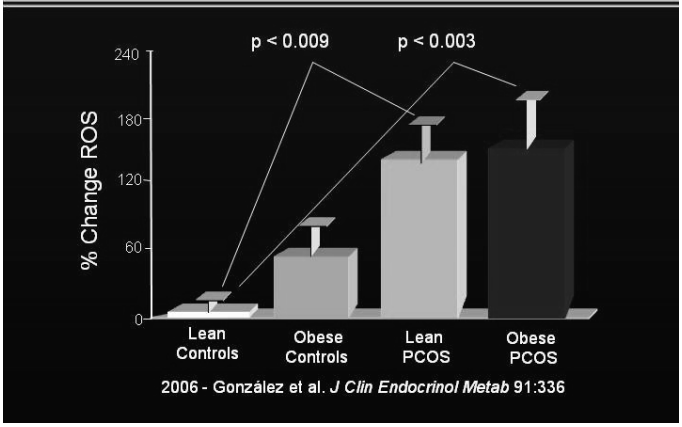
2005 - González et al. *J Clin Endocrinol Metab* 90:5336

Oxidative Stress

ROS generation and p47^{phox} protein expression

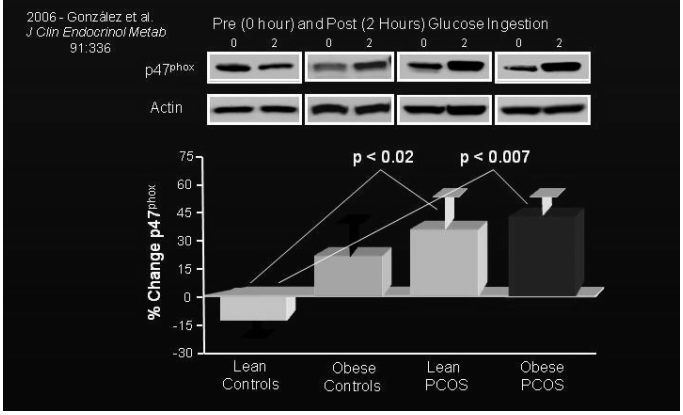


ROS Generation

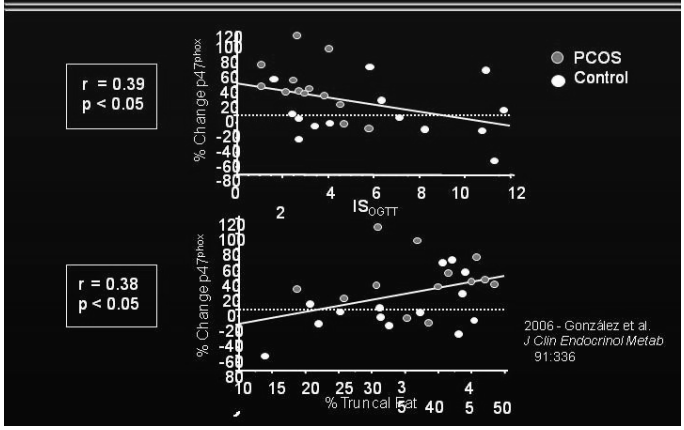


2006 - González et al. *J Clin Endocrinol Metab* 91:336

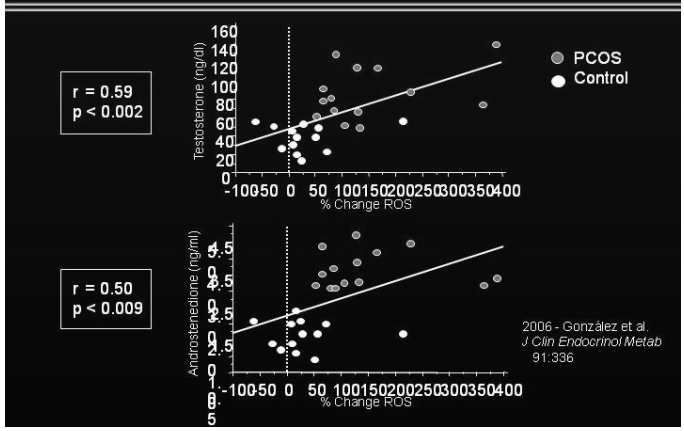
p47^{phox} Protein Expression



Correlations with p47phox

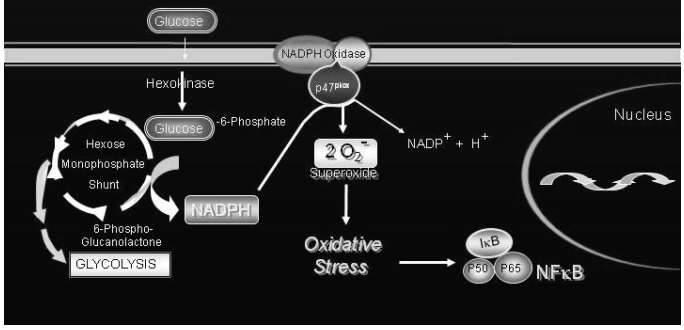


ROS Generation vs. Androgens



NFκB Activation

IκB and p65 protein expression,
and intranuclear NFκB quantification



NFκB Activation

IκB and p 65 protein expression,
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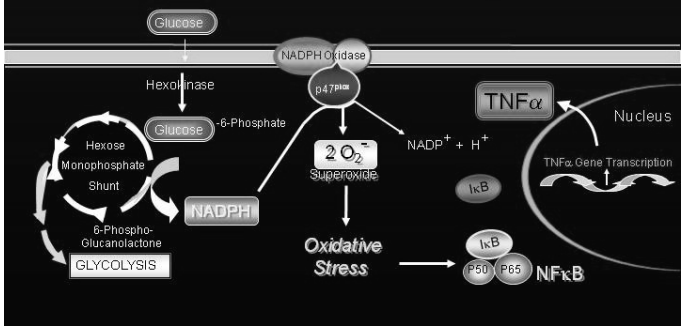
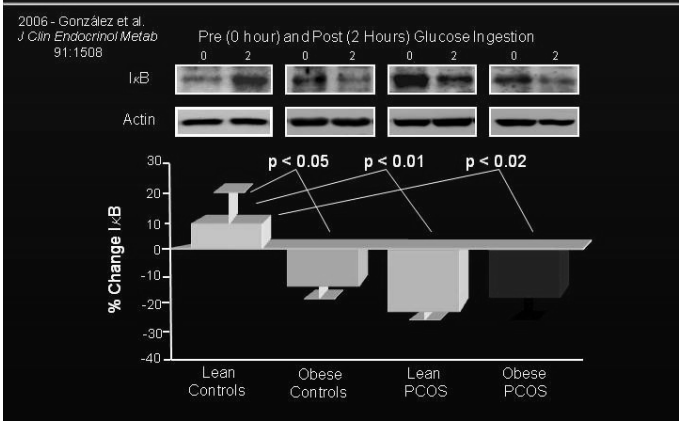
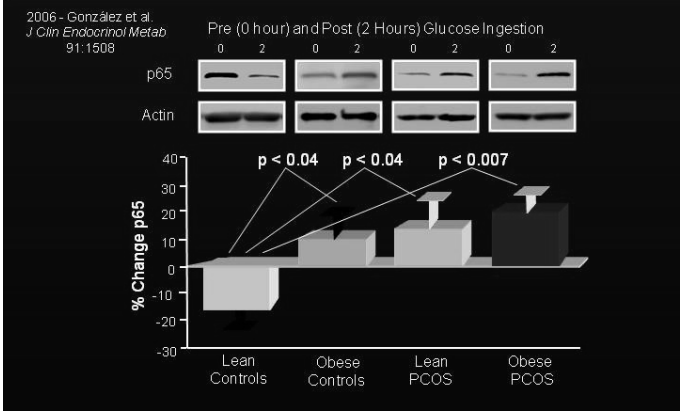
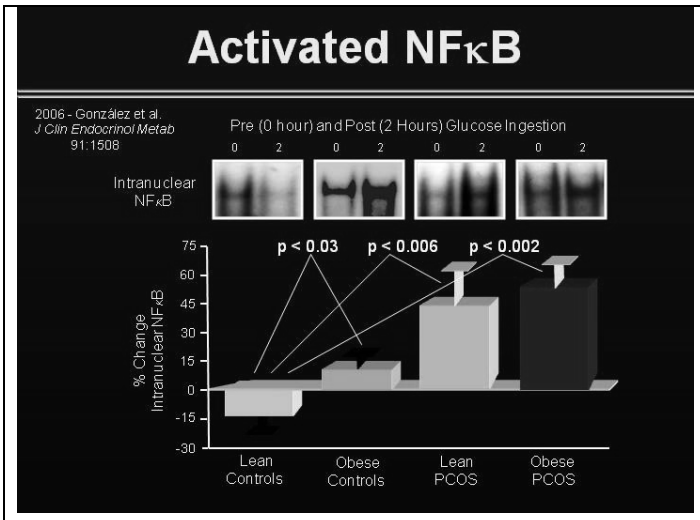


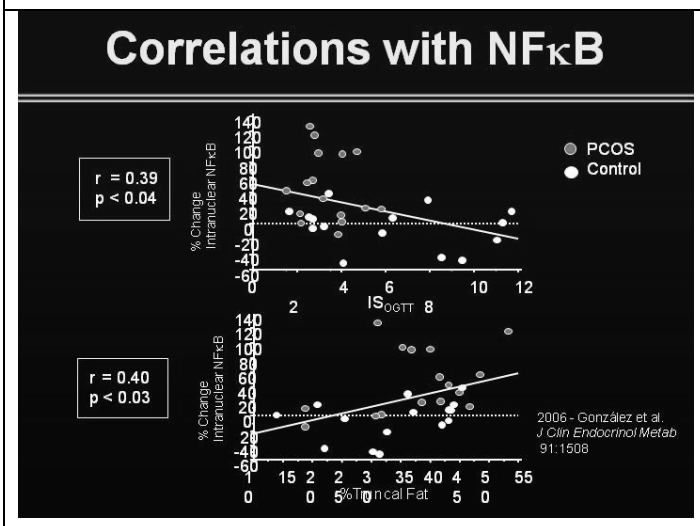
IκB Protein Expression

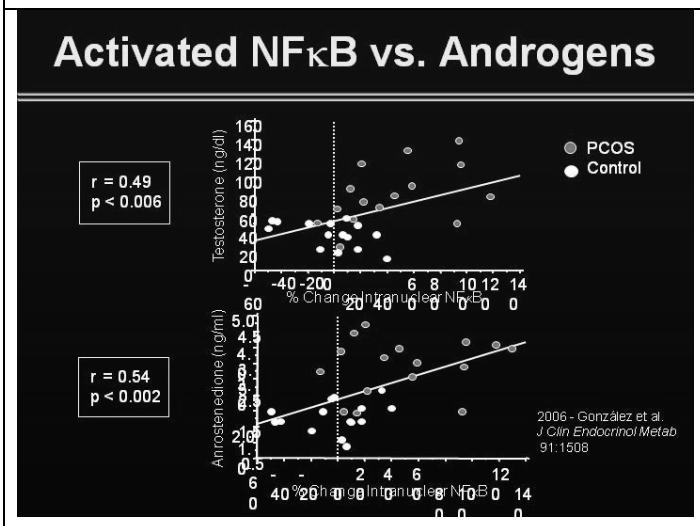


p65 Protein Expression

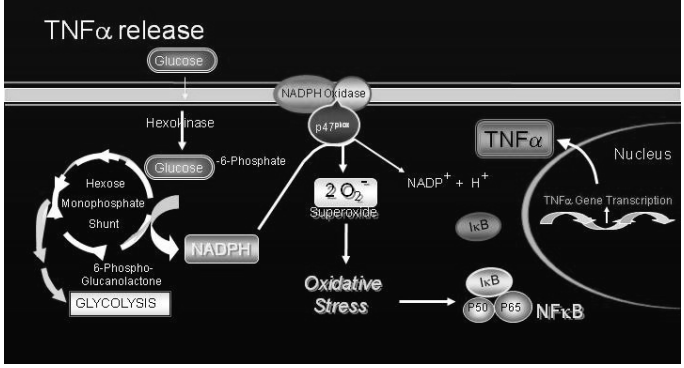



Activated NFκB
2006 - González et al.
J Clin Endocrinol Metab
91:1508
Pre (0 hour) and Post (2 Hours) Glucose Ingestion
0 2 0 2 0 2 0 2
Intranuclear NFκB
p < 0.03
p < 0.006
p < 0.002
% Change Intranuclear NFκB
75 60 45 30 15 0 -15 -30
Lean Controls
Obese Controls
Lean PCOS
Obese PCOS

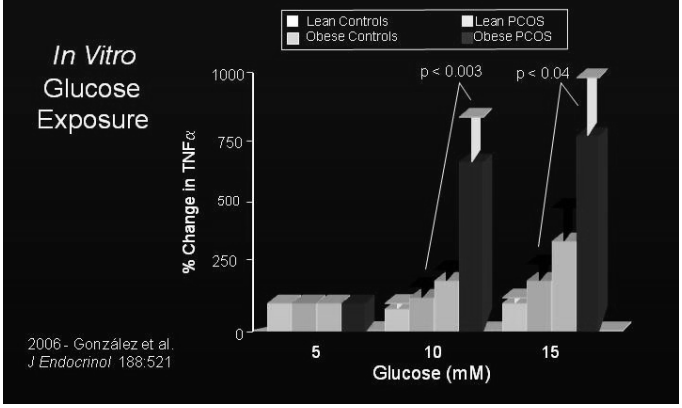

Correlations with NFκB
r = 0.39
p < 0.04
% Change Intranuclear NFκB
PCOS
Control
IS OGTT
r = 0.40
p < 0.03
% Change Intranuclear NFκB
% Truncal Fat
2006 - González et al.
J Clin Endocrinol Metab
91:1508


Activated NFκB vs. Androgens
r = 0.49
p < 0.006
Testosterone (ng/dl)
PCOS
Control
% Change Intranuclear NFκB
r = 0.54
p < 0.002
Anrostenedione (ng/ml)
% Change Intranuclear NFκB
2006 - González et al.
J Clin Endocrinol Metab
91:1508

TNFα Release from mononuclear cells (MNC)



TNFα Release from MNC



Correlations with TNFα Release

% Change MNC-derived TNFα Release vs. HOMA-IR, % Truncal Fat and Androgens; * P<0.05

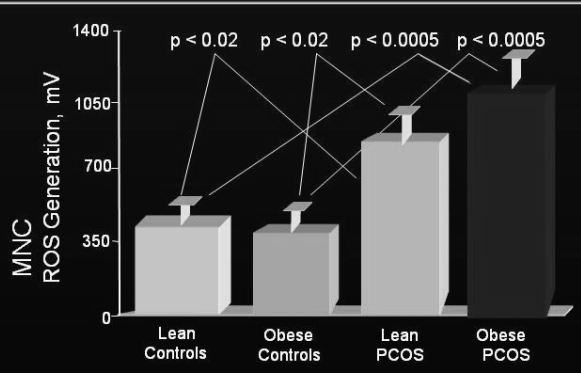
10mM Glucose		Combined Groups (n=24)	PCOS (n=12)
HOMA-IR	ρ	0.397	0.392
	P	0.049*	0.194
% Truncal Fat	ρ	0.448	0.510
	P	0.032*	0.090
Androstenedione ng/mL	ρ	0.645	0.587
	P	0.002*	0.048*
Testosterone ng/dL	ρ	0.271	0.182
	P	0.193	0.547

Correlations with TNFα Release

% Change MNC-derived TNFα Release vs. HOMA-IR, % Truncal Fat and Androgens; * P<0.05

15mM Glucose		Combined Groups (n=24)	PCOS (n=12)
HOMA-IR	ρ	0.257	0.175
	P	0.217	0.562
% Truncal Fat	ρ	0.346	0.175
	P	0.097	0.562
Androstenedione ng/mL	ρ	0.525	0.245
	P	0.012*	0.417
Testosterone ng/dL	ρ	0.290	0.594
	P	0.164	0.048*

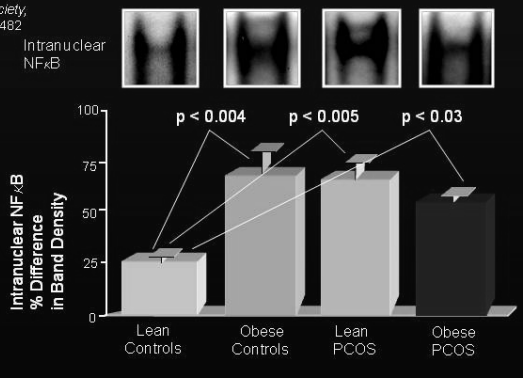
Fasting ROS Generation



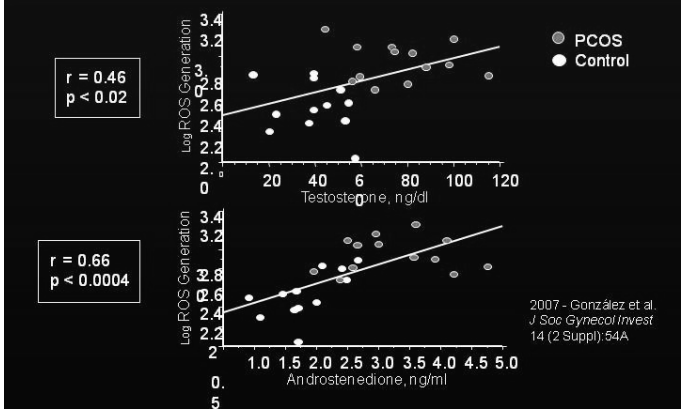
2007 - González et al. *Reproductive Sci* 14 (2 Suppl):215A

Fasting Activated NFκB

2007 - González et al. *89th Meeting of the Endocrine Society*, Program, Pg 482

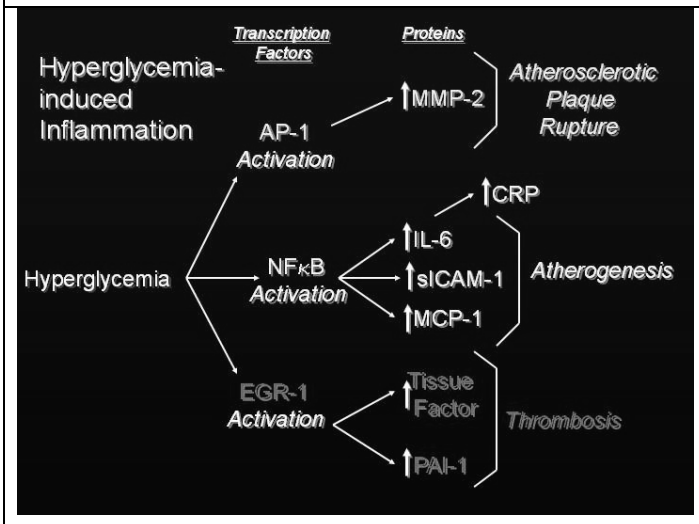


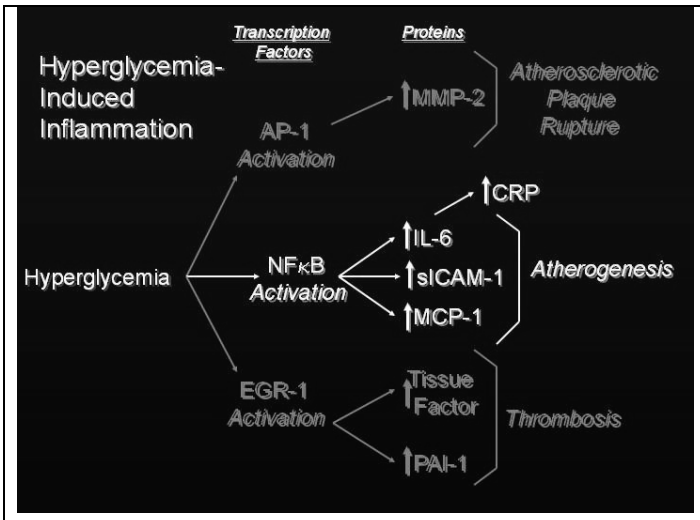
Correlation with Androgens



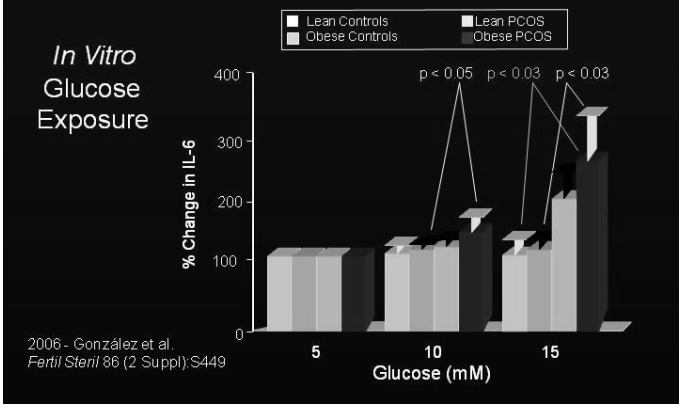
Atherogenesis in PCOS

- In PCOS, there is a high prevalence of dyslipidemia and type 2 diabetes
- In type 2 diabetes, insulin resistance is associated with a greater risk of accelerated atherogenesis
- Chronic low-grade inflammation is a major contributor to the development of atherosclerosis
- Hyperglycemia is proinflammatory due to its ability to upregulate molecular pathways in MNC that promote atherosclerotic plaque formation and rupture

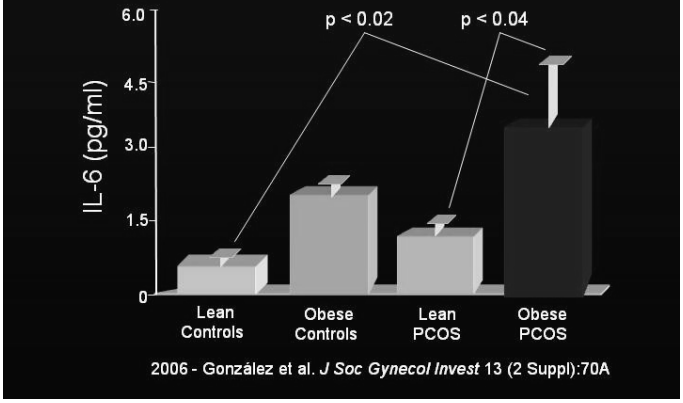




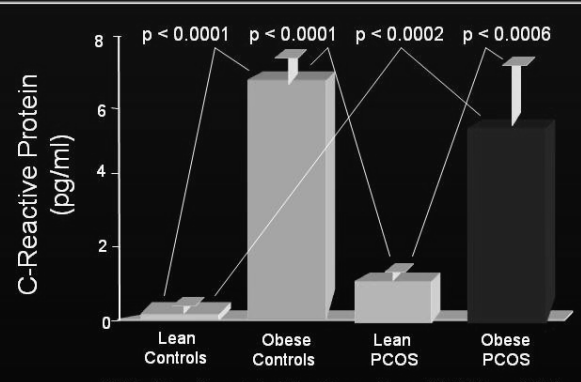
IL-6 Release from MNC



Plasma IL- 6

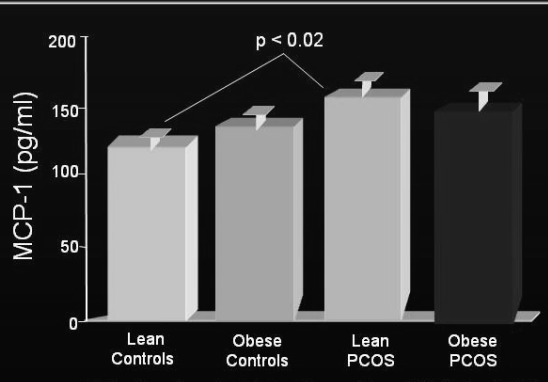


Plasma C-Reactive Protein



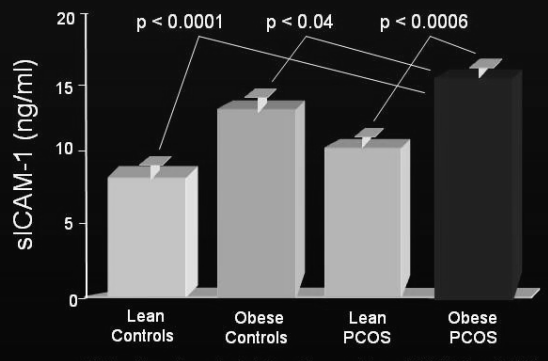
2006 - González et al. *J Soc Gynecol Invest* 13 (2 Suppl):70A

Plasma MCP-1



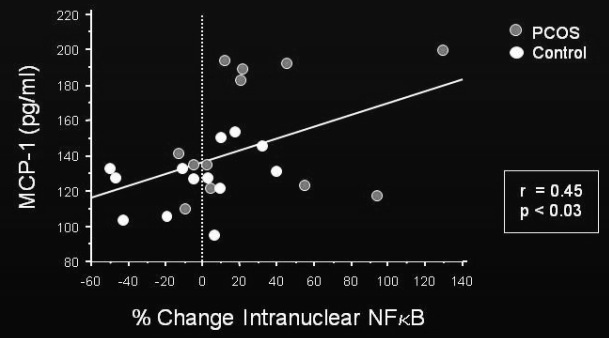
2006 - González et al. *J Soc Gynecol Invest* 13 (2 Suppl):70A

Plasma sICAM-1

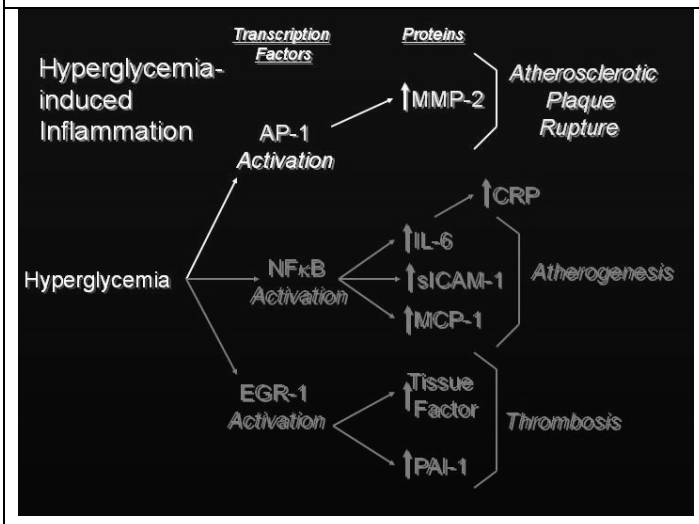


2006 - González et al. *J Soc Gynecol Invest* 13 (2 Suppl):70A

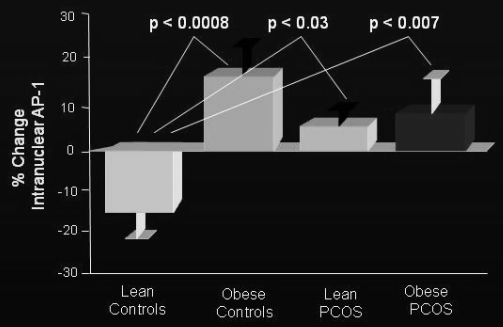
Correlation with Intranuclear NFκB



2006 - González et al. *J Soc Gynecol Invest* 13 (2 Suppl):70A

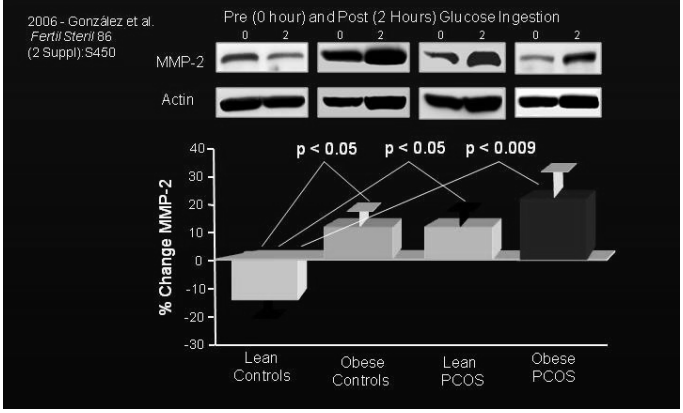


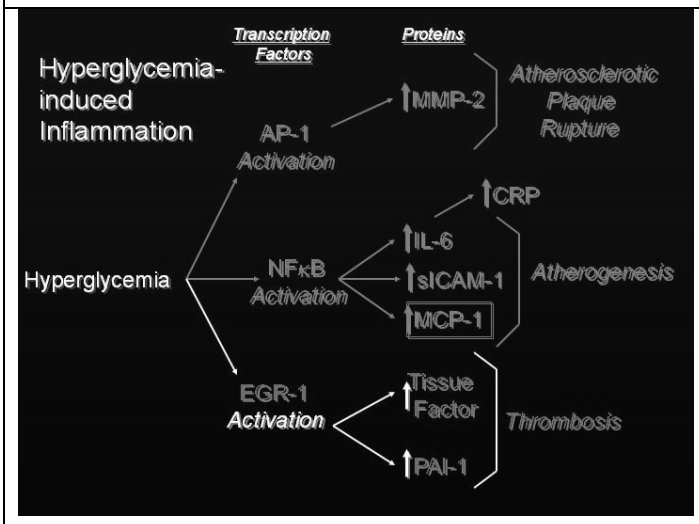
Activated AP-1



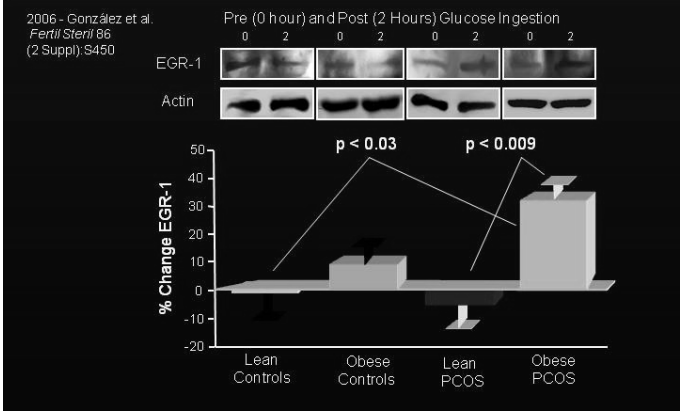
2006 - González et al. Fertil Steril 86 (2 Suppl):S450

MMP-2 Protein Expression

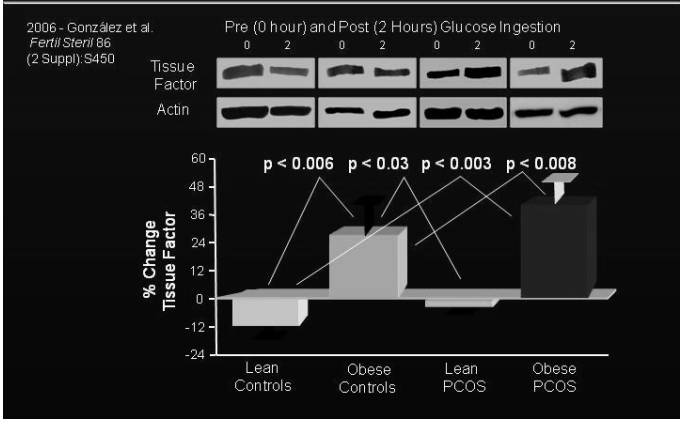




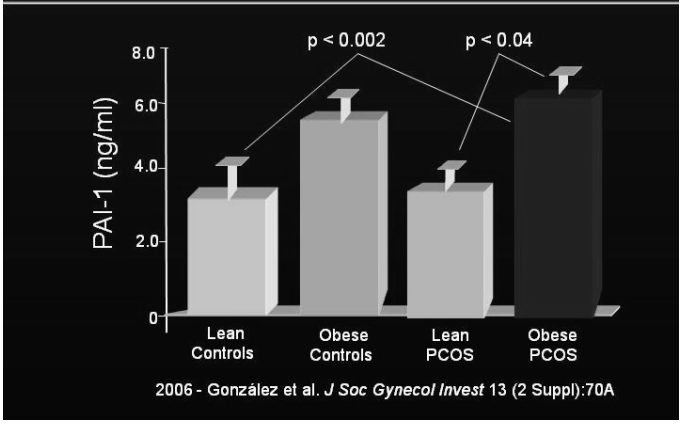
EGR-1 Protein Expression



Tissue Factor Protein Expression



Plasma PAI-1



Correlation with % Truncal Fat

% Truncal Fat vs.; * P<0.05		Combined Groups	PCOS
IL-6 (pg/ml)	ρ	0.620	0.589
	P	0.0008*	0.028*
CRP (pg/ml)	ρ	0.845	0.870
	P	0.0001*	0.0008*
MCP-1 (ng/ml)	ρ	0.077	0.326
	P	0.675	0.223
sICAM (ng/ml)	ρ	0.723	0.723
	P	0.0001*	0.005*
PAI-1 (ng/ml)	ρ	0.590	0.654
	P	0.002*	0.014*

Correlation with % Truncal Fat

% Truncal Fat vs. % Change Protein Expression of EGR-1, Tissue Factor and MMP-2; * P<0.05

		Combined Groups	PCOS
% Change EGR-1	r	0.626	0.777
	P	0.004*	0.002*
% Change Tissue Factor	r	0.619	0.605
	P	0.0008*	0.037*
% Change MMP-2	r	0.412	0.051
	P	0.037*	0.870

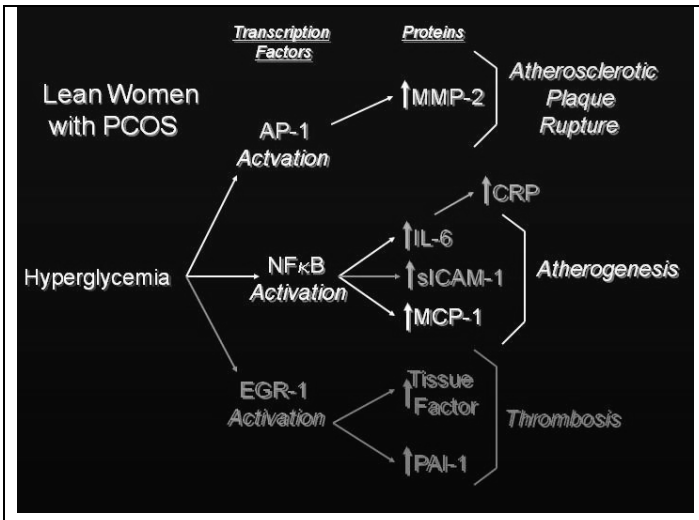
Conclusion

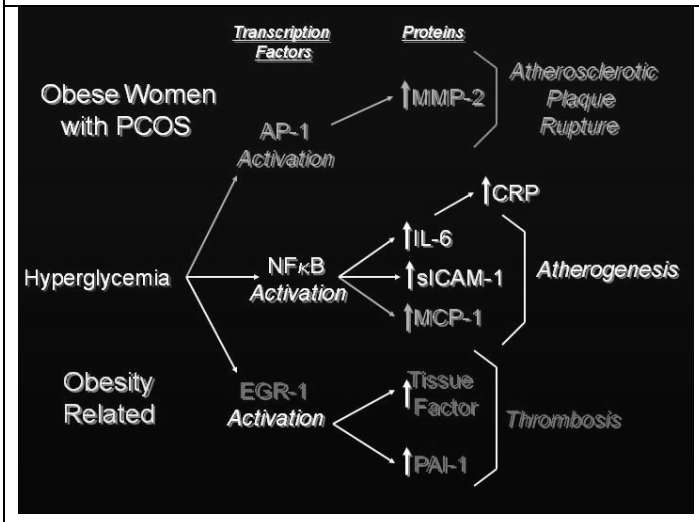
In PCOS, physiologic hyperglycemia stimulates a prooxidant, proinflammatory response from MNC that is independent of obesity and manifested by:

- An increase in NADPH oxidase-induced ROS generation
- A decrease in IκB protein expression, the cytoplasmic inhibitor of NFκB
- An increase in the amount, and activation of NFκB, the cardinal signal of inflammation

Conclusion

Increased TNFα release from MNC in response to hyperglycemia is evident when the combination of PCOS and increased adiposity is present





Conclusion

- Women with PCOS demonstrate a unique proinflammatory, proatherogenic risk profile that is exacerbated by physiologic hyperglycemia and can be independent of obesity
- Abdominal adiposity, in particular, is an additional perpetuator of inflammation and the resultant features of metabolic syndrome in women with PCOS

Speculation

In PCOS:

- Hyperglycemia-induced inflammation may contribute to insulin resistance and atherogenesis, independent of obesity
- Hyperandrogenemia may promote pre-activation of MNC

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7. González F, Rote NS, Minium J, Kirwan JP. Increased activation of nuclear factor □B triggers inflammation and insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91:1508-12.
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NOTES

LIFESTYLE MODIFICATION: PRESCRIPTION #1 FOR MANAGING METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

Enrico Carmina, M.D.
Department of Clinical Medicine
University of Palermo
Palermo, Italy

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the results that may be obtained with a lifestyle modification program for patients with PCOS.
2. List the reasons for failure of lifestyle modification programs.
3. Develop a lifestyle modification program for your patients with PCOS.

LIFESTYLE MODIFICATION: PRESCRIPTION #1 FOR MANAGING METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

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DISCLOSURE

Enrico Carmina, M.D.

No disclosures

LIFESTYLE MODIFICATION

A strategy to modify the lifestyle:

1. Diet
2. Regular physical exercise
3. Psychological support
4. No smoking, alcohol or drugs

LIFESTYLE MODIFICATION

- Lifestyle modification has become a popular way to treat all conditions associated with increased cardiovascular risk or with cardiovascular diseases, especially when there is evidence of:
  - Metabolic syndrome
  - Abdominal obesity

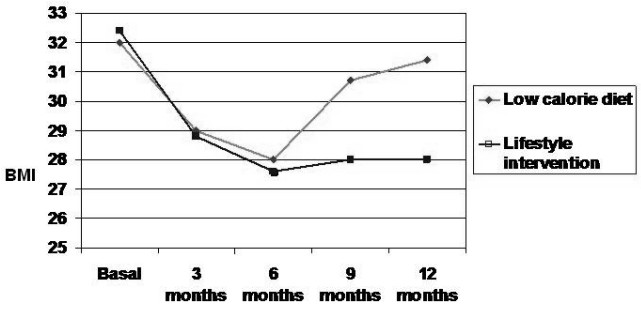
LIFESTYLE MODIFICATION IN THE TREATMENT OF METABOLIC SYNDROME

The Diabetes Prevention Program Randomized Trial has shown that the incidence of metabolic syndrome is reduced by:

- 41% with lifestyle modification
- 17% with metformin therapy

Orchard et al. Ann Intern Med 2005; 142: 611-9

LIFESTYLE INTERVENTION IN THE TREATMENT OF ABDOMINAL OBESITY



LIFESTYLE MODIFICATION IN PCOS

- Few data exist on the results of lifestyle intervention in metabolic syndrome as it relates to PCOS
- Most available data have been obtained with the use of a low-calorie diet in obese women with PCOS

EFFECT OF LOW-CALORIE DIET IN OBESE WOMEN WITH PCOS

24 obese women with PCOS were treated with a low-calorie diet.

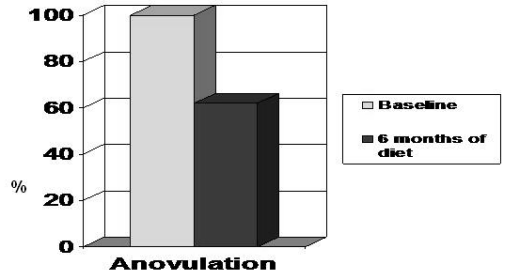
9 out of 19 (47%) anovulatory patients developed regular cycles after 6 months of following the study diet.

No changes in gonadotropins or total testosterone were found, but a significant decrease in serum insulin and a significant increase in SHBG were observed.

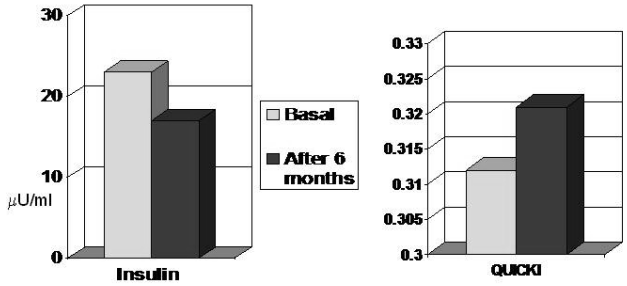
A small (<5%) decrease in body weight was sufficient to decrease serum insulin and cause regular cycles.

Kiddy et al. *Clin Endocrinol* 1992; 36:105

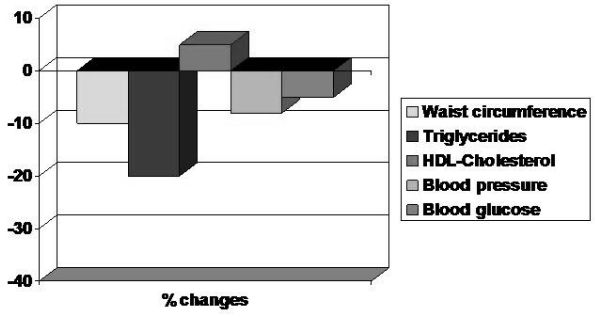
EFFECTS OF LOW-CALORIE DIET IN OBESE WOMEN WITH PCOS



EFFECT OF LOW-CALORIE DIET IN OBESE WOMEN WITH PCOS



EFFECT OF A 6-MONTH LOW-CALORIE DIET ON COMPONENTS OF METABOLIC SYNDROME IN OBESE WOMEN WITH PCOS



RELATIONSHIPS BETWEEN WEIGHT LOSS AND IMPROVEMENT OF CV RISK FACTORS IN PCOS

It has been shown that a small amount of weight loss (5%) causes:

- A significant reduction in insulin, waist circumference and triglycerides
- No changes in HDL cholesterol and C-reactive protein

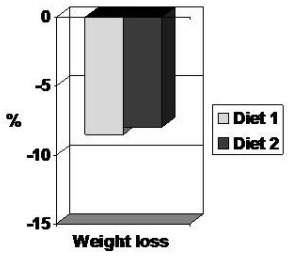
Moran et al. *J Clin Endocrinal Metab* 2007; 92:2944

DIET INTERVENTION IN OBESE WOMEN WITH PCOS

- Modest weight loss (5%) is sufficient to improve the clinical and biologic presentation of the syndrome
- Beneficial reproductive alterations are obtained early and may depend more on energy restriction than on weight loss
- Improvement of metabolic syndrome and CV risk factors needs more time and is more related to weight loss
- The main problems are the early dropout and the maintenance of the results

EFFECT OF TWO DIFFERENT LOW-CALORIE DIETS IN OBESE WOMEN WITH PCOS

- Diet 1
  - CHO 55%
  - Proteins 15%
  - Fat 30%
- Diet 2
  - CHO 40%
  - Proteins 30%
  - Fat 30%



WHAT KIND OF DIET FOR PCOS?

When comparing a high-protein diet with a conventional low-fat, low-calorie diet:

- Most studies do not show significant differences in short-term weight loss
- Similar results for restoration of menstrual cycles and improvement in the lipid profile
- However, a high-protein diet has a better compliance rate because it reduces depression scores in obese subjects

PHYSICAL EXERCISE IN PCOS

- Very few data
- Physical exercise has been used in some lifestyle intervention programs, but mostly in conjunction with a diet intervention

ROLE OF PHYSICAL EXERCISE

- Regular physical exercise has been shown to increase weight loss and to improve insulin sensitivity and metabolic alterations
- Some of these effects occur independently of a diet intervention
- Diet and physical exercise have an additive effect on weight loss and the improvement of metabolic parameters

PHYSICAL EXERCISE AND IMPROVEMENT OF METABOLIC SYNDROME

In the general population:

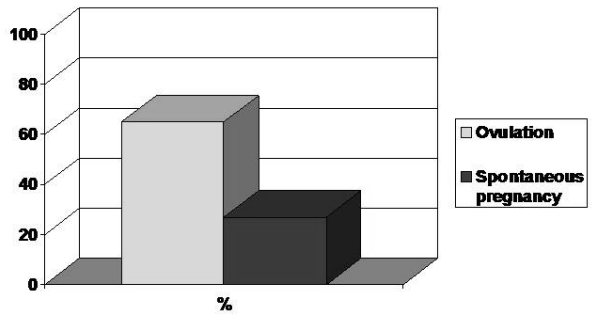
- Improvement in the lipid profile and reduction of waist circumference requires at least 25-30 minutes of low intensity physical exercise, 5 times a week

RESULTS OF A LIFESTYLE MODIFICATION PROGRAM IN PCOS

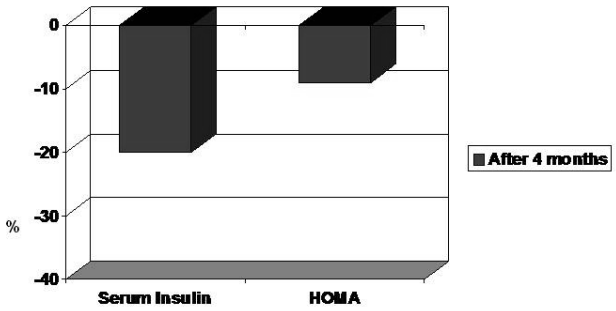
The Australian Experience

- Reproductive Medicine Unit, University of Adelaide, Australia
- Lifestyle intervention includes a low-calorie diet with regular physical exercise and prohibition of alcohol and smoking
- Duration of the lifestyle modification program is at least 6 months
- Only obese and overweight patients are included in the program (mean BMI 37.5 kg/m^2)
- Main focus is on enhancement of fertility

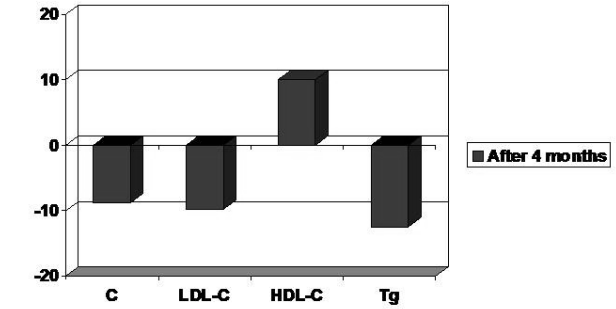
RESULTS OF AUSTRALIAN LIFESTYLE MODIFICATION PROGRAM



RESULTS OF AUSTRALIAN LIFESTYLE MODIFICATION PROGRAM



RESULTS OF AUSTRALIAN LIFESTYLE MODIFICATION PROGRAM



RESULTS OF A LIFESTYLE MODIFICATION PROGRAM IN PCOS

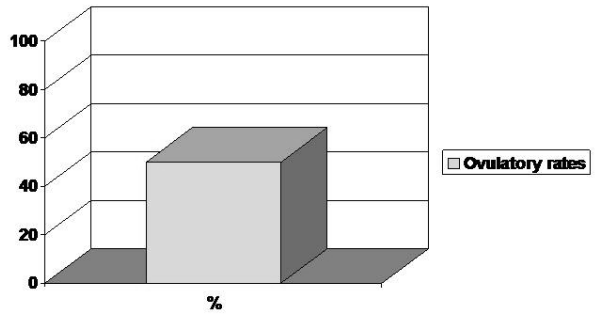
The Rochester Experience

- Department of Obstetrics and Gynecology, University of Rochester, USA
- The program consisted of a diet intervention and physical exercise
- Only obese women with PCOS were included in the program (mean BMI 39)
- The duration of the program was 1 year

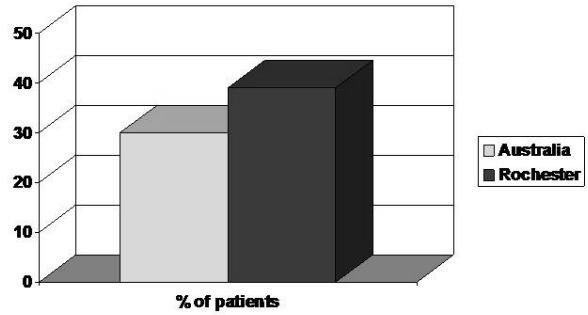
RESULTS OF THE ROCHESTER LIFESTYLE MODIFICATION PROGRAM

- Modest weight loss
- 50% of anovulatory patients normalized menstrual cycles
- Ovulation only in patients who lost weight
- No significant androgen reduction
- 39% dropout rate

RESULTS OF THE ROCHESTER LIFESTYLE MODIFICATION PROGRAM



DROP-OUT RATE IN TWO LIFESTYLE MODIFICATION PROGRAMS



DROPOUT RATE IN LIFESTYLE MODIFICATION PROGRAMS

- Dropout rate is very high:
  - 30% in Australian Program
  - 39% in Rochester Program
- Psychological support is an important component of any lifestyle modification program

LIFESTYLE MODIFICATION PROGRAM IN PCOS

The Palermo Experience

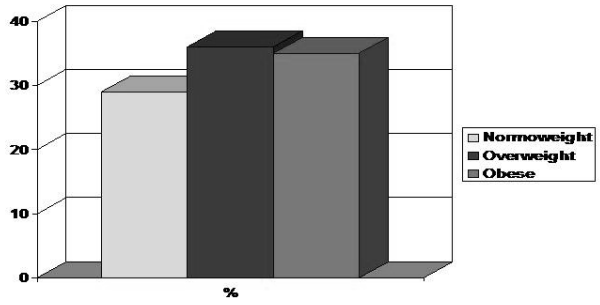
- Department of Medicine, University of Palermo
- Main focus is on metabolism
- The program consists of a diet intervention in association with regular physical exercise
- Psychological support is an important component of the program
- The duration of the program is 12 months
- Only unresponsive patients are shifted to pharmacological treatment

LIFESTYLE MODIFICATION PROGRAM IN PCOS

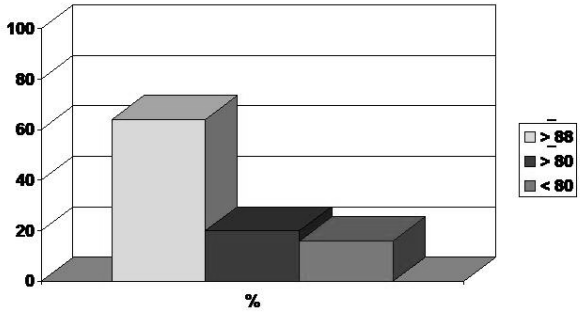
The Palermo Experience

- The program is for all women with PCOS who have increased waist circumference
- In normoweight patients with increased waist circumference, a controlled Mediterranean normocaloric diet is recommended

PREVALENCE OF OBESITY IN 301 ITALIAN WOMEN WITH PCOS



WAIST CIRCUMFERENCE IN ITALIAN WOMEN WITH PCOS



LIFESTYLE MODIFICATION IN NORMOWEIGHT WOMEN WITH PCOS

- We hypothesized that lifestyle modification may also reduce CV risk in normoweight or overweight women with PCOS who have an increased waist circumference (≥ 80 cm) by:
  - Reducing insulin resistance
  - Improving the lipid profile
  - Reducing endothelial dysfunction and markers of vascular inflammation

PALERMO LIFESTYLE MODIFICATION PROGRAM

The Diet

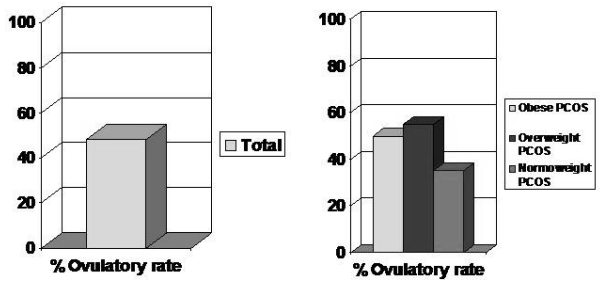
- Low-calorie short-term (3 months) diet is used in obese and overweight women with PCOS, followed by a normocaloric Mediterranean diet thereafter
- Normocaloric Mediterranean diet is used from the beginning in normoweight women with PCOS

PALERMO LIFESTYLE MODIFICATION PROGRAM

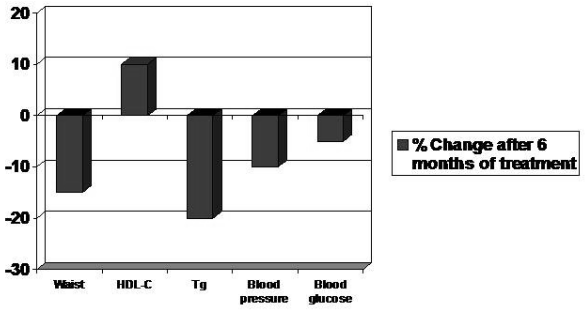
Physical Exercise

Suggested physical exercise	Walking at a brisk pace
Alternative physical exercise	Swimming, cycling, cross-country skiing
Duration of physical exercise	At least 30 minutes daily
Intensity	40-60% increase in heart rate

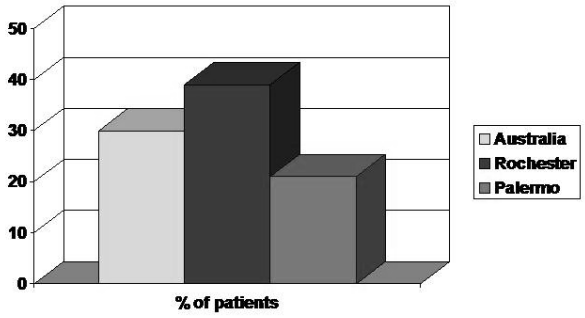
PALERMO LIFESTYLE MODIFICATION PROGRAM



PALERMO LIFESTYLE MODIFICATION PROGRAM



DROPOUT RATE



CONCLUSIONS

- Lifestyle modification should be the first step in the treatment of obese women with PCOS
- Lifestyle modification is also useful in the treatment of normoweight and overweight women with PCOS who have abdominal obesity
- Only lasting lifestyle changes will result in prolonged beneficial metabolic effects
- Pharmacological treatment of women with PCOS should be considered only in unresponsive patients

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NOTES

MEDICAL MANAGEMENT OF METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

Jean-Patrice Baillargeon, M.D., M.Sc.
Department of Internal Medicine
University of Sherbrooke
Sherbrooke, Quebec
Canada

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the benefits of insulin-sensitizing agents in the treatment of women with PCOS with metabolic syndrome and prevention of its complications.
2. Discuss the potential long-term consequences of oral contraceptive use on the exacerbation of metabolic syndrome in women with PCOS.
3. Choose the most suitable medical treatment for long-term management of women with PCOS when considering the effects of metabolic syndrome and its associated risks.

Medical Management of Metabolic Syndrome in Polycystic Ovary Syndrome

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DISCLOSURE

Jean-Patrice Baillargeon, M.D., M.Sc.

Received honoraria for conferences from:

Glaxo Smith Kline and Abbott Pharmaceuticals

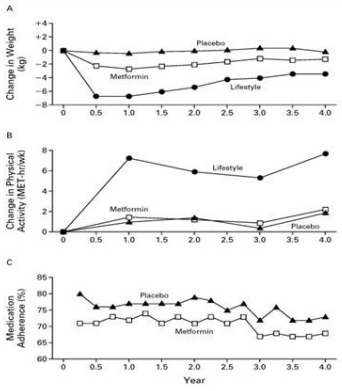
Does the improvement of insulin sensitivity in women with PCOS decrease the risk for developing type 2 diabetes?

NIH Diabetes Prevention Project

- 3,234 high risk individuals enrolled at 27 centers
- 25-85 years of age with impaired glucose tolerance (IGT) and a mean BMI of 34 kg/m^2
- Subjects were assigned to one of three treatment groups:
  - Placebo
  - Metformin 850 mg twice daily
  - Diet and exercise - 7% weight-reduction goal
- Study terminated early after an average of 3 years of follow-up

Knowler WC et al. *N Engl J Med* 2002; 346:393

Changes in Body Weight, Physical Activity and Adherence to Medication Regimen According to Study Group



Knowler WC et al.
N Engl J Med
2002; 346:393-403

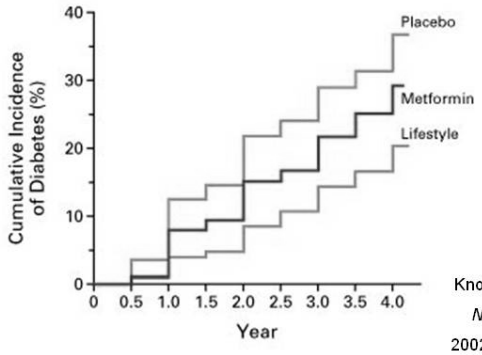
NIH Diabetes Prevention Project

	Conversion to Diabetes
Placebo	29%
Metformin	22%
Diet & exercise	14%

	Risk Reduction
Metformin	31%
Diet & exercise	58%

Knowler WC et al. *N Engl J Med* 2002; 346:393-403

Cumulative Incidence of Type 2 Diabetes



Knowler WC et al. *N Engl J Med* 2002; 346:393-403

TRIPOD Study (Troglitazone in Prevention of Diabetes)

- 235 Hispanic women with recent gestational diabetes
- Randomized to two groups:
  - Placebo
  - Troglitazone 400 mg daily
- Results
  After median of 30 months, the annual conversion to type 2 diabetes was:
  - 12.1% for the placebo group
  - 5.4% for the troglitazone group

Buchanan TA et al. *Diabetes* 2002; 51:2796-2803

Metformin and Prevention of Glucose Intolerance in PCOS

- Retrospective chart review study of clinical practice
- All women started on metformin within a 5-year period
- Inclusion criteria:
  - **No evidence of type 2 diabetes at baseline**
  - **At least one year follow-up that included a repeat oral glucose tolerance test (OGTT)**

Sharma & Nestler. *Endocr Pract* 2007; 13:373-379

Metformin and Prevention of Glucose Intolerance in PCOS

- Cohort of 50 women with PCOS
- At baseline:
  - **78% (n = 39) had normal glucose tolerance (NGT)**
  - **22% (n = 11) had impaired glucose tolerance (IGT)**
- Average duration of follow-up:
  - **43.3 months for NGT group**
  - **27.5 months for IGT group**

Sharma & Nestler. *Endocr Pract* 2007; 13:373-379

Metformin and Prevention of Glucose Intolerance in PCOS

At follow-up:

- No subjects developed type 2 diabetes
- IGT Group
  - **45% (5 of 11 subjects) continued to have IGT**
  - **55% (6 of 11 subjects) reverted to NGT**
- NGT Group
  - **6.4% (2 of 32 subjects) converted to IGT**
  - **93.6% (20 of 23 subjects) continued to have NGT**

Sharma & Nestler. *Endocr Pract* 2007; 13:373-379

Metformin and Prevention of Glucose Intolerance in PCOS

- Annual conversion rate from NGT to IGT was 1.4%
- Significantly lower (p=0.01) than the conversion rates reported in other studies
  - **16% -** Legro at al. *J Clin Endocrinol Metab* 2005; 90:3236-3242
  - **19% -** Ehrmann et al. *Diabetes Care* 1999; 22:141-146

Sharma & Nestler. *Endocr Pract* 2007; 13:373-379

Does the improvement of insulin sensitivity in women with PCOS decrease the risk of cardiovascular diseases?

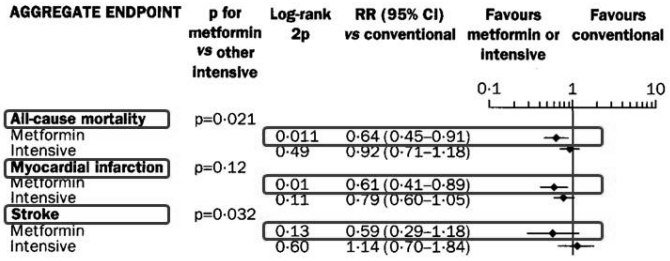
Metformin and Prevention of Cardiovascular Diseases

United Kingdom Prevention of Diabetes Study

- Overweight individuals with newly diagnosed type 2 diabetes were treated with metformin
- Subjects were randomized to either:
  - Conventional therapy, i.e., diet intervention (n=411)
  - Intensive therapy, i.e., metformin (n=342) or other medications (n=951) with the goal of decreasing fasting glucose to <126 mg/dl
- Median follow-up of 10.7 years
- Median hemoglobin A1c
  - 8.0% for conventional therapy
  - 7.4% for metformin therapy

UKPDS Group. *Lancet* 1998; 352:854

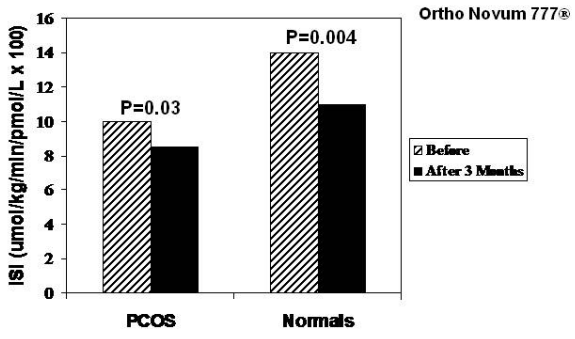
Metformin and Prevention of Cardiovascular Diseases



UKPDS Group, *Lancet* 1998; 352:854

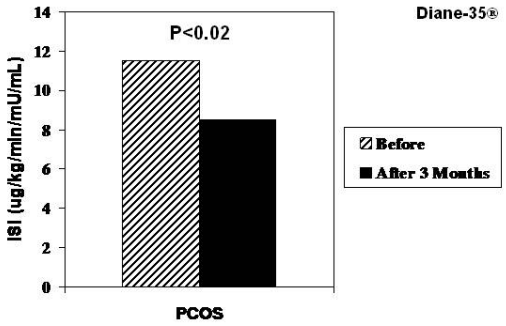
Do oral contraceptive pills (OCP) affect insulin sensitivity or glucose tolerance?

Effect of an Oral Contraceptive on the Insulin Sensitivity Index (ISI)



Korytkowski M et al. *J Clin Endocrinol Metab* 1995; 80:3327

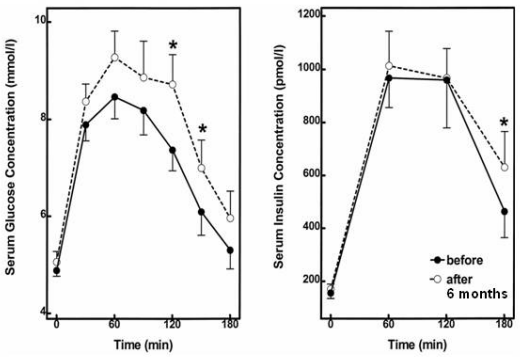
Effect of an Oral Contraceptive on the Insulin Sensitivity Index (ISI)



Diane-35®

Vrbíková J et al. *Eur J Endocrinol* 2004; 150:215

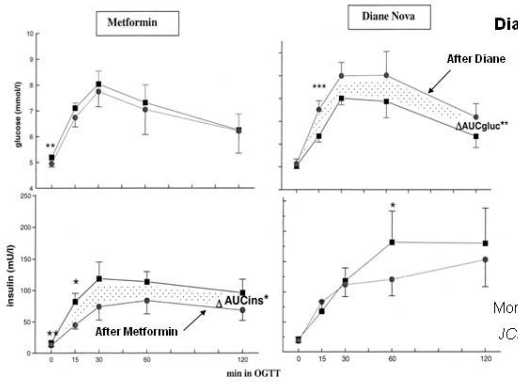
Effect of 6 Months of OCP Use on Glucose Tolerance



Desogen®

Nader S et al.
J Clin Endorinol Metab
1997; 82:3074

OCP Use Compared to Metformin Therapy in PCOS



Diane Nova®

Morin-Papunen L et al.
JCEM 2000; 85:3161

Cohort Studies: OCP Use and Risk of Type 2 Diabetes

Nurses Health Study (NHS) I

- 115,117 women followed for 12 yrs since 1976
- Mean age at follow up was 58 years
- 2,265 women were newly diagnosed with type 2 diabetes
- 10% increased risk for developing type 2 diabetes in those who used OCPs compared to those who never used OCPs (95%CI = 1.01-1.21)

Rimm EB, et al *Diabetologia* 1992; 35:967

Cohort Studies: OCP Use and Risk of Type 2 Diabetes

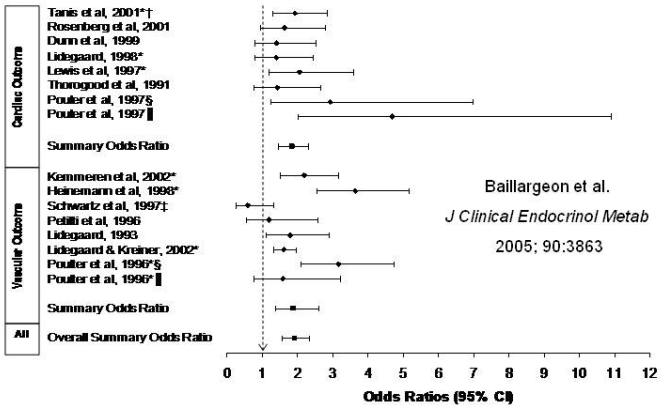
Nurses Health Study (NHS) II

- 116,686 women followed for 4 yrs since 1989
- Mean age at follow up was 38 years
- Relative risk of 1.2 for past OCP users (170 cases) – no statistical significance
- Relative risk of 1.6 for current OCP users (46 cases) – no statistical significance

Chasan-Taber L, *Diabetes Care* 1997; 20:330

Do oral contraceptives increase cardiovascular risk?

Oral Contraceptive Pills Increase Risk for Cardiac & Vascular Disease



OCP Use and Cardiovascular Risk: Special Considerations in PCOS

- Women with PCOS may have an increased baseline risk for cardiovascular disease compared to women without the disorder
- Women with PCOS may take OCPs for a longer period of time than women in the general population

Oral Contraceptive Pills for the Long-term Management of PCOS

Traditional Goals of Therapy
OCP Use Compared to Insulin Sensitizers

	OCP	Insulin-Sensitizers
Decreased endometrial CA risk	+++	? (+++ ONLY if regular ovulation resumes)
Decreased serum androgens	+++	++
Decreased hirsutism	++	+ (++)
Decreased acne	+++	+

Insulin Sensitizers and Endometrial Cancer in PCOS

- Ovulation every 2-3 months should obviate risk
- Physiologic ovulation *may be* more protective than an induced withdrawal bleed
- Insulin resistance may contribute to the risk of endometrial cancer

Nagamani M, et al. *Am J Obstet Gynecol* 1991; 165:1865
Nagamani M, et al. *J Clin Endocrinol Metab* 1992; 74:172

Traditional Therapy for PCOS: Oral Contraceptive Pills

Pros

- Reduce the risk for endometrial carcinoma
- Suppress ovarian androgen production
- Ameliorate hirsutism and acne

Cons

- Worsen insulin resistance
- May cause glucose intolerance
- May increase triglycerides
- May increase risk of cardiovascular disease

What is the most suitable pharmacologic management of PCOS when considering metabolic syndrome?

Long-term Therapy: OCPs versus Insulin-Sensitizers

OCP in PCOS

- May worsen insulin resistance
- May induce glucose intolerance
- May increase serum triglycerides
- May increase risk for DM2
- May increase risk for cardiovascular disease

Insulin Sensitizers in PCOS

- Improve insulin sensitivity
- Improve glucose tolerance
- May reduce serum triglycerides
- Reduce plasma PAI-1
- Reduce endothelin-1
- Reduced CRP

Insulin Sensitizers in IGT or GDM

- Prevent progression to DM2
- May decrease CV disease

When Contraception Is Needed

- Benefits of OCP use outweigh any potential risks in most women with PCOS
- When a women with PCOS has IGT or type 2 diabetes:
  - **Recommend another contraceptive method and prescribe an insulin sensitizer such as metformin**

  OR
  - **Prescribe an insulin sensitizer to use concomitantly with OCP use**

When Contraception Is Not Needed

- First-line therapy can consist of either OCP use or an insulin sensitizer
- Evidence is lacking regarding the superiority of OCP use compared to treatment with an insulin sensitizer for the long-term management of both the symptoms of PCOS and the risks associated with metabolic syndrome

When Contraception Is Not Needed

The ideal profile for OCP use is the following:

- Nonobese women with PCOS with normal waist circumference (≤35 inches); AND
- Absence of metabolic syndrome – normal OGTT, HDL ≥50 mg/dL, triglycerides <150 mg/dL and normal blood pressure; AND
- No clinical evidence of insulin resistance – no acanthosis nigricans and normal SHBG; AND
- No first-degree family history of type 2 diabetes or early cardiovascular disease, and no strong second-degree family history

Minimizing OCP Risks in PCOS

Before and after 3-4 months of OCP use:

- Check blood pressure
- Perform an OGTT
- Measure lipids (triglycerides)

When Contraception Is Not Needed

Insulin sensitizers may be useful in:

- Obese women with PCOS
- Presence of metabolic syndrome
- Clinical evidence of insulin resistance – acanthosis nigricans or low SHBG
- Positive first-degree family history of type 2 diabetes or early cardiovascular disease, or strong second-degree family history

Menstrual Cycle Induction and Minimization of Metformin Risks

Over a period of 3-6 months:

- Begin metformin at low dose (250 mg bid) and ↑ dose progressively by 500 mg/d every 7 days, based on tolerance
- Verify side effects and adjust dosage or change to another insulin sensitizer
- Document menstrual frequency of at least every 2-3 months

CONCLUSION

Summary & Key Points

- Insulin sensitizers may improve features of the metabolic syndrome in women with PCOS, and may retard the progression toward type 2 diabetes and cardiovascular disease in those who have IGT
- OCP use can decrease glucose tolerance in women with PCOS in the short term, and *may* increase the risk of developing type 2 diabetes or cardiovascular disease in the long term
- Treatment with an insulin sensitizer is a metabolically favorable alternative to OCP use for women with PCOS, and should be considered when contraception is not needed

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NOTES

NOTES

SURGICAL MANAGEMENT OF OBESITY TO AMELIORATE METABOLIC SYNDROME IN POLYCYSTIC OVARY SYNDROME

Frank González, M.D
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College of Medicine, Mayo Clinic
Rochester, MN

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Discuss the surgical approach to weight loss to ameliorate the symptoms of metabolic syndrome and PCOS in the morbidly obese.
2. Describe the outcome of bariatric surgery to achieve weight loss and improvement of metabolic parameters in PCOS.
3. Describe the complications of bariatric surgery in relation to the benefits of this approach in morbidly obese women with PCOS.

Surgical Management of Obesity to Ameliorate Metabolic Syndrome in Polycystic Ovary Syndrome

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MAYO CLINIC

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Disclosure

Frank González

No Disclosures

Prevalence of Morbid Obesity

- Obesity is an epidemic in the United States
- Prevalence of morbid obesity
  - Women, 7% (**19 million** people!)
  - Men, 3% (**8 million** people!)
- Success of nonoperative weight loss programs - <5%*

* 2 to 5 year maintenance of significant weight loss

Achievement of Weight Loss

- Weight loss by lifestyle modification revolving around a healthy diet and regular exercise is effective in ameliorating the symptoms of PCOS in obese women with the disorder
- Morbidly obese individuals (BMI >40 kg/m^2) tend to be less successful in achieving weight loss by lifestyle modification
- Bariatric surgery may be the best alternative to achieve sufficient weight loss in morbidly obese women with PCOS

Achievement of Weight Loss

Standard Recommendations:

- Low-fat, low-calorie diet
- Exercise program (i.e., at least 45 minutes of aerobic exercise 3 times a week)
- Metformin therapy in the face of a weight loss diet and regular exercise
- Adjunctive sibutramine or orlistat therapy to suppress the appetite

Achievement of Weight Loss

- Standard recommendations do not achieve adequate weight loss in the morbidly obese population
- Bariatric surgery can assist morbidly obese individuals to achieve sufficient weight loss to decrease the risk of medical illness
- Modern surgical approaches with some degree of reversibility facilitate weight loss in the morbidly obese high-risk population

Bariatric Surgery Goal

- Improve health and survival !!
- Lose ≥50% of excess body weight
  - Cosmesis
  - Improve self-image

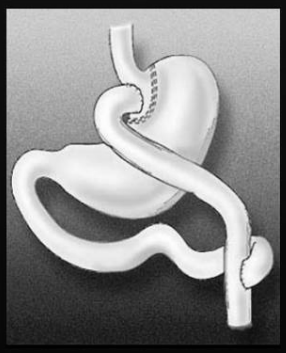
History of Surgery for Obesity

Jejuno-ileal bypass	1956
Gastric bypass	1966
Gastric partitioning	1976
Vertical banded gastroplasty	1980
Partial pancreato-biliary bypass	1984
Laparoscopic gastric banding	2000

Bariatric Surgery - Operative Approaches

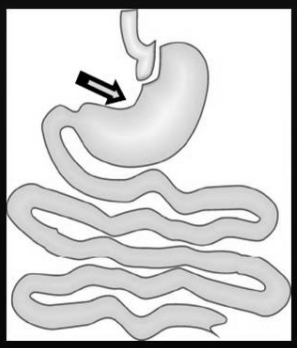
Global malabsorption	Jejuno-ileal bypass
Gastric restriction	Stomach stapling
	Laparoscopic banding
Combination malabsorption & restriction	Roux-en-Y gastric bypass
Selective maldigestion	Pancreato-biliary bypass

Roux-en-Y Gastric Bypass



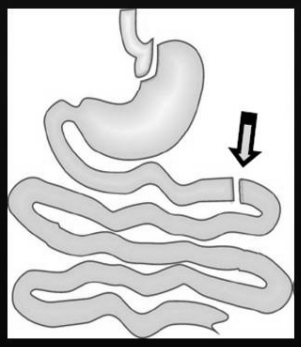
- The most commonly performed weight loss surgery in the U.S.
- Primarily causes weight loss by restricting food intake
- A small amount of malabsorption also contributes to weight loss

Roux-en-Y Gastric Bypass



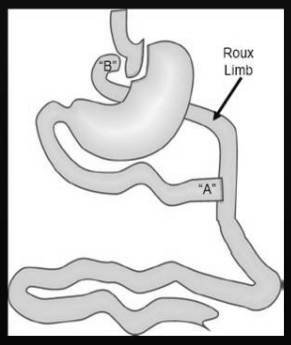
- The stomach is divided by stapling into a small proximal pouch and a larger distal portion that remains dormant
- The proximal pouch is only 5% the size of the entire stomach

Roux-en-Y Gastric Bypass



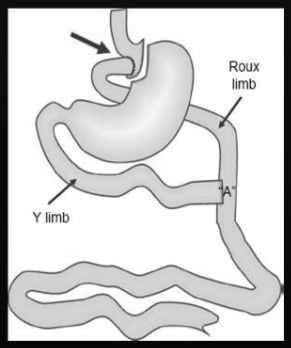
- The proximal jejunum is divided by surgical staples 3 feet from the end of the stomach

Roux-en-Y Gastric Bypass



- The proximal jejunum coming from the stomach ("A") is reattached to the small intestine 3-5 feet away from the recently stapled end to form the Roux limb
- The proximal Roux limb ("B") is brought next to the proximal stomach pouch

Roux-en-Y Gastric Bypass

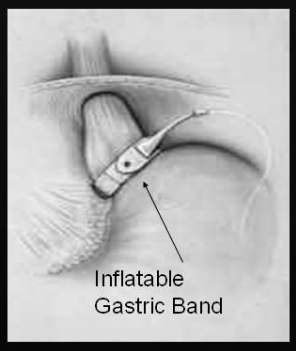


- The proximal Roux limb is attached to the proximal stomach pouch (red arrow)
- The Roux limb carries food to the intestines
- The Y limb carries digestive secretions from the pancreas, liver and duodenum to the intestines
- Food and digestive secretions mix where the 2 limbs meet ("A")

Roux-en-Y Gastric Bypass

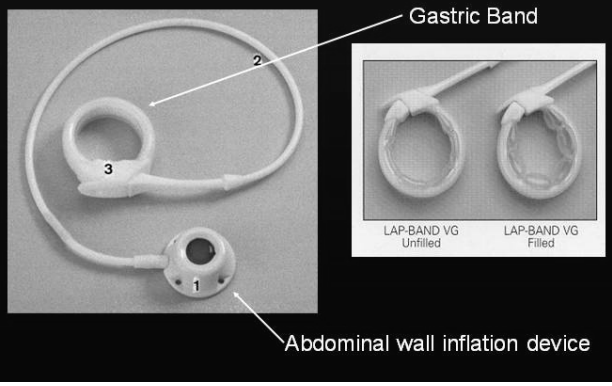
Advantages	Disadvantages
Effective	Malabsorption of Iron, calcium, vitamin B_{12}
Dumping anatomy reduces maladaptive eating	Technically difficult
Early satiety	Higher morbidity

Laparoscopic Banding



- Anatomically creates a 10-15 ml pouch with a 12 mm stoma
- Physiologically causes:
  - Early satiety
  - Decreased appetite
  - Behavior modification
  - Diet modification
- Long-term follow up is essential for band adjustment

Laparoscopic Banding



Laparoscopic Banding

- Laparoscopic adjustable gastric banding is associated with fewer surgical complications and more gradual weight loss compared to the Roux-en-Y gastric bypass that partially relies on malabsorption to achieve weight loss
- Adjustment of the inflatable gastric balloon within the gastric band permits a decrease in gastric constriction during pregnancy to increase nutritional intake

Perioperative Program

- 6-month preoperative nutrition and exercise program using a multidisciplinary approach
- Preoperative goal is to uncover any nutritional, metabolic or psychological issues that might interfere with the success of the surgery
- Postoperative goal is to monitor the response to the surgery and to screen for nutritional deficiencies

Swedish Obese Subjects Trial

- Obese individuals (men – BMI >34 kg/m^2; women - BMI >38 kg/m^2) were offered bariatric surgery (n =2,010) **versus** standard medical and behavioral therapy (n = 2,037)
- Mean age was 48, and mean BMI was 41 kg/m^2
- After 10 years of follow-up, weight had decreased by a mean of 23% in the surgery group, and increased by a mean of 0.1% in the medical-behavioral group
- The surgery group demonstrated better control of blood glucose and blood pressure, increases in HDL and decreases in uric acid

1998 – Karlson et al. Int J Obes 22:113
2004 – Sjostrom et al. N Engl J Med 351:2683

Efficacy of Bariatric Surgery in PCOS

- Changes in menstrual cycles, hirsutism, infertility and type 2 diabetes were evaluated following Roux-en-Y gastric bypass surgery in 24 morbidly obese women with PCOS
- Regular menstrual cycles occurred in all subjects within 3 months of surgery
- Hirsutism scores improved in half of the patients who underwent surgery
- One quarter of the patients conceived with the aid of clomiphene citrate therapy postoperatively

2005 – Eid et al. Surg Obes Related Dis 1:77

Mortality Rate Following Bariatric Surgery

- Study performed in the U.S. evaluating morbidity and mortality in morbidly obese individuals who underwent bariatric surgery compared with those who did not (n = 7,925 in each group)
- Subjects were matched for age, sex and BMI and followed for 7 years
- 40% lower mortality rate in the surgical group
- Reduction in mortality rate related to lower incidence of type 2 diabetes by 92%, and cardiovascular disease by 56% in the surgery group

2007 – Adams et al. N Engl J Med 357:753

Remission of Type 2 Diabetes Following Bariatric Surgery

- Randomized study of 60 obese (BMI >30 kg/m^2) patients with type 2 diabetes comparing bariatric surgery to conventional diabetes therapy (i.e., weight loss and antihyperglycemia medications)
- Remission of diabetes was achieved in 73% of subjects in the surgery group compared to only 13% in the conventional therapy group
- Surgery group lost 21% of their body mass compared to only 1.7% in the conventional therapy group
- Remission was highly correlated with the magnitude of weight loss

2008 – Dixon et al. JAMA 298:316

Complications of Bariatric Surgery

- Bariatric surgery complications vary with patient co-morbidity, the technical skill and experience of the surgical team, and the type of procedure
- Overall, the 30-day operative mortality rate is <1% regardless of the type of procedure
- Re-operation rate following laparoscopic gastric banding is ~15% due to stomal obstruction, band erosion, band slippage, port malfunction, esophagitis or infection
- Bowel obstruction should be suspected in the presence of nausea, vomiting, fever and abdominal pain
- The most common nutritional abnormalities following bariatric surgery are iron, vitamin B_{12}, folate and thiamine deficiencies

2002 - Kothari et al. Surgery 131:625

Pregnancy Following Bariatric Surgery

- Pregnancy should be avoided for 12 to 18 months, or until weight loss reaches a plateau following bariatric surgery
- Several pregnant women have died following bariatric surgery due to a delay in intervention of a surgical emergency, such as bowel obstruction

2007 – Wax et al. Obstet Gynecol Surv 62:595

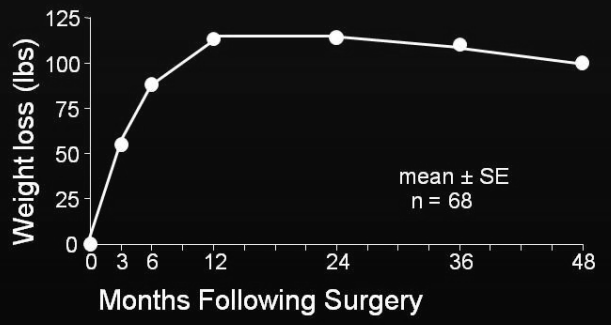
Mayo Experience – Roux-en-Y (1990-1998)

• Operative mortality	2/250*
• Serious morbidity	3/250
• Minor morbidity	~10%
• Long-term morbidity	
– Stomal ulcer	4/250†
– GI bleeding	0/250
– Incisional hernia	~15%

* 1 patient had severe hepatic steatosis
† All related to NSAID use

2000 – Balsiger et al. Mayo Clin Proceed 75:673

Roux-en-Y Gastric Bypass



2000 – Balsiger et al. Mayo Clin Proceed 75:673

Postoperative Amelioration of Co-morbidity

	Prevalence (%)	Cured(%)	Improved (%)
Asthma	10-15	> 95	100
Diabetes	15-20	90-95	100
Dyslipidemia	15-25	70	85
Heart failure	10	60	90
Hypertension	30-60	60-65	90

2001 - Kral et al. Clin Perspect Gastroenterol 4:298

Conclusion

- In morbidly obese women with PCOS, the degree of weight loss is significantly greater following bariatric surgery compared to conventional therapy
- Bariatric surgery can ameliorate the metabolic abnormalities in morbidly obese women with PCOS
- Surgical complications related to bariatric surgery are relatively low
- Bariatric surgery offers significant metabolic benefits for women with PCOS, which may promote fertility

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NOTE

NOTES

Course #7 Test Questions

1. Which of the following conditions is not part of the National Cholesterol Education Program Adult Treatment Panel II criteria to diagnose the metabolic syndrome?

a. Abdominal adiposity (waist circumference >88 cm)
b. Serum triglycerides ≥150 mg/dl
c. C-reactive protein >3 mg/L
d. Blood pressure ≥130/>85 mm Hg
e. Fasting glucose level ≥110 mg/dl
f.

2. A 26-year-old patient with PCOS has a BMI of 30 kg/m^2 but is otherwise healthy, and has a normal blood pressure during two office visits. Her fasting lipid profile and fasting glucose level are both normal. What would be the best approach to initially screen for impaired glucose tolerance?

a. A repeat fasting glucose level
b. A 75-gm oral glucose tolerance test regardless of her fasting glucose level
c. Weight and exercise followed by a 75-gm oral glucose tolerance test
d. No further screening is necessary because her fasting glucose is normal
e. No further screening is necessary because she does not have another risk factor for impaired glucose tolerance

3. A 24-year-old patient with PCOS with a BMI of 28 kg/m^2 does not smoke and has an unremarkable past medical history. Which one of the following affirmations regarding cardiovascular disease applies to this patient?

a. There is no published data to suggest that she may have increased coronary artery calcifications (a marker of established atherosclerosis)
b. There is no published data to suggest that she may have increased carotid intima-media thickness (a marker of established atherosclerosis)
c. There is no published data to suggest that she may have increased femoral intima-media thickness (a marker of established atherosclerosis)
d. There are published data to suggest that she may have increased coronary artery calcifications along with carotid and femoral intima-media thickness
e. There are data from prospective cohort studies of women with PCOS showing that she is at increased risk for cardiovascular events

4. What is the prevalence of obesity in American women with PCOS based on the majority of most studies performed in the United States?

a. 0-20%
b. 20-40%
c. 40-60%
d. 60-80%
e. 80-100%
f.

5. Mononuclear cell-derived markers of oxidative stress and inflammation are associated with all of the following measurements except:

a. Abdominal adiposity
b. Bone density
c. Insulin sensitivity
d. Serum testosterone
e. Serum androstenedione

6. To improve metabolic syndrome, low intensity physical exercise is indicated at least:

a. 1 time a week
b. 2 times a week
c. 3 times a week
d. 4 times a week
e. 5 times a week

7. A 25-year-old patient with PCOS and impaired glucose tolerance (IGT) requires contraception. Her hyperandrogenemia is suppressed with an oral contraceptive pill (OCP) containing 35 µg of ethinyl estradiol (EE). Other than lifestyle modification, what is the best management of this patient who has IGT?

a. Nothing else, continue the OCP
b. Change to an OCP with a lower dose of EE
c. Change to an OCP with a lower dose of EE, and add an insulin sensitizing drug such as Metformin
d. Change to an OCP with a lower dose of EE, and add an anti-androgen such as Spironolactone
e. Discontinue OCP use, and advise her to use another method of contraception

8. A 32-year-old patient with PCOS with a BMI of 50 kg/m^2 has secondary amenorrhea, hirsutism, type 2 diabetes and dyslipidemia. Weight loss was recommended in an effort to ameliorate these conditions. Which of the following is the most effective approach to achieve weight loss in this patient?

a. Lifestyle modification
b. Bariatric surgery
c. Metformin therapy
d. Sibutramine use
e. Nonsteroidal anti-inflammatory agents