Forty-second Annual
Postgraduate Program

October 18, 2009
Atlanta, GA

PCOS:
Origins and Destiny

Course
13

Developed in
Cooperation with the
Society for Reproductive
Endocrinology and
Infertility

Sponsored by the
American Society for
Reproductive Medicine

New Procedure to Obtain CME Credits

Dear Postgraduate Course Participant:

The Accreditation Council for Continuing Medical Education now requires that ASRM document learning for participants in CME programs. Thus, the procedure for claiming CME credits has changed. We ask your cooperation in following the steps below to ensure that your credits are provided correctly to you.

1. Within 3 days after the Annual Meeting you will be sent an email asking you to complete an online evaluation of this postgraduate course. A personalized Web link to the evaluation will be provided in your email. Please do not share this unique link.
2. In late November you will be sent a second email with a personalized Web link asking you to complete the post-test on the content of the course. This test is identical to the pre-test and will enable ASRM to assess the effectiveness of this postgraduate course as a learning activity. For your convenience, the test questions are printed in the course syllabus.

After both steps have been completed, you will be able to claim your CME credits and/or ACOG Cognates and receive a printable CME certificate. Please note that you must provide your 10-digit ACOG Membership Number to have your ACOG Cognates reported to ACOG. Results of both the course evaluation and the post-test are anonymous.

Both steps must be followed completely by **December 31, 2009** in order to receive CME credits. A maximum of 6.5 CME credits can be claimed for the postgraduate course. Please be aware that some email systems flag emails with Web links as junk mail, and you may need to check your junk-email folder for your notifications.

Please DO NOT forward the links. In case of difficulty please email pfenton@asrm.org

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********Deadline for receiving CME credits = December 31, 2009********

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 competence or performance; second, be documented to be effective at increasing physician skill or performance; and third, conform to the ACCME Standards for Commercial Support.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Developed in Cooperation with the

SOCIETY FOR REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

October 18, 2009

"POLYCYSTIC OVARY SYNDROME: ORIGINS AND DESTINY"

Chair: **Nanette Santoro, M.D.**
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Director of Reproductive Endocrinology
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All speakers at the 2009 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:

Nanette Santoro, M.D.: QuatRx: Consultant, Ferring: Grant support

Daniel A. Dumesic, M.D.: Schering-Plough, Ferring Pharmaceuticals: Grant support

Kathleen M. Hoeger, M.D.: Nothing to disclose

Richard S. Legro, M.D.: Solvay Pharmaceuticals Study Investigator, Merck-Serono: Consultant

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 1 Credits™*. 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 6.5 cognate credits to this activity.

American Board of Bioanalysis (ABB)
The American Society for Reproductive Medicine has been approved to provide Professional Enrichment Education Renewal (PEER) credit through the American Board of Bioanalysis. PEER credit information for eligible courses is located in the front of this syllabus.

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

Thank you.

POLYCYSTIC OVARY SYNDROME: ORIGINS AND DESTINY

NEEDS ASSESSMENT AND COURSE DESCRIPTION

Physicians are often confused about the best methods for identification and treatment of PCOS in adolescents, as well as the most appropriate, evidence-based treatments for fertility enhancement. In addition, there is a relative lack of understanding of the genetic correlates of PCOS in family members. This lack of knowledge results in ineffective therapies (e.g., metformin) being given for ovulation induction, delayed diagnosis of PCOS in adolescence with resulting increased hyperandrogenic symptoms, and a lack of an appropriately focused approach to family members of women with PCOS who may well visit the same physician.

This course is aimed at physicians, nurses and nurse practitioners who care for women with polycystic ovary syndrome. Topics to be covered include the genetic basis for PCOS and its phenotypic expression in relatives; the Rotterdam and NIH criteria, and their differences and their relative effectiveness in diagnosing PCOS; and the Barker hypothesis and its ramifications. Participants will be better equipped to provide the most appropriate care, understand and apply the appropriate criteria in order to facilitate diagnosis, and provide the best possible care for pregnant women with PCOS, thus ensuring the health of the next generation of offspring of PCOS women.

ACGME COMPETENCY

Patient Care
Medical Knowledge

LEARNING OBJECTIVES

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

1. Describe the potential prenatal (programming) and genetic underpinnings of PCOS.
2. Detect PCOS in childhood and adolescence.
3. Define PCOS in clinical practice.
4. Develop short- and long-term treatment strategies for women with PCOS of varying phenotypes.

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ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

October 18, 2009

"PCOS: ORIGINS AND DESTINY"

Nanette Santoro, M.D., Chair

Sunday, October 18, 2009

08:15 – 08:30	Course Introduction and Orientation **Nanette Santoro, M.D.**
08:30 – 09:05	Prenatal Programming: The Role of the Intrauterine Environment in Predicting Future Insulin Resistance **Daniel A. Dumesic, M.D.**
09:05 – 09:15	Questions and Answers
09:15 – 09:50	Genetics of PCOS 2009: Implications for Clinical Practice **Richard S. Legro, M.D.**
09:50 – 10:00	Questions and Answers
10:00 – 10:30	Break
10:30 – 11:05	Childhood and Adolescent Manifestations Of PCOS—How Early and How Effectively Can It Be Treated? **Kathleen M. Hoeger, M.D.**
11:05 – 11:15	Questions and Answers
11:15 – 11:50	Debate: Have the Rotterdam Criteria Simplified the Diagnosis of PCOS? Pro: **Richard S. Legro, M.D.** Con: **Kathleen M. Hoeger, M.D.**
11:50 – 12:00	Questions and Answers
12:00 – 13:00	Lunch
13:00 – 13:35	Preventing the Long-term Sequelae of Insulin Resistance in PCOS **Richard S. Legro, M.D.**
13:35 – 13:45	Questions and Answers
13:45 – 14:20	Prevention of Hirsutism **Daniel A. Dumesic, M.D.**

Sunday, October 18, 2009 (continued)

14:20 – 14:30	Questions and Answers
14:30 – 15:00	PCOS 101: First Line Ovulation Induction: Weight Loss, Clomiphene and Its Variations **Richard S. Legro, M.D.**
15:00 – 15:30	Break
15:30 – 16:00	Gonadotropin Regimens for ART **Daniel A. Dumesic, M.D.**
16:00 – 16:30	Long-term Cardiovascular Issues and Their Prevention **Kathleen M. Hoeger, M.D.**
16:30 – 17:00	Menopause: It's Different If You Have PCOS **Nanette Santoro, M.D**

PRENATAL PROGRAMMING: THE ROLE OF THE INTRAUTERINE ENVIRONMENT IN PREDICTING FUTURE INSULIN RESISTANCE

Daniel A. Dumesic, M.D.
Clinical Professor, Division of Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
University of Wisconsin, Madison
Affiliated Scientist, National Primate Research Center
University of Wisconsin, Madison

LEARNING OBJECTIVES

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

1. Define two alterations during fetal development that could permanently program adult physiology.
2. Contrast differences in fetal growth between prenatally androgenized female rhesus monkeys and sheep.
3. Formulate a mechanism by which prenatal androgenization in rhesus monkeys promotes increased infant weight gain.

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Disclosure

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Schering-Plough Pharmaceuticals
Ferring Pharmaceuticals

Polycystic Ovary Syndrome (PCOS)

Reproductive abnormalities
- Luteinizing hormone (LH) hypersecretion
- Ovarian hyperandrogenism
- Polycystic ovaries
- Hirsutism/anovulation

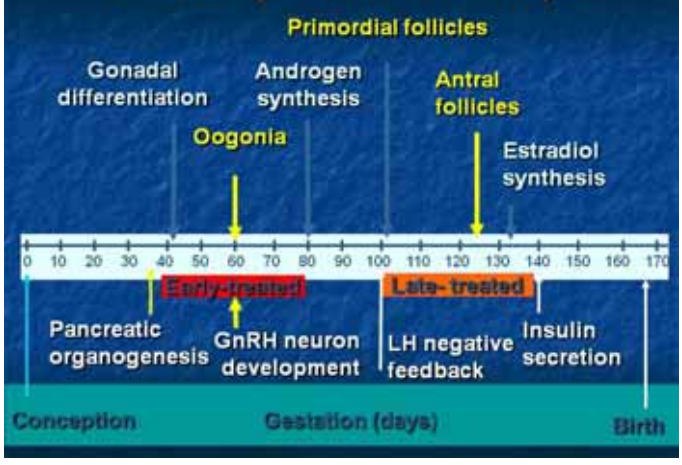
Metabolic abnormalities
- Hyperinsulinemia from insulin resistance
- Abdominal adiposity
- Impaired pancreatic β-cell function
- Type 2 diabetes mellitus

PCOS-like Phenotype: Prenatally Androgenized (PA) Female Rhesus Monkeys and Sheep

	PA monkeys early-treated	PA monkeys late-treated	PA sheep
Ovarian hyperandrogenism	Yes	Yes	Ovarian androgen upregulation
Anovulation	Yes	Yes	Yes
Enlarged polyfollicular ovaries	Yes	Yes	Yes
LH hypersecretion	Yes	No	Yes
Reduced steroid negative feedback on LH	Yes	Yes	Yes
Impaired embryonic development	Yes	Yes	Impaired fertility

Dumesic D et al. 2007

Fetal Development in Rhesus Monkeys



Prenatal Entrainment of LH Hypersecretion (16 Adult Pregnant Female Rhesus Monkeys)

Before conception: females had similar ages and body weights.

Gestational days 30±2 (mean±SEM): female fetuses were identified by absence of Y-chromosomal DNA in maternal blood.

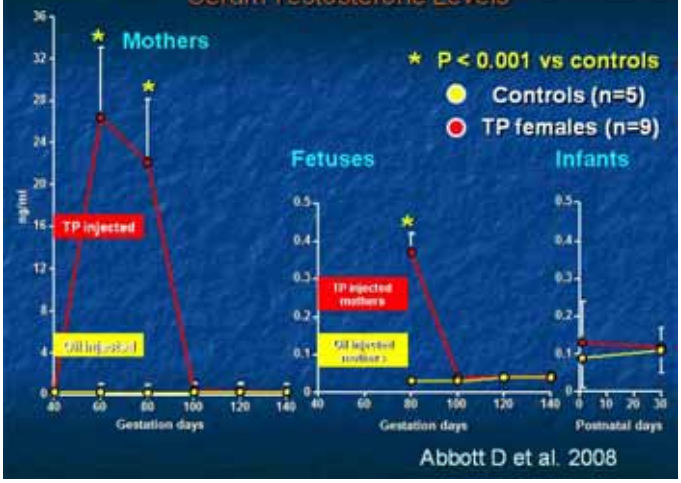
Gestational days 40-80: pregnant females received 15 mg testosterone propionate (TP) subcutaneously (sc) daily [n=9] or vehicle control [n=7].

Maternal blood was obtained from a peripheral vessel.

Fetal blood was obtained by ultrasound-guided cardiocentesis of the left ventricle using a 25-gauge aspiration needle.

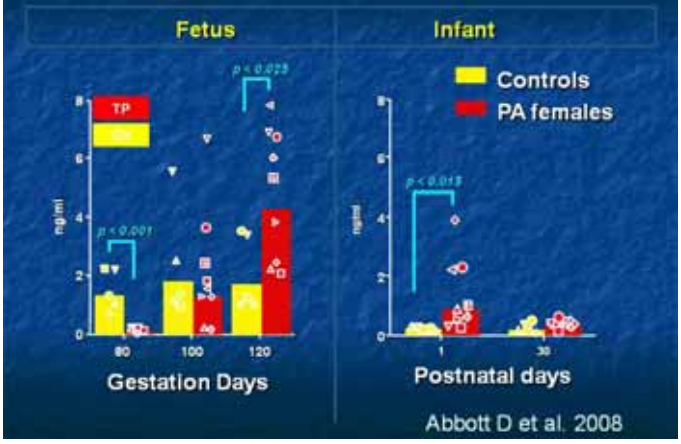
Infant blood was obtained from the umbilical artery at term C-section (postnatal day 1) and from the femoral vein on postnatal day 30.

Serum Testosterone Levels



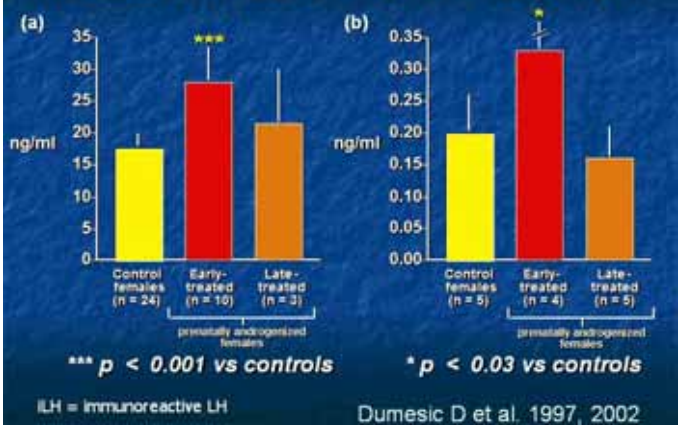
Abbott D et al. 2008

Serum Biological LH (BioLH) Levels



Abbott D et al. 2008

Serum Levels of A) iLH in 13- to14-Year-Old Females and B) bioLH in 18- to 20-Year-Old Females During IVF



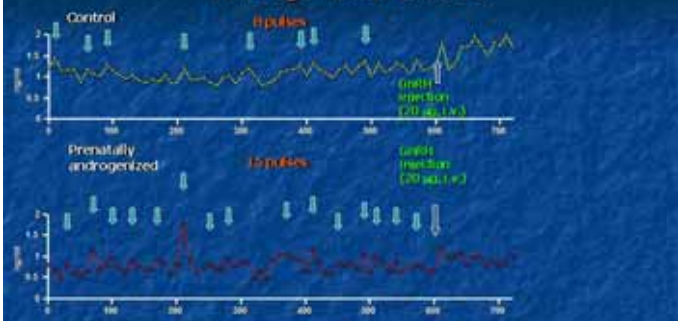
*** $p < 0.001$ vs controls

* $p < 0.03$ vs controls

iLH = immunoreactive LH

Dumesic D et al. 1997, 2002

Increased LH Pulse Frequency in Adult Prenatally Androgenized Females



PA: $p < 0.04$ vs. controls

LH Pulse identified by PULSAR

PCOS-like Abnormalities in Prenatally Androgenized (PA) Female Rhesus Monkeys

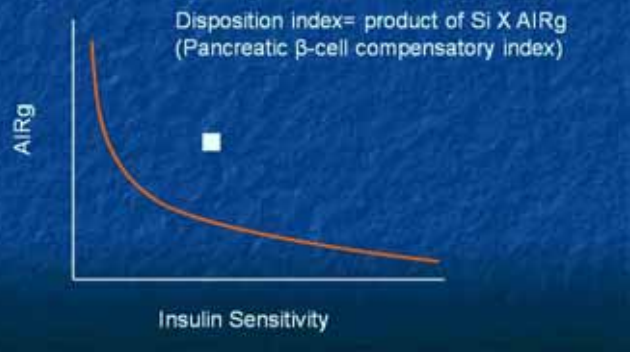
	PA monkeys early-treated	PA monkeys late-treated
Visceral obesity	Yes	No
Insulin resistance	Yes	No
β cell impairment	Yes	No
Glucose intolerance	Yes	yes
Increased type 2 diabetes	Yes	No

Abbott D et al. 2007

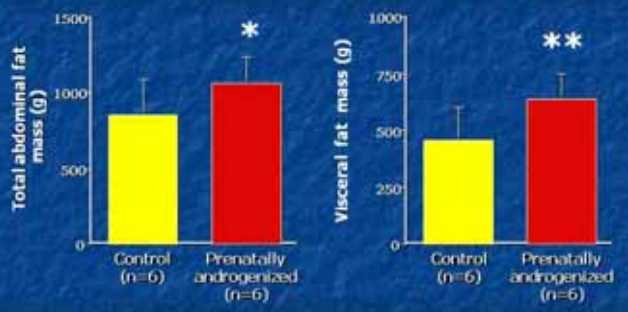
Metabolic Effects of Early Prenatal T-Treatment

- **Maternal Effects**
  - Increased weight gain at midgestation
  - Mild to moderate glucose intolerance
  - Hyperinsulinemia
- **Fetal Effects**
  - Elevated serum insulin levels
  - Increased biparietal diameter
  - **Neonatal Effects**
  - Normal birth weight
  - Increased postnatal weight gain
  - Increased insulin sensitivity and disposition index

Hyperbolic Relationship Between Insulin Sensitivity (Si) and Acute Insulin Release to Glucose (AIRg)



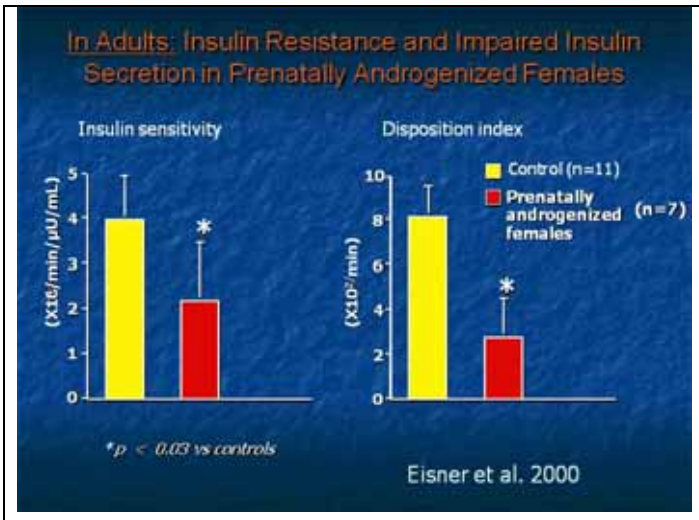
In Adults, Increased Abdominal Adiposity in Prenatally Androgenized Compared to Controls

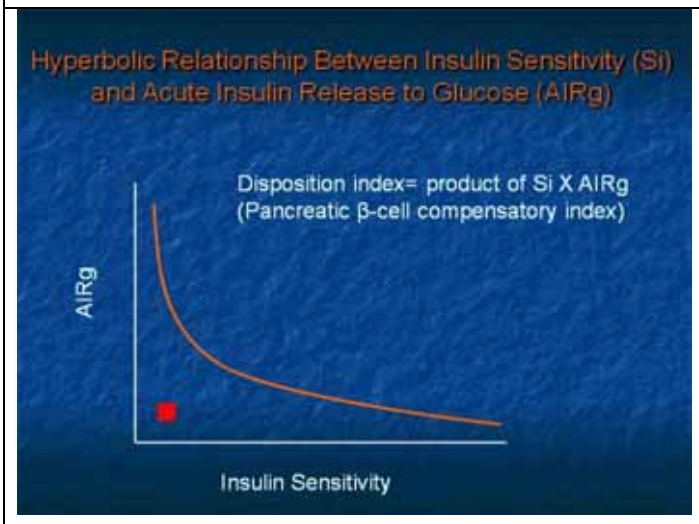


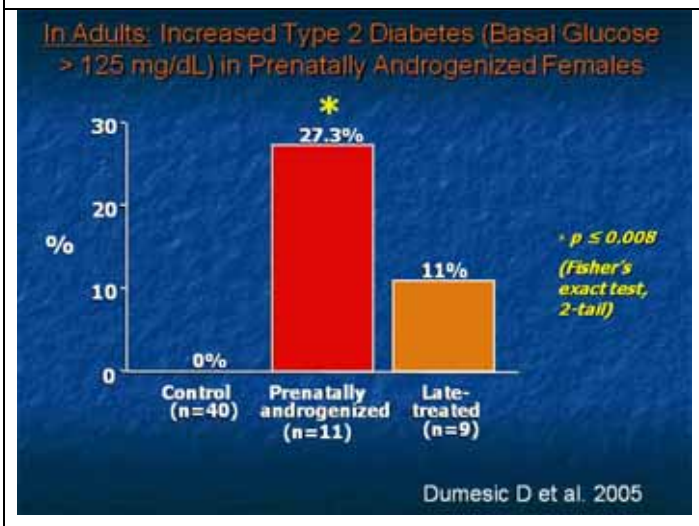
* $p \leq 0.04$ vs. control

** $p \leq 0.01$ vs. control

Eisner J et al. 2003


In Adults: Insulin Resistance and Impaired Insulin Secretion in Prenatally Androgenized Females
Insulin sensitivity
Disposition index
(Xit/min/μU/mL)
(X10⁴/min)
Control (n=11)
Prenatally androgenized females (n=7)
*p < 0.03 vs controls
Eisner et al. 2000


Hyperbolic Relationship Between Insulin Sensitivity (Si) and Acute Insulin Release to Glucose (AIRg)
Disposition index= product of Si X AIRg
(Pancreatic β-cell compensatory index)
AIRg
Insulin Sensitivity


In Adults: Increased Type 2 Diabetes (Basal Glucose > 125 mg/dL) in Prenatally Androgenized Females
%
27.3%
11%
0%
Control (n=40)
Prenatally androgenized (n=11)
Late-treated (n=9)
* p ≤ 0.008
(Fisher's exact test, 2-tail)
Dumesic D et al. 2005

Proposed Metabolic Aspects of Androgen Excess Action on Offspring

Maternal exogenous androgen excess

↓

Mild-to-moderate maternal glucose intolerance

↓

Mild-to-moderate hyperglycemic pregnancy

↓

Increased fetal growth (e.g., biparietal diameter)

↓

Infants: traits of *in utero* hyperglycemia
50% prevalence of low blood glucose
Insulin sensitive without compensation of pancreatic insulin responses to glucose
Hyperinsulinemia promotes infant weight gain

↓

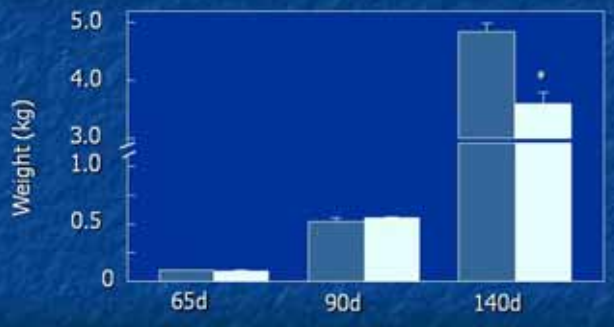
Adults: increased abdominal adiposity, hyperlipidemia, insulin resistance, pancreatic beta cell defects and increased type 2 diabetes

Association Between Hyperinsulinemia and Ovarian Hyperandrogenism During Human Fetal Development

- Insulin, insulin-like growth factor (IGF)-I/-II receptors and 17-alpha hydroxylase exist in mid-gestional fetal ovaries, at which time serum T levels in 40% of female fetuses are elevated into the normal male range.
- In diabetic pregnancies, amniotic fluid T levels are elevated.
- Female stillbirth offspring of diabetic mothers have hirsutism, ovarian theca-lutein cysts and thecal cell hyperplasia.

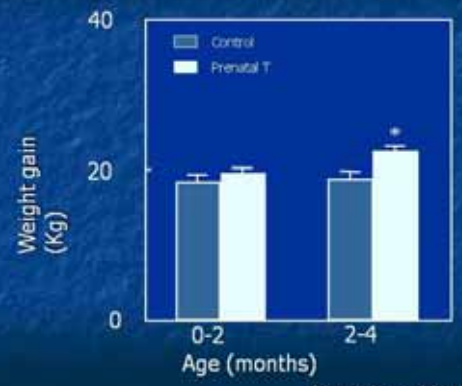
Shifren et al. 1993; Cole et al. 2006; Barbieri et al. 1986; Hultquist et al. 1981; Driscoll et al. 1960; Beck-Peccoz et al. 1991

Fetal Weight in the Prenatally Androgenized Sheep Model



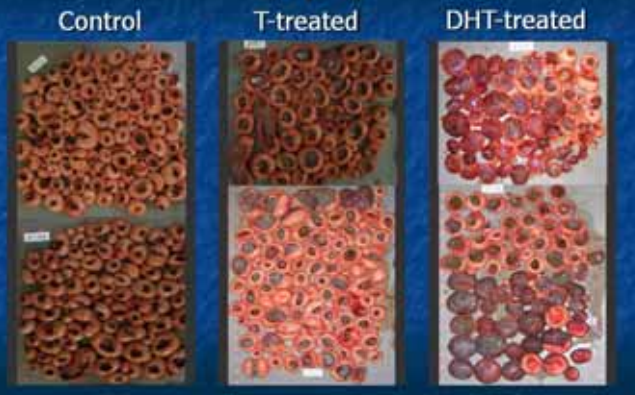
Steckler T et al. 2005

Neonatal Catch-Up Growth in the Prenatally Androgenized Sheep Model



Manikkam M et al. 2004

Androgens Advance Placentome Differentiation (day 90)



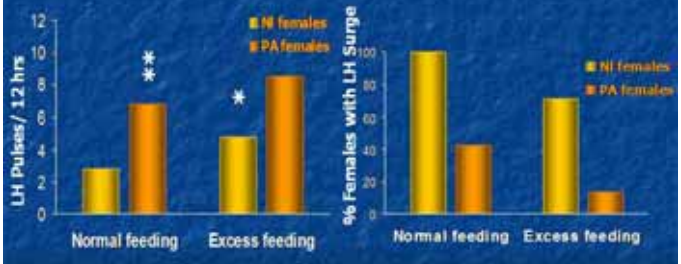
DHT = Dihydrotestosterone

Neonatal Development: Prenatally Androgenized (PA) Female Rhesus Monkeys and Sheep

	Early-treated PA monkeys	PA Sheep
Fetal BPD	Increased	Normal
Birth weight	Normal	Decreased
Neonatal growth	Enhanced	Catch-up
Placental morphology	Normal	Abnormal

Dumesic D et al. 2007

Excess Weight Gain in Pubertal Sheep



*, P<0.05, weight gain effect
**, P<0.001, prenatal T effect

Steckler T et al. 2009

The Two-Hit Hypothesis

- An early perturbation from *in utero* androgen excess resets the reproductive trajectory, while a later-onset metabolic abnormality influences the severity of the adult reproductive phenotype.
- An altered fetal environment may permanently program adult disease by modifying genetic susceptibility to disease after birth.

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18. Steckler T, Wang J, Bartol FF, Roy SK, Padmanabhan V: Fetal programming: prenatal testosterone treatment causes intrauterine growth retardation, reduces ovarian reserve and increases ovarian follicular recruitment. Endocrinology 146: 3185-93, 2005.
19. Steiner RA, Clifton DK, Spies HG, Resko JA: Sexual differentiation and feedback control of luteinizing hormone secretion in the rhesus monkey. Biol Reprod 15: 206-12, 1976.

NOTES

NOTES

GENETICS OF PCOS 2009: IMPLICATIONS FOR CLINICAL PRACTICE

Richard S. Legro, M.D.
Department of Obstetrics and Gynecology
Penn State College of Medicine
M.S. Hershey Medical Center
Hershey, Pennsylvania

LEARNING OBJECTIVES

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

1. Describe family phenotypes in polycystic ovary syndrome (PCOS) families.
2. Identify the characteristics of a good genetic study.
3. Discuss the role of genetic testing in the diagnosis and management of PCOS.
4. Explain possible mechanisms in the intrauterine environment could lead to PCOS.

Genetics of PCOS 2009: Implications for clinical practice

Richard S. Legro, M.D.
Department of Obstetrics and Gynecology
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Learning Objectives

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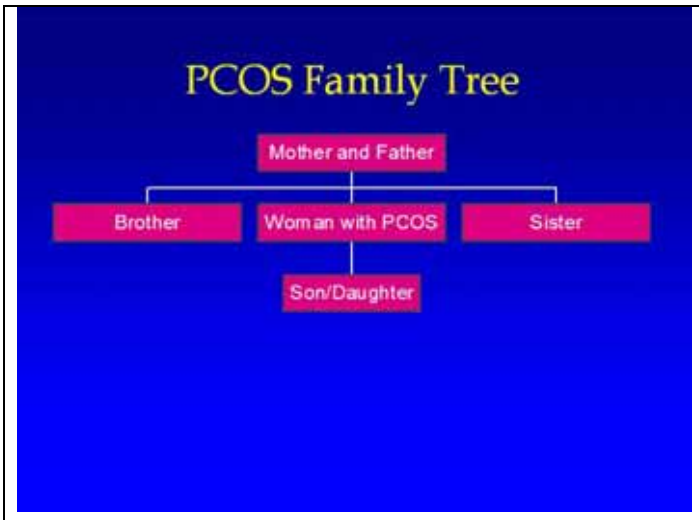
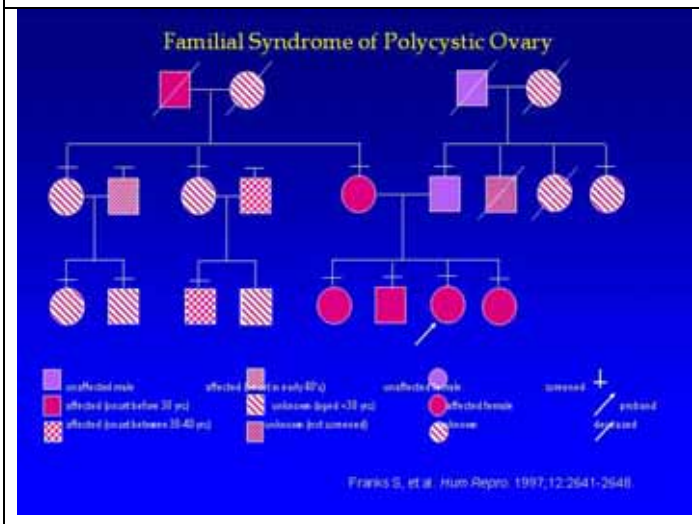
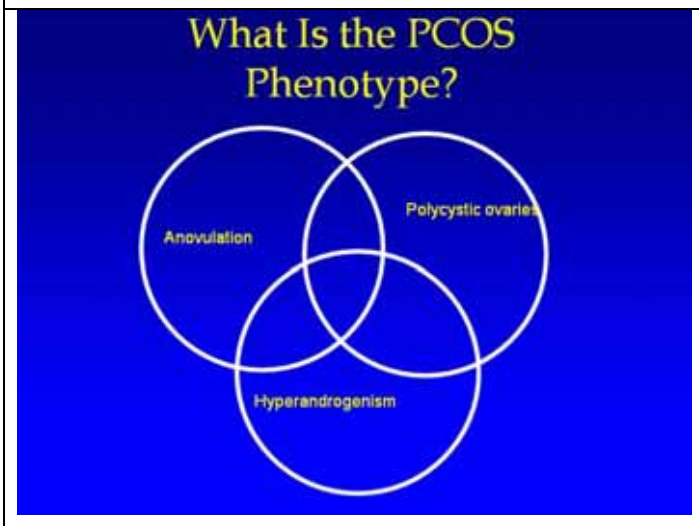
Disclosures

- Study Investigator - Solvay Pharmaceuticals
- Consultant - Merck-Serono


PCOS Family Tree
Mother and Father
Brother
Woman with PCOS
Sister
Son/Daughter


Familial Syndrome of Polycystic Ovary
Franks S, et al. Hum Repro. 1997;12:2641-2648

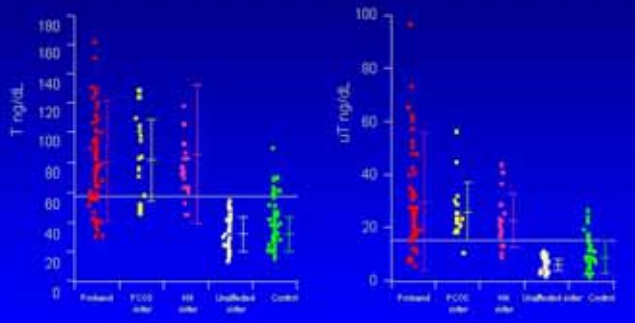

What Is the PCOS Phenotype?
Anovulation
Polycystic ovaries
Hyperandrogenism

Correlation of PCOS Traits in Twins/Sisters

	Monzygotic twins N =1,332 R (95% CI)	Dizygotic twins/sisters N = 1,873 R (95% CI)
Oligomenorrhea	0.67 (0.49 to 0.80)	0.07 (–0.19 to 0.34)
Acne	0.78 (0.69 to 0.84)	0.44 (0.30 to 0.56)
Hirsutism	0.86 (0.75 to 0.92)	0.28 (0.05 to 0.50)
PCOS	0.71 (0.43 to 0.88)	0.38 (0.00 to 0.66)

Vink et al, JCEM, 2006

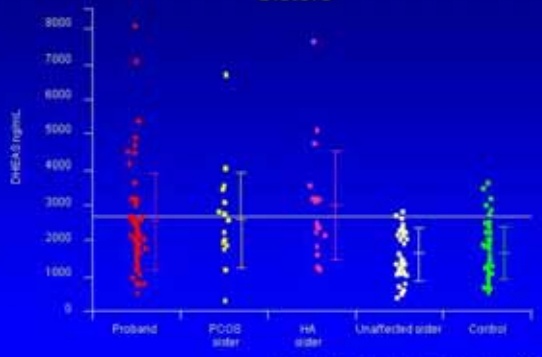
Elevated Testosterone Levels in Affected Sisters



HA = hyperandrogenemia

Legro et al, Proc Natl Acad Sci 95:14956, 1998

Adrenal Androgen Levels Are Elevated in Affected Sisters



Legro et al, Proc Natl Acad Sci 95:14956, 1998

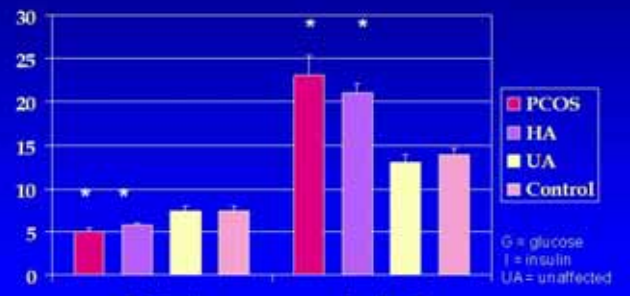
FERTILITY AND STERILITY®
VOL. 75, NO. 1, JANUARY 2001

Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS

Melissa D. Kahsar-Miller, Ph.D.,[a] Christa Nixon, B.S.,[b] Larry R. Boots, Ph.D.,[b] Rodney C. Go, Ph.D.,[c] and Ricardo Azziz, M.D., M.P.H.[b,d]
University of Alabama at Birmingham, Birmingham, Alabama

40% of sisters affected with PCOS (hyperandrogenemia or hirsutism) vs. 4% of control population

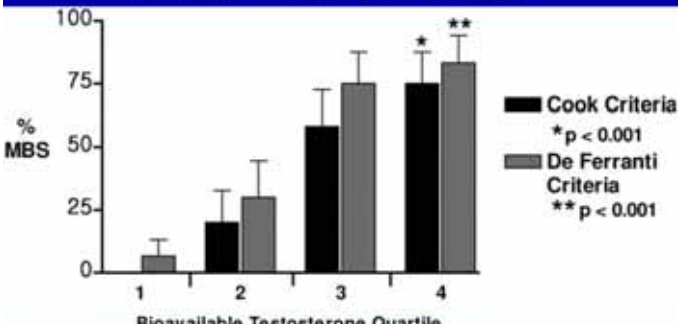
Hyperandrogenemia Tracks with Insulin Resistance in PCOS Sisters



Legro et al, JCEM, 2002

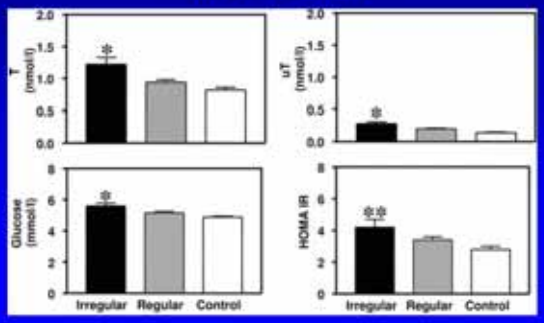
* P < .05 vs. UA/Control

Increasing Bioavailable Testosterone Associated with Metabolic Syndrome (MBS) in Adolescent PCOS



Coviello, A. D. et al. J Clin Endocrinol Metab 2006;91:492-497

Mothers of Women with PCOS have Hyperandrogenemia and Insulin Resistance



Sam, Susan et al. (2006) Proc. Natl. Acad. Sci. USA 103, 7030-7035

Role of Androgens in Metabolic Abnormalities in PCOS Mothers

- In a multivariate regression analysis, the only predictors of LDL levels in mothers were their daughters's LDL levels (r^2 = 0.11, $P < 0.001$) and mothers' own uT levels (r^2 = 0.04, P = 0.03).
- Age, BMI, HOMA IR, tobacco use, alcohol intake, and exercise were not significant predictors of LDL levels in mothers.

LDL = low density lipoprotein
BMI = body mass index
HOMA-IR = homeostasis model assessment of insulin resistance

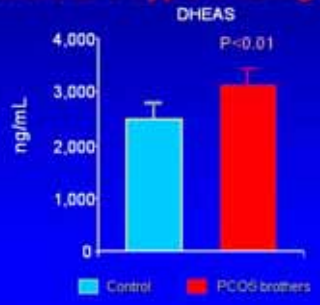
Sam S, PNAS, 2007

Proposed Male Phenotypes in PCOS Families

- Abnormalities in male hair distribution
  - Increased body hair
  - Premature male balding
- Abnormalities in circulating androgens and gonadotropins
- Insulin resistance

What Are the Male Phenotypes?

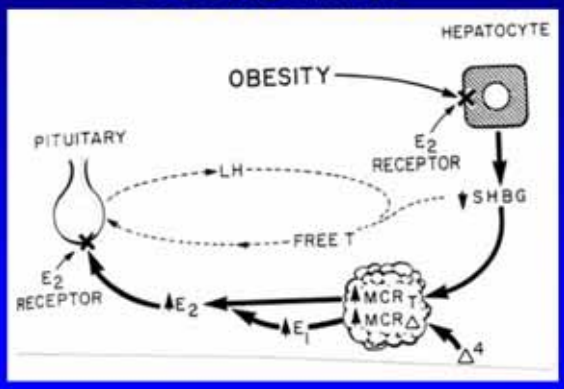
Brothers are hyperandrogenemic



DHEAS = dehydroepiandrosterone

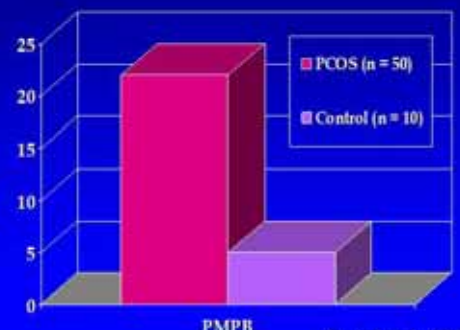
Legro et al J Clin Endocrinol Metab 87:2134-38, 2002

Mechanisms of Hypogonadism in Obese Males



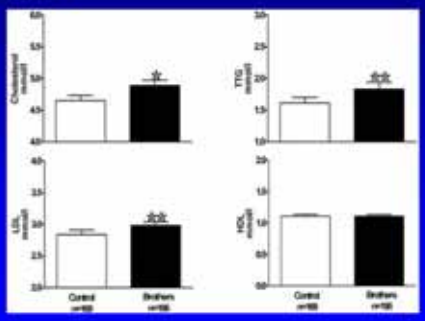
Schneider G, JCEM, 1979

Increased Prevalence of Male Premature Male Pattern Baldness in PCOS Families



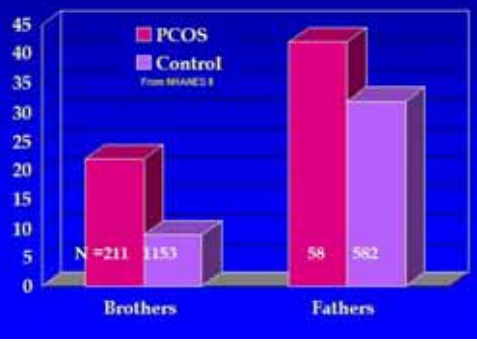
Govind et al, JCEM, 1999

Increased Prevalence of Dyslipidemia and IR in Brothers



Sam et al, Diabetes Care 2008, Metabolism 2008

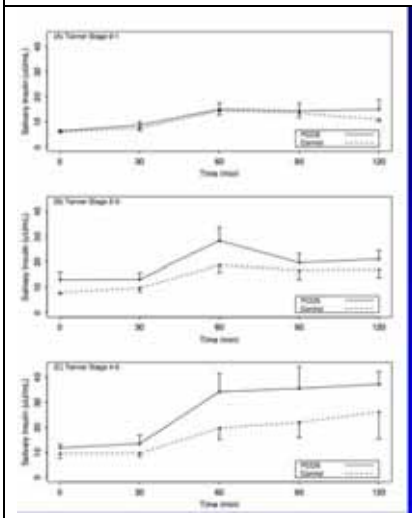
Increased Prevalence of Metabolic Syndrome in First-Degree Male Relatives of PCOS Women



What About the Children of Mothers with PCOS?

Daughters of PCOS Mothers Have PCO

Battaglia et al, Hum Reprod, 2002



Salivary Insulin Levels Increase During Puberty in PCOS Children

N = 32 PCOS children and
N = 36 Control

Kent et al, JCEM 2008

Summary: Family PCOS Phenotypes

- There is evidence that stigmata of PCOS, i.e., PCO, hyperandrogenism and oligomenorrhea, cluster in female relatives.
- Hyperandrogenemia identifies female relatives with insulin resistance/metabolic syndrome.
- Males show some phenotypic similarity: hyperandrogenemia/insulin resistance, but not as pronounced as females.

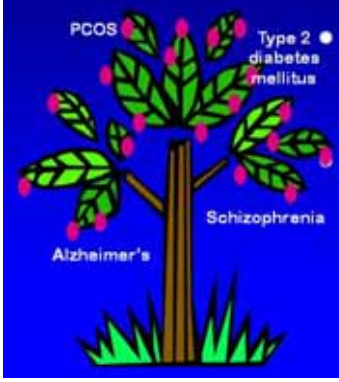
Limitations: Familial Studies of PCOS

- Lack of prospective design
- Small sample size
- Phenotype unknown except in reproductive-age women
  - Changes with age/hormones/pregnancy
- All first-degree relatives not examined
  - Phenotypic heterogeneity apparent when more relatives and families examined

Evidence That a Disease Is Genetic

- Familial clustering
  - Increased risk in relatives compared to the larger population
  - Risk increases with closer relationship
- Heritable
  - Traits are passed on to offspring
- Gene/DNA sequence
  - Associated with/causes the disease

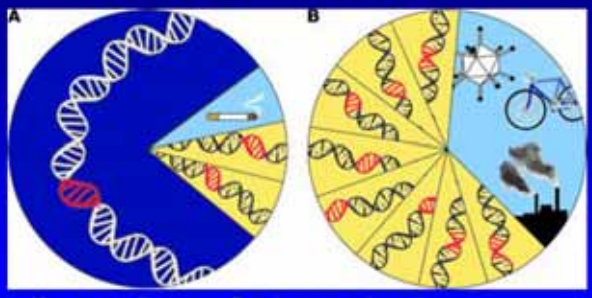
Complex Genetic Diseases



- Positional cloning of a highly penetrant mendelian disorder is now straightforward.
- Identifying a susceptibility gene for a non-mendelian disorder can be vexing.

Francis Collins

Monogenic (A) vs. Complex (B) Disease Genetics

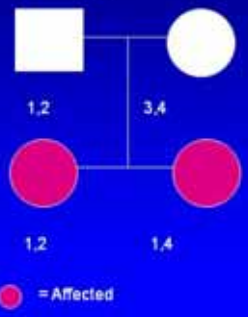


Many genes with modest effects in complex disease!

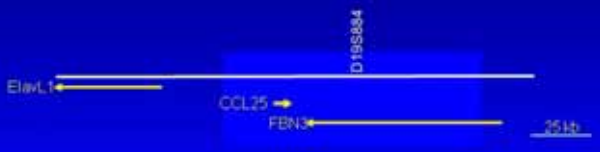
Manolio et al, JCI 2008

Modes of Genetic Analysis

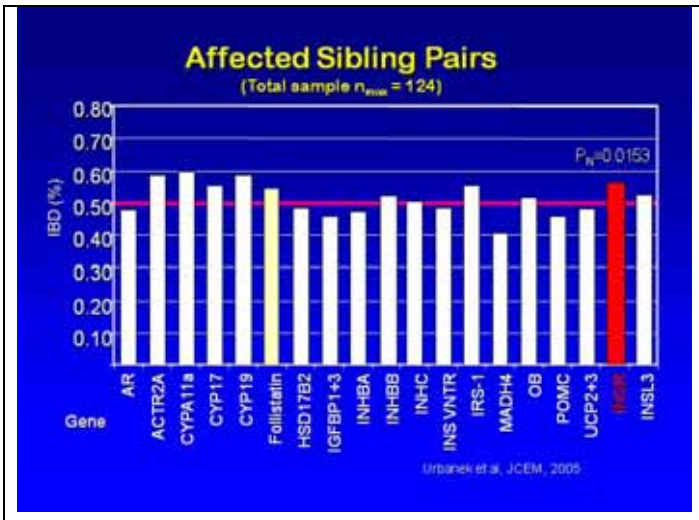
- Association studies
  - Case/control: frequency of allele in an affected and control population linkage analysis
- Linkage studies
  - Family: determination of "linkage" between a polymorphic DNA marker and disease
- Hybrid forms
  - Transmission disequilibrium test (TDT)

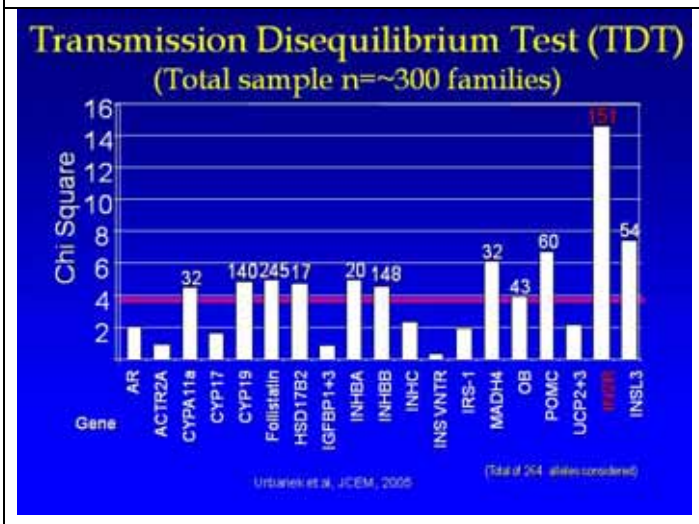


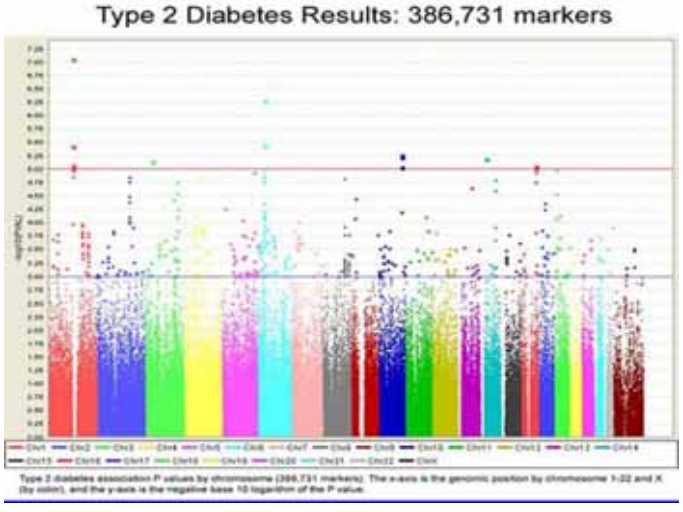
D19S884 Region Linkage Disequilibrium ~50 kb



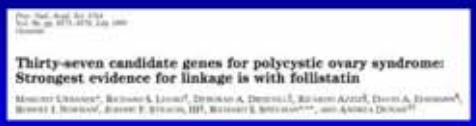
- *FBN3*-Fibrillin 3 (FBN1=Marfan's syndrome, major constituent of extracellular microfibrils, controls TGFβ activation in the lung; FBN2=congenital contractural arachnodactyly)


Affected Sibling Pairs
(Total sample n_{max} = 124)
IBD (%)
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
P_N=0.0153
Gene
AR
ACTR2A
CYPA11a
CYP17
CYP19
Follistatin
HSD17B2
IGFBP1+3
INHBA
INHBB
INHC
INS VNTR
IRS-1
MADH4
OB
POMC
UCP2+3
INSL3
Urbanek et al, JCEM, 2005


Transmission Disequilibrium Test (TDT)
(Total sample n=~300 families)
Chi Square
16
14
12
10
8
6
4
2
32
14
0
24
5
17
20
148
32
43
60
151
54
Gene
AR
ACTR2A
CYPA11a
CYP17
CYP19
Follistatin
HSD17B2
IGFBP1+3
INHBA
INHBB
INHC
INS VNTR
IRS-1
MADH4
OB
POMC
UCP2+3
INSL3
Urbanek et al, JCEM, 2005
(Total of 264 alleles considered)

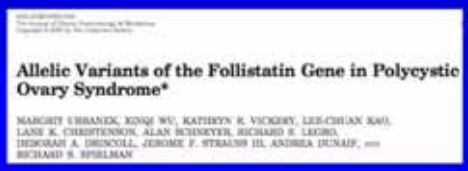

Type 2 Diabetes Results: 386,731 markers

Which Reported Gene Is Truly a Gene?



Thirty-seven candidate genes for polycystic ovary syndrome: Strongest evidence for linkage is with follistatin

Yes

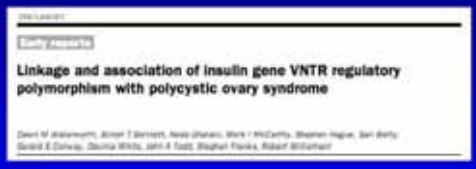


Allelic Variants of the Follistatin Gene in Polycystic Ovary Syndrome*

MARGRIT URBANEK, XINQI WU, KATHRYN S. VICKERY, LEE-CHUAN KAO, LANE K. CHRISTENSON, ALAN SCHNEYER, RICHARD S. LEGRO, DEBORAH A. DRISCOLL, JEROME F. STRAUSS III, ANDREA DUNAIF, AND RICHARD S. SPIELMAN

No

A Not Uncommon Event



Linkage and association of insulin gene VNTR regulatory polymorphism with polycystic ovary syndrome

Yes

Analysis of Multiple Data Sets Reveals No Association between the Insulin Gene Variable Number Tandem Repeat Element and Polycystic Ovary Syndrome or Related Traits

No

TDT results for D19S884 Allele 8: Three Consecutive Independent Samples

	Data set	Number of families	T*	Not-T*	Total	%T*	χ^2	P-value
Set 1	Urbanek et al (2000)	150	54	34	88	0.61	4.1	0.033
Set 2	Urbanek et al (2005)	217	91	58	149	0.61	7.3	<0.007
Set 3	Stewart et al, (2006)	98	35	20	55	0.63	4.1	0.043
Total		465	180	112	292	0.616	15.8	<0.00007

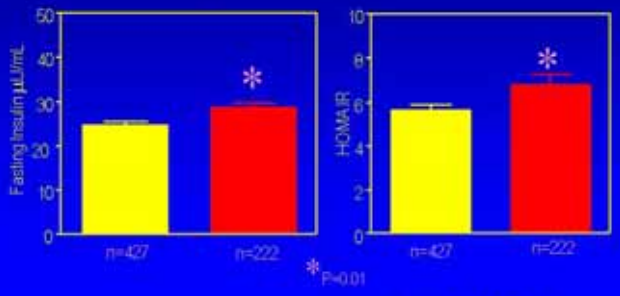
All JCEM

Limited Replication

Marker	Location	P value
D19S216	20.0	0.891
D19S869	23.0	0.092
INSR	25.2	0.150
D19S406	25.2	0.116
D19S567	25.2	0.785
D19S873	25.2	0.475
D19S905	25.2	0.750
D19S884	26.4	0.006**
D19S912	27.1	0.561
D19S922	27.2	0.178

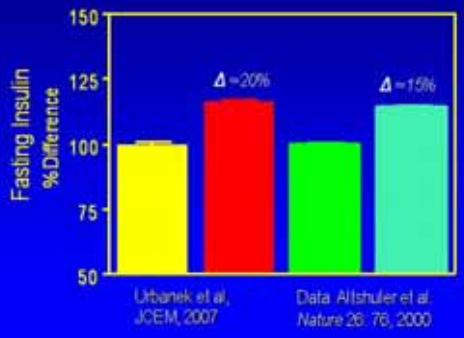
Tucci et al. J Clin Endocrinol Metab 86:446-49, 2001

Evidence for Insulin Resistance A8+ PCOS Independent of BMI



Urbanek et al JCEM, 2007

A8 Effect in PCOS Similar to PPARγ Pro/Pro in Type 2 Diabetes



Summary: PCOS Susceptibility Gene

- Evidence for linkage and association with an allele of a marker (A8) on chromosome 19p13.2 in the region of the fibrillin 3 gene
- A8 associated with a metabolic phenotype in PCOS
- Overall, however, there have been few breakthroughs in understanding the genetics of PCOS.

To Identify PCOS Genes, We Want…

- Genome-wide association study (GWAS)
  - ◆Large sample size
  - ◆Full genome scan
  - ◆Multi-stage design with replication built in

Ten Basic Questions to Ask About a Genome-wide Association Study Report

1. Are the cases defined clearly and reliably so that they can be compared with patients typically seen in clinical practice?
2. Are case and control participants demonstrated to be comparable to each other on important characteristics that might also be related to genetic variation and to the disease?
3. Was the study of sufficient size to detect modest odds ratios or relative risks (1.3-1.5)?
4. Was the genotyping platform of sufficient density to capture a large proportion of the variations in the population studied?
5. Were appropriate quality control measures applied to genotyping assays, including visual inspection of cluster plots and replication on an independent genotyping platform?
6. Did the study reliably detect associations with previously reported and replicated variants (known positives)?
7. Were stringent corrections applied for the many thousands of statistical tests performed in defining the *P* value for significant associations?
8. Were the results replicated in independent population samples?
9. Were the replication samples comparable in geographic origin and phenotype definition, and if not, did the differences extend the applicability of the findings?
10. Was evidence provided for a functional role for the gene polymorphism identified?

Pearson and Manolio, JAMA 2008

"The genome wide approach can also be problematic because the massive number of statistical tests performed presents an unprecedented potential for false-positive results."

Pearson and Manoli, JAMA 2008

Results of Recent GWAS for Complex Disease

Manolio et al, JCI 2008

Are Variants Associated with Type 2 DM also Associated with PCOS?

Genes Contributing to Type 2 DM

Year	Gene	Disease mechanism
2000	PPARG	Insulin sensitivity
2003	CAPN10	Glucose transport
2003	KCNJ11	Beta-cell dysfunction
2006	TCF7L2	Beta-cell dysfunction
2007	CDKAL1	Beta-cell dysfunction
2007	CDKN2A/2B	Beta-cell dysfunction
2007	HHEX/IDE	Beta-cell dysfunction
2007	SLC30A8	Beta-cell dysfunction
2007	IGF2BP2	Beta-cell dysfunction
2007	WFS1	Unknown
2007	TCF2	Unknown
2007	FTO	Obesity
2008	MC4R	Obesity
2008	NOTCH2	Unknown
2008	ADAMTS9	Unknown
2008	THADA	Unknown
2008	TSPAN8/LGR5	Unknown
2008	CDC123/CAMK1D	Unknown
2008	JAZF1	Unknown
2008	KCNQ1	Beta-cell dysfunction cell

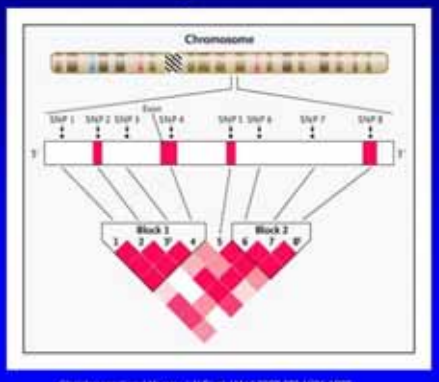
Ridderstrale, Mol Cell Endo, 2009

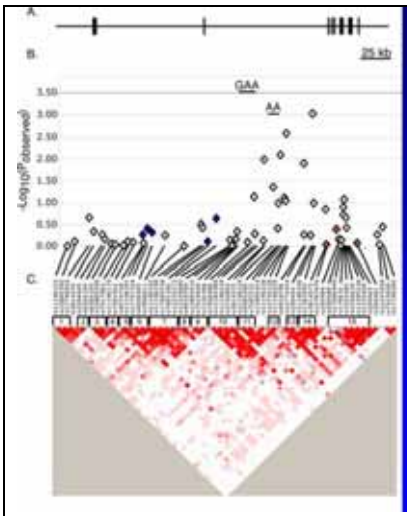
PCOS and TCF7L2

- Of the recently identified T2D susceptibility loci, TCF7L2 confers the greatest relative risk for T2D and significantly predicts conversion to T2D in persons with impaired glucose tolerance.
- TCF7L2 is, therefore, also a strong candidate gene for polycystic ovary syndrome (PCOS)

Biyasheva et al, JCEM, 2009

Mapping the Relationships among SNPs





TCF7L2 Association Study in PCOS

Biyasheva et al, JCEM, 2009

Conclusions

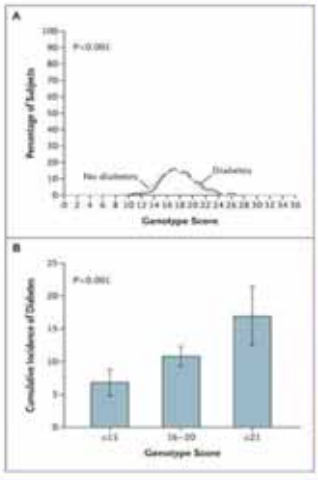
- We have observed evidence of association with two independent TCF7L2 loci in a PCOS cohort, including a novel locus. This study suggests that variation in different regions of a susceptibility gene contributes to distinct phenotypes.

Biyasheva et al, JCEM, 2009

Promise of Genome-wide Association Studies

1. Discovery of candidate genes
2. Explore pathophysiology/treatment
   - Etiology
   - Gene-environment interactions
   - Pharmaceutical targets
3. Establish utility of genetic markers for risk prediction
   - For individual or public health decisions
   - For response to medication/adverse effects

Are There Genes that Predict Response to Therapy or Long- term Outcomes?

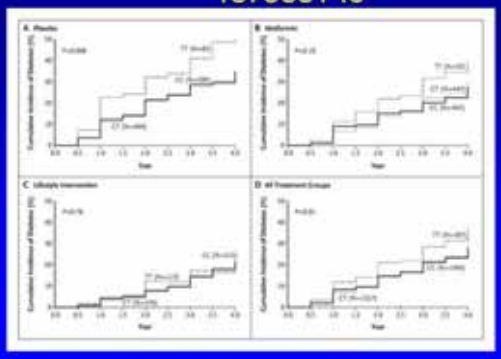


Distribution of Genotype Score and Cumulative Incidence of Type 2 Diabetes According to Genotype Score among Participants in the Framingham Offspring Study

A genotype score based on 18 risk alleles predicted new cases of diabetes in the community, but provided only a slightly better prediction of risk than knowledge of common risk factors alone.

Meigs J et al. N Engl J Med 2008;359:2208-2219

Incidence of Diabetes According to Treatment Group and Genotype at TCF7L2 Variant rs7903146



The risk-conferring genotypes in TCF7L2 are associated with impaired beta-cell function but not with insulin resistance

Florez J et al. N Engl J Med 2006;355:241-250

Primary PPCOS* Genetic Substudy Hypotheses-Ovulation Predictors

- The primary hypothesis is that polymorphisms of the estrogen receptor alpha (and CYP 450 enzymes and a microsatellite marker D19S884) will be associated with ovulatory response to clomiphene citrate in PPCOS.
- Polymorphisms of a liver kinase (LKB1) will be associated with ovulatory response to metformin

Pregnancy in Polycystic Ovary Syndrome

Legro et al, JCEM 200

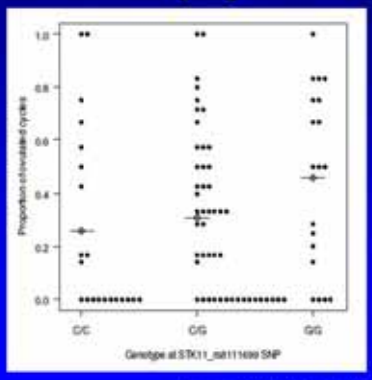
Genes and Markers

GENE	MARKER ID	ALLELES (MAF*)	DESCRIPTION
STK11	rs741765	C/T (T: 0.22)	Intron
STK11	rs8111699	C/G (C: 0.5)	Intron
ESR1	rs2234693	C/T (C: 0.44)	Intron: IVS-401/PvuII (14)
CYP2C9	rs1934963	C/T (C: 0.16)	Intron
CYP2C9	rs1799853	C/T (T: 0.12)	Mis-sense mutation: Cys144Arg
CYP2D6	rs3892097	C/T (T: 0.16)	Acceptor splice site: 1846G>A
FBN3	D19S884	A8/X** (A8: 0.19)	Intron (12)

* Minor allele frequency (MAF) derived from genotype data reported in this study

Legro et al, JCEM 2008

Proportion of Ovulated Cycles for Patients in the Metformin Group by LKB1 Genotype



Legro et al, JCEM, 2008

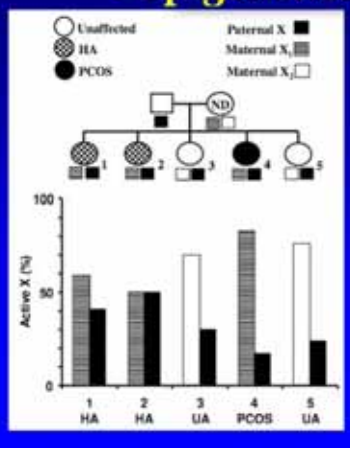
Summary - Genes and PCOS

- There are no genes to date that accurately predict the diagnosis or prognosis of women with PCOS.
- There are no genes that identify response to therapy in ovulation induction in women with PCOS.

Nature or Nurture?

- Nature
  - Complex genetic disease
  - Familial clustering
  - Disease alleles identified
- Nurture
  - Obesity
  - Birth environment
  - Medications
    - Valproate
  - Environmental disrupters???

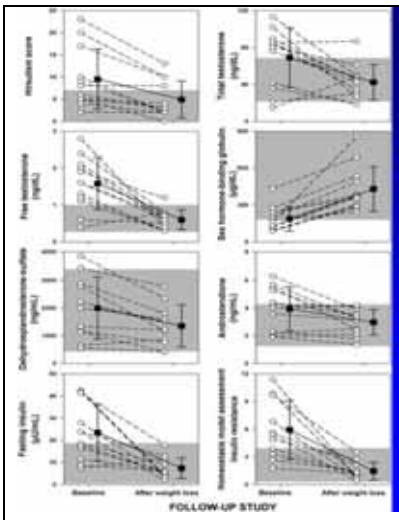
? Epigenetics of PCOS



Sister pairs with differing patterns of X-chromosome inactivation are much more likely to have divergent phenotypes

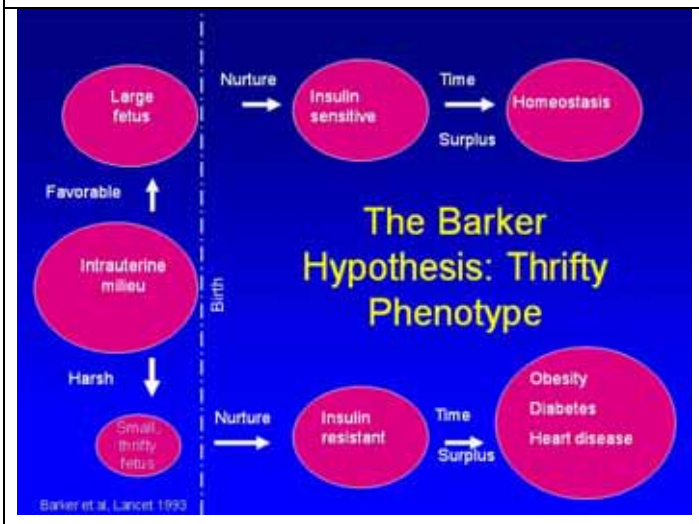
OR 28.9 (4.0-286.0)

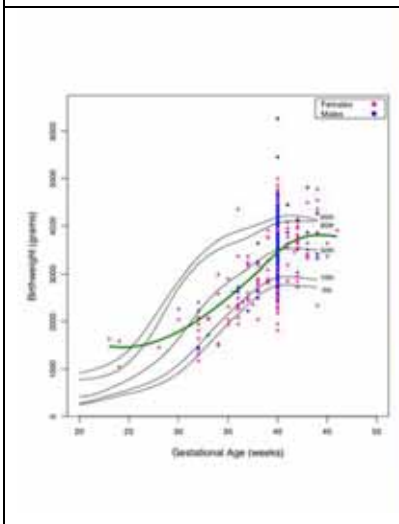
Hickey et al, JCEM, 2006



Clinical and Biochemical Characteristics of the Morbidly Obese PCOS Patients Submitted to Bariatric Surgery, Before and After Weight Loss

Escobar-Morreale, H. F. et al. JCEM 2005





Normal Birthweight for Gestational Age in PCOS Families

Little Association between Birthweight and PCOS Phenotype (N = 1018)

- There were no significant associations between phenotype and birthweight in males.
- Only a marginally significant inverse linear association with ovarian volume in PCOS probands(P = 0.03).
- In first degree female relatives, there was a U-shaped categorical association between oligomenorrhea/bioavailable testosterone and birthweight (P < 0.05).

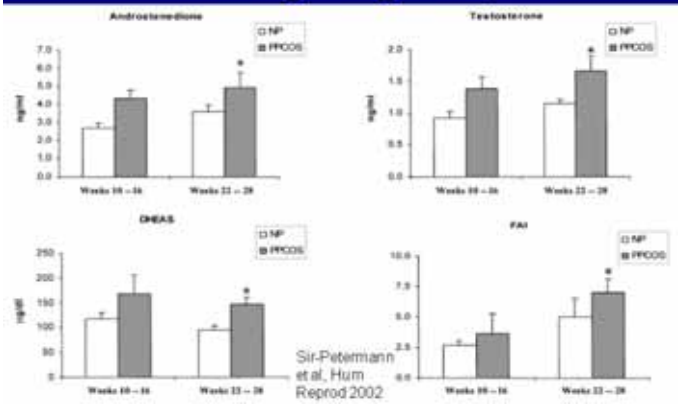
Does Prenatal Androgenization Influence the Development of PCOS?

Spotted Hyena

- Fetuses exposed in utero to elevated levels of androgens
  - ?reduced hyena placental aromatase activity
- Females exhibit male-like genitalia and dominance over males
  - ? Endocrine/ metabolic abnormality similar to PCOS
- Birth through tip of clitoris due to virilization

Yalcinkaya et al, Science 1993

Elevated Androgens in PCOS During Pregnancy



Sir-Petermann et al, Hum Reprod 2002

Freemartin: Sterile Female Born as a Twin of a Bull Calf

Prevalance of PCOS Is Not Different in Women from Opposite-Sex and Same-Sex Twin Pairs

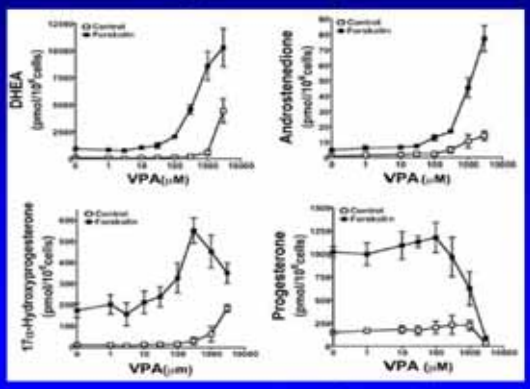
- Data from 1325 monozygotic twins, 1191 dizygotic twins (711 women from same-sex twin pairs and 480 women from opposite-sex twin pairs), 745 sisters of twins and 218 spouses of male twins were evaluated.

Kuijper et al, JCEM 2009

Epilepsy and PCOS

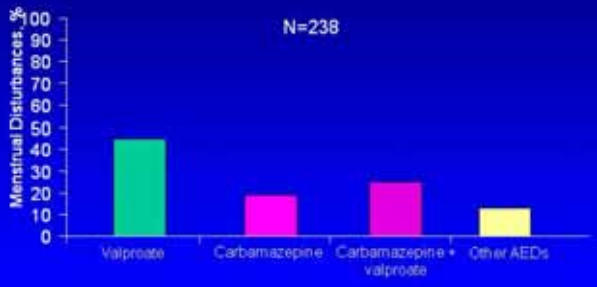
- Women with epilepsy often display stigmata of PCOS.
- Epilepsy and PCOS may be caused by a common factor, such as a dysfunction in neurotransmission or a genetic vulnerability.
- Certain drugs appear to exacerbate PCOS stigmata suggesting an environmental modifier.
  - ◆Valproate

Valproate Stimulates Thecal Cell Androgen Biosynthesis



Nelson et al, Endocrinology, 2004

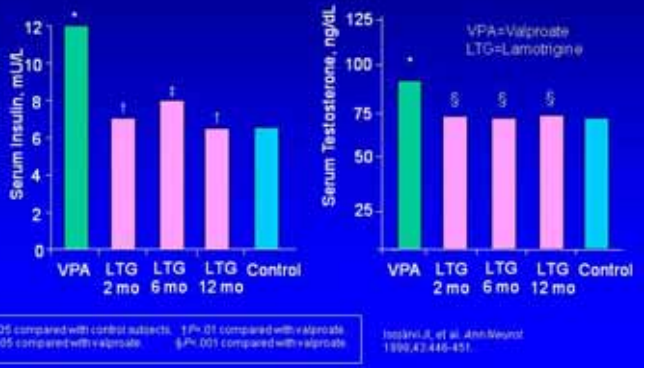
Correlation Between Anti-epiliptic Drugs and Menstrual Disturbances



AEDs = Antiepileptic drugs

Isojärvi JI, et al. *N Engl J Med* 1993;329:1383-1388

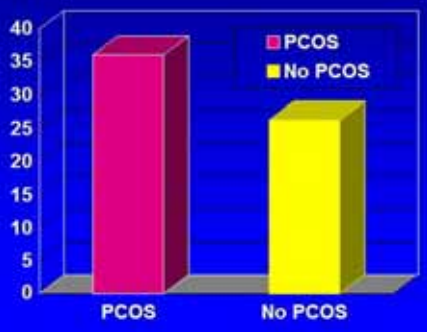
Improved Reproductive/Metabolic Abnormalities After Switch from Valproate to Lamotrigine



*P< .05 compared with control subjects. †P< .01 compared with valproate.
‡P< .05 compared with valproate. §P< .001 compared with valproate.

Isojärvi JI, et al. Ann Neurol 1998;43:446-451.

Median BMI Among Valproate Users With and Without PCOS



P < 0.01

Joffe et al, Biol Pscyh 2006

Summary - Nurture

- Obesity exacerbates and may bring out PCOS in vulnerable individuals.
- The effects of the birth environment on later PCOS are tantalizing but still murky.
- Drugs (or environmental disruptors!) associated with weight gain may also bring out PCOS.

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NOTES

NOTES

CHILDHOOD AND ADOLESCENT MANIFESTATIONS OF PCOS—HOW EARLY AND HOW EFFECTIVELY CAN IT BE TREATED?

Kathleen Hoeger, M.D.
Associate Professor of Obstetrics and Gynecology
University of Rochester Medical Center
Rochester, New York

LEARNING OBJECTIVES

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

1. Identify the peripubertal manifestations of polycystic ovary syndrome (PCOS).
2. Diagnose PCOS in patients prior to age 18.
3. Screen adolescents appropriately for coexisting morbidity.
4. Initiate appropriate therapy for control of hirsutism and endometrial hyperplasia.

Childhood and Adolescent Manifestations of Polycystic Ovary Syndrome (PCOS)—How Early and How Effectively Can It Be Treated?

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- Initiate appropriate therapy for control of hirsutism and endometrial hyperplasia.

Disclosure

- No commercial or financial relationships to disclose
- Discussion of non-FDA-approved indications for use of some agents

Presentation of PCOS

- PCOS typically presents in adolescence around the time of menarche.
- Presentation can be heterogeneous, but classically involves irregular menses.
- Elevated serum androgens are a hallmark of the syndrome.

Franks, Int J Obesity 2008

Menstrual Irregularity

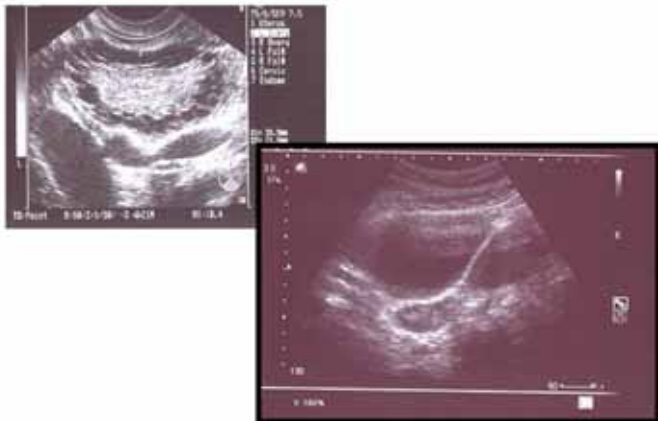
- This is the primary diagnostic criterion in adolescence.
- Adolescents presenting with primary amenorrhea—lack of menstruation by age 16 or two years after thelarche—or secondary amenorrhea, should be evaluated with PCOS in the differential diagnosis.
- Oligomenorrhea, however, is frequent in the first year or two after menarche.
- However, in a prospective study of menstrual cycles in European adolescents, 75% of those with irregular cycles at age 15 continued to demonstrate irregular cycles at age 18.

Van Hooff et al Hum Reprod 2004

Hyperandrogenism

- Most challenging assessment in the adolescent
- Ferriman-Gallwey score of >/=8 is considered diagnostic of hirsutism in adults.
- Acne alone not helpful in the diagnosis.
- Serum androgen/free hormone is most helpful, but typical clinical assay is unreliable
- Calculated free androgen index is preferable using sex hormone-binding globulin (SHBG) (immunoassay) and total testosterone
- Free androgen index (FAI) =
  Total T(ng/dL)/SHBG(nmol/L) x 3.47

PCOS Ovary on Ultrasound



Ovarian Findings in Adolescence

- Ovarian ultrasound typically done via a transabdominal approach in the adolescent—less specific findings on morphology
- Criteria developed for transvaginal approach
- Definition >11 follicles 2-9 mm in diameter or increased ovarian volume (>10 cm^3)

Balen et al Hum Reprod Update, 2003

Adolescents With and Without PCOS

- Body mass index (BMI)-matched adolescents with (n=39) and without (n=28) a clinical diagnosis of PCOS based on clinical hyperandrogenism and menstrual irregularities
- Mean age of 15; BMI 34-35 kg/m^2
- Transabdominal ultrasound (US)
- Ovarian volume (cm^3) 7.76 vs. 4.93
- Accurate follicle counts could not be performed

Rossi, et al JCEM 2008

PCOS Prevalence in Adolescence

- Population sample of white European normal-weight adolescents with a mean age of 15.3 years: 18% experienced menstrual irregularity, with 5.5% demonstrating significant oligo-amenorrhea.
- In the group with oligo-amenorrhea, the majority had androgen profiles consistent with PCOS.

Van Hooff et al. Hum Reprod 1999.

Differential Diagnosis

- Non-classic congenital adrenal hyperplasia (NCAH)(21-OH deficiency)
- Androgen-secreting tumor
- Cushing's syndrome

Non-classic Adrenal Hyperplasia—21-OH Deficiency

- NCAH is found in 1-6% of patients presenting for hyperandrogenism evaluation.
- Virilization is uncommon, and regular menstrual cycles are seen in approximately 50%.
- Obtain follicular phase anti-müllerian (AM) hormone level of 17-hydroxyprogesterone.
- Values <2 ng/mL have been associated with a low false-negative rate.
- Follow-up with adrenocorticotropic hormone (ACTH) stimulation test if unclear

Endocrine Evaluation

- Serum testosterone
- SHBG-calculation of FAI
- Dehydroepiandrosterone (DHEAS)
- AM 17-hydroxyprogesterone
- Thyroid stimulating hormone (TSH)/Prolactin to rule out other causes of oligomenorrhea
- Possibly follicle-stimulating hormone (FSH)/luteinizing hormone (LH) - not part of the definition and is not diagnostic, particularly in obese girls

Development of PCOS and Childhood Precursors

- Presentation of PCOS in adolescence suggests that there is an underlying predisposition to ovarian and metabolic abnormalities before the onset of puberty.
- Clinical manifestations of androgen excess have been reported in pre-pubertal girls.

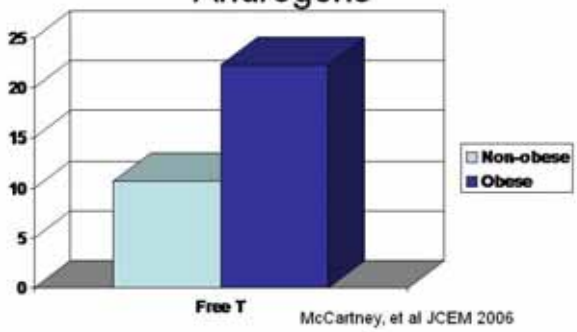
Rosenfield, JCEM 2007

Obesity and Androgens in the Pubertal Transition

- Obese adolescents in early pubertal transition demonstrate increased testosterone that is directly correlated with BMI.
- In Tanner stages 1-3, obese girls demonstrated 2.9 times higher total testosterone levels and 50% lower SHBG levels

McCartney, et al JCEM 2006

Obesity in Tanner Stages 1-3 Non-Hirsute Adolescents and Androgens

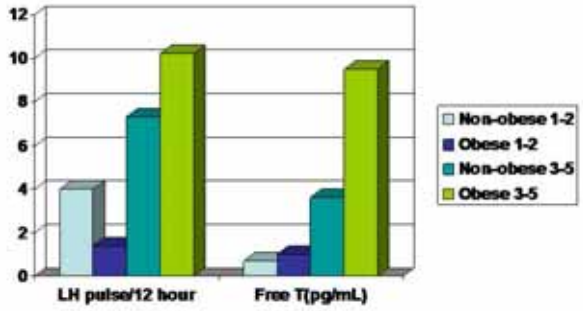


McCartney, et al JCEM 2006

Development of PCOS and Childhood Precursors

- Expression of PCOS occurs during the maturation of the hypothalamic-puitary-ovarian axis that occurs during puberty.
- Increased LH secretion occurs during puberty, and this may be exaggerated in girls predisposed to PCOS, amplifying ovarian androgen production.

LH Frequency, Androgens and Obesity by Tanner Stage

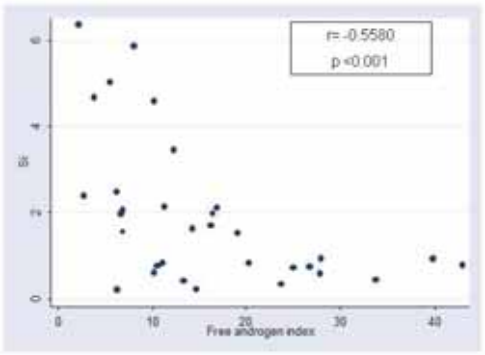


McCartney, et al JCEM 2009

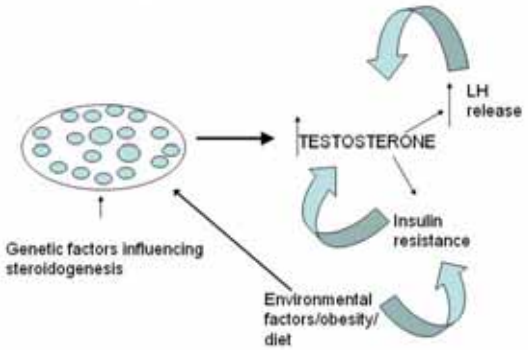
Hyperinsulinism and Androgens

- Hyperinsulinemia suppresses SHBG production by the liver.
- Total testosterone is also correlated with BMI.
- Insulin demonstrates a direct effect on the theca cell androgen production.

Androgens and Insulin Sensitivity in Adolescent Women with PCOS



Hyperandrogenism in the Development of PCOS in Adolescence



Premature Adrenarche

- Linked to higher insulin levels in puberty

Vuguin et al JCEM 1999

- Acanthosis nigricans
- Reduced insulin sensitivity

Oppenheimer et al JCEM 1995

- This may predispose to PCOS, but longitudinal prospective trials are not reported.

Premature Adrenarche: Precursor to PCOS?

- Isolated premature adrenarche, the development of pubic hair before age 8 but not associated with accelerated bone maturation or breast development, may be associated with adolescent diagnosis of PCOS.
- Ibanez et al. described a series of adolescent girls with a history of premature adrenarche.
- 45% had diagnosis of PCOS with oligomenorrhea and ovarian hyperandrogenism with a relationship to low birth weight in those who developed PCOS

Ibanez et al Hum Reprod 2007

Glucose Tolerance in Adolescent Women with PCOS

- Palmert et al. studied 27 obese adolescents (aged 13-19) with PCOS with a mean BMI of 38.4 kg/m^2.
- Oral glucose tolerance test was performed.
- 8 had impaired glucose tolerance and 1 had diabetes (33%).

Palmert, et al JCEM 2002

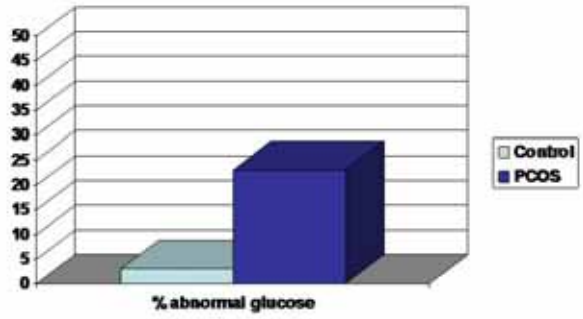
Obesity in Adolescents with PCOS

- 43 obese adolescents with PCOS were compared to 31 age- and weight-matched control adolescents with regular menses and no hirsutism.

	Control (31)	PCOS (43)
Age (years)	14.8	15.6
BMI (kg/m^2)	34.4	36.6

Rossi et al JCEM 2008

Abnormal Glucose Tolerance in Adolescents with PCOS

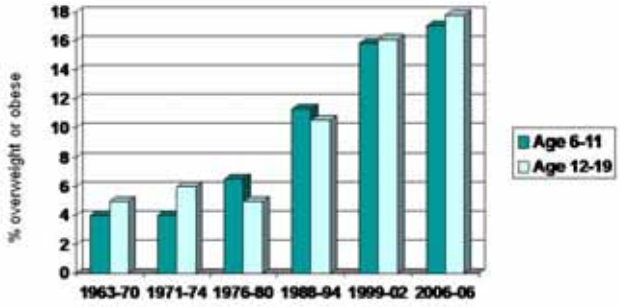


Rossi et al JCEM 2008

Glucose Tolerance in Adolescent Women with PCOS

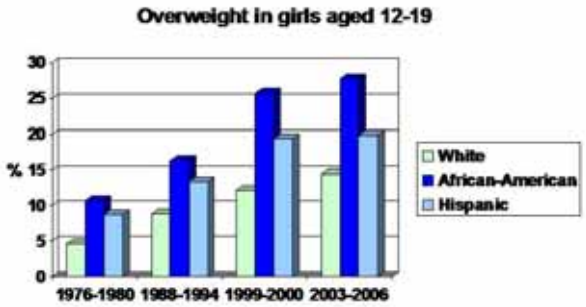
- Disturbances of glucose metabolism are seen at an early age in PCOS.
- Adolescents with PCOS should be screened for type 2 diabetes mellitus (DM), preferably with a 2-hour glucose tolerance test.
- Obesity is a significant modifier of glucose tolerance in adolescence.

Obesity in Children and Adolescents in the U.S.



Ogden et al JAMA 2008

Obesity in Adolescent Women by Ethnicity



CDC health statistics

Obesity and PCOS

- In a U.S. prevalence study of PCOS in an unselected population defined by hyperandrogenic criteria:
  - 45% of subjects had a BMI >25
  - 36% were obese (BMI >30)

Azziz, et al JCEM 2004

Obesity and PCOS

- There are no data available on the prevalence of obesity in adolescents with PCOS.
- It is reasonable to assume that both the national trends and the adult PCOS associations with obesity will be present in adolescent women with PCOS.

Obesity and PCOS in Adolescents

- Silfen et al. compared 11 normal-weight and 22 obese adolescents with PCOS.
- Overall, obese adolescents demonstrated higher insulin levels and greater insulin resistance.
- Low density lipoprotein (LDL) cholesterol was higher and high density lipoprotein (HDL) cholesterol lower in obese girls.
- Sex hormone-binding globulin (SHBG) was lower in obese girls, but total testosterone was similar. Free testosterone was slightly higher but did not reach statistical significance.
- Although clinical parameters were not compared, it appears, as in adults, obesity worsens the parameters of PCOS in adolescence.

Silfen, et al JCEM 2003

Quality of Life (QOL)

- 97 PCOS adolescents were compared with 186 adolescents attending an adolescent medicine practice.
- BMI was significantly greater in PCOS (31.7 vs 23.5).
- Patients with PCOS scored >7 points lower on the general health perceptions subscale and 4 points lower on the physical function scale.
- Severity of disease as measured by the clinician did not correlate with QOL perception.

Trent 2002

Quality of Life and BMI

- The impact of BMI was reviewed in this cross-sectional study.
- Mean BMI of PCOS was 31.7, compared with 23.5 in the controls
- BMI was associated with PCOS status and score on the health-related quality of life (HRQL)
- When BMI was added to the multivariate linear regression models, coefficients became insignificant.

Trent 2005

PCOS and Adolescence

- Many questions remain regarding the management of PCOS in adolescence.
- Are there benefits to intervening in adolescence?
- What are the best interventions for this age group?
- What about the impact of obesity on management?

Management of PCOS in Adolescents

- Management of PCOS in younger women should have 3 main objectives:
- Control of menstrual function
- Control of androgen-excess symptoms
- Prevention of long-term metabolic risk

Use of Oral Contraceptives (OCs)

- Oral contraceptives are effective in regulating menses and may reduce androgenic concerns.
- There are few placebo-controlled trials in adolescent women, but several randomized trials comparing 2 different regimens suggest potential worsening of lipid profile and insulin resistance in PCOS adolescent populations.

Comparison of type of OC

- Mastorakas, et al. compared desogestrel/ethinyl estradiol with cyproterone acetate (CA)/ethinyl estradiol for 12 months.
- 36 adolescent women with PCOS and a mean age of 17 years
- Mean BMI of 25.6
- Ferriman-Gallwey score of 16-17

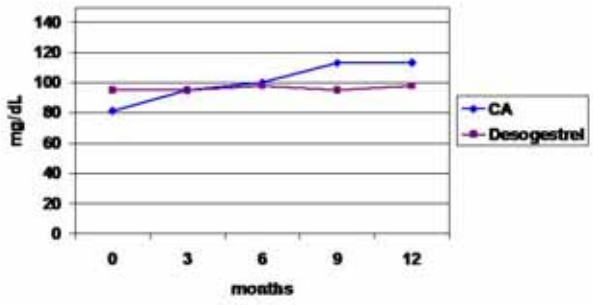
Mastorakis, et al Fertil Steril 2006

OC Use in Adolescents with PCOS

- Homeostasis model assessment (HOMA)-measured insulin resistance worsened in both groups after 12 months.
- CA-treated women had worsening of the area under the curve (AUC) insulin, compared to those treated with desogestrel.
- Neither changed glucose parameters or other clinical metabolic parameters.

Mastorakis, et al Fertil Steril 2006

Triglyceride Changes with OCs



Mastorakos, et al Fertil Steril 2002

Lifestyle Modification in Adolescents with PCOS

- The rising prevalence of obesity in adolescent women makes the role of lifestyle (LS) modification with weight reduction important for the management of PCOS.
- Lifestyle modification is challenging in the adolescent and there are no large scale trials of LS treatment-only in adolescents with PCOS.
- Androgens have been shown to decrease with weight loss in obese children (Reinehr, et al JCEM 2005) and adolescents (Wabitsch et al JCEM 1995).

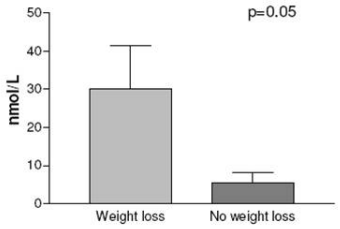
Lifestyle Modification Trials

- In a small, multiple-arm pilot trial in obese adolescent women with PCOS, lifestyle modification reduced free testosterone, primarily through reduction in SHBG.
- 8/11 subjects continued the 6-month lifestyle program, with 50% demonstrating weight reduction.

Hoeger et al JCEM 2008

Lifestyle Modification in PCOS

SHBG changes with weight reduction in subjects enrolled in lifestyle modification

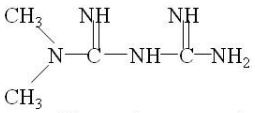


Hoeger et al JCEM 2008

Management of Insulin Resistance in PCOS

- There is currently much interest in the use of insulin sensitizers in women with PCOS.
- Many unanswered questions remain with regard to their use, however.
  - Is there an "insulin-resistance cutoff" for effective use?
  - Should they be used in adolescent women with PCOS?
  - What indications are best for use?

Metformin and PCOS



- There is now a large body of evidence on the use of metformin in the treatment of PCOS in obese women, although is not FDA-approved for this indication.
- Its mechanism of action is still not clearly understood, despite its introduction in 1957.
- It inhibits hepatic glucose production and significantly lowers insulin levels.

Metformin and PCOS

Side effects and toxicity:

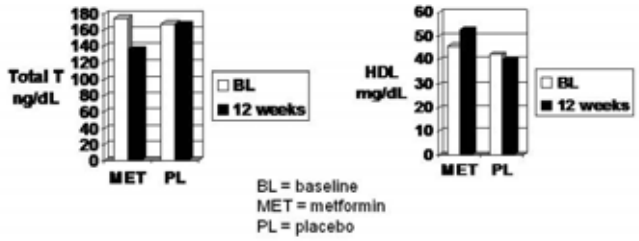
- GI side effects occur in about 30% of patients
- Reduces B12 absorption
- Lactic acidosis (5/100,000 treated patients)
  - Associated with decreased renal function
  - **Exclusion criteria**
    - Liver disease
    - Heart or respiratory failure
    - Alcohol abuse
    - Renal failure
    - Elevated serum creatinine

Studies of Metformin in Adolescents with PCOS

- Randomized trial of 22 adolescent women
- No change in weight was noted with metformin 1500 mg/day over 12 weeks
- Mean age was 16 years and mean BMI was 32 kg/m^2
- Menses restored in 10/11 adolescents on metformin compared with 4/11 on placebo

Bridger et al Arch Pediatr Adolesc Med 2006

Androgens and HDL Cholesterol



BL = baseline
MET = metformin
PL = placebo

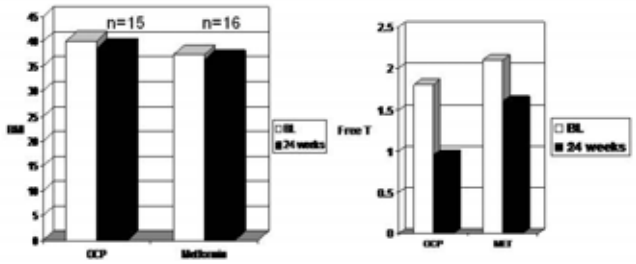
Bridger Arch Pediatr Adolesc Med 2006

Metformin Treatment in Adolescents with PCOS

- What about oral contraceptive pills (OCPs) compared with metformin?
- Allen et al. compared oral contraceptive therapy to metformin in 35 obese adolescent women for 6 months.
- Both the metformin group and the OCP group showed similar decreases in BMI (1 kg/m^2) and hirsutism score over 6 months, and had improved menstrual rates.

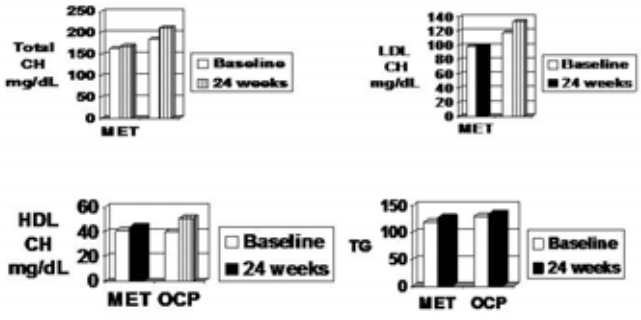
Allen, et al J Pediatr Endocrinol Metab2005

Impact of OCP or Metformin in Adolescents with PCOS



Allen, et al J Pediatr Endocrinol Metab2005

Lipid Profiles



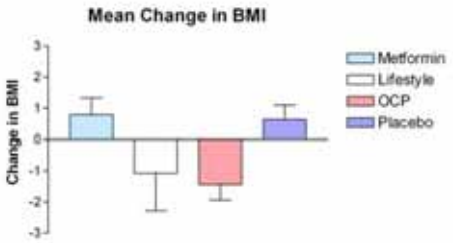
Allen et al J Pediatr Endocrinol Metab2005

Metformin, Lifestyle Modification or OC treatment in PCOS

- Pilot trial of 43 obese adolescents with PCOS randomized to metformin, placebo, lifestyle modification or oral contraceptive for 6 months

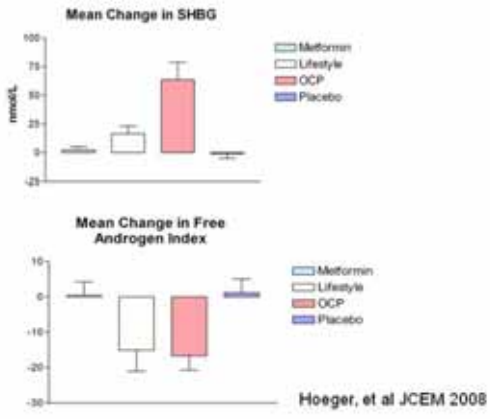
Hoeger, et al JCEM 2008

Weight Changes by Group



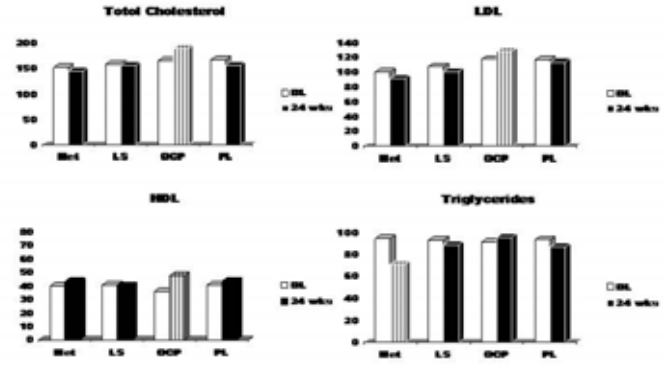
Hoeger, et al JCEM 2008

Change in Androgens



Hoeger, et al JCEM 2008

Lipid Changes

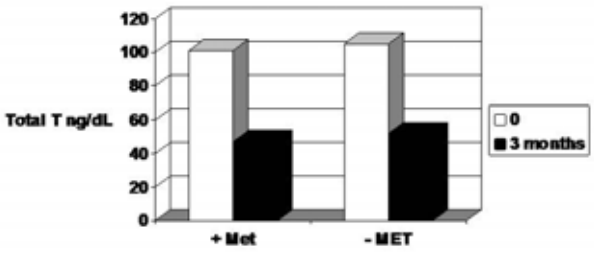


Hoeger et al JCEM 2008

Combination Therapy in Adolescents with PCOS

- Several studies have been published comparing oral contraceptives alone, or in combination with or in comparison to metformin and/or antiandrogens.
- Ibanez et al. studied oral contraceptive (ethinylestradiol-drosperinone) and flutamide with or without metformin for 3 months in 31 lean adolescents with PCOS.

OCP + Flutamide With or Without Metformin



Ibanez et al JCEM 2005

Management of PCOS in Adolescence

What is the best treatment for PCOS in adolescence complicated by obesity?

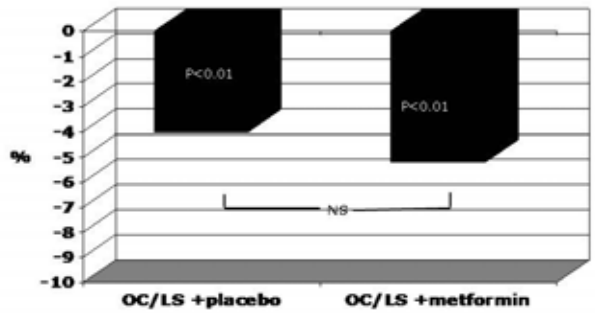
What is the impact of the OCP on PCOS in adolescence complicated by obesity?

Combination Therapy for Obese Adolescents

- Trial of 36 obese adolescents treated with oral contraceptive (ethinyl estradiol + drosperinone) with metformin or placebo
- All received lifestyle modification program

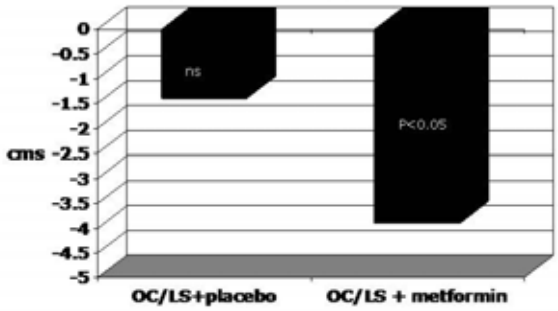
Hoeger et al JCEM 2008

Reduction in Weight over 24 Weeks



Hoeger et al JCEM 2008

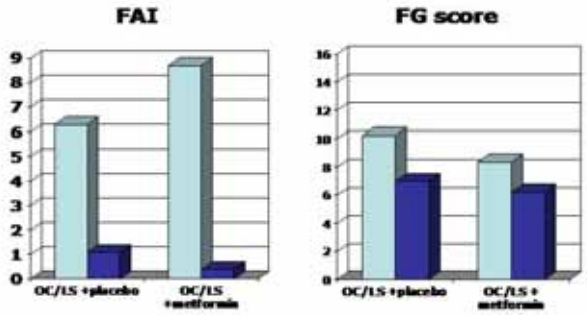
Reduction in Waist Circumference



ns = not statistically significant

Hoeger et al JCEM 2008

Free Androgen Index (FAI) and Ferriman-Gallwey (FG) Scores



Hoeger et al JCEM 2008

Conclusions

- PCOS is a relatively common disorder of adolescence.
- Hyperandrogenism and obesity in childhood predispose to the development of PCOS.
- Diagnosis is possible in adolescence with a high index of suspicion for menstrual irregularities persisting past age 15 or more than one year post menarche.

Conclusions

- Adolescents with PCOS, particularly if accompanied by obesity, have significantly abnormal metabolic profiles, placing them at high risk for adverse metabolic events.
- Incidence of impaired glucose tolerance or diabetes is > 20%.
- Androgens and cardiovascular risk parameters correlate with insulin sensitivity, and adolescent women with PCOS are insulin resistant.

Conclusions

- Menstrual abnormalities and androgen excess are successfully treated by oral contraceptive therapy; however, metabolic impact is unclear, particularly in obesity.
- Role for adjunctive metformin is still evolving, with further study needed.
- Lifestyle modification is a mainstay of treatment in obese adolescent women; however, there is considerable difficulty with compliance and long-term commitment.

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NOTES

DEBATE: HAVE THE ROTTERDAM CRITERIA SIMPLIFIED THE DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME (PCOS)?

Pro: Richard Legro, M.D.
Con: Kathleen Hoeger, M.D., M.Sc.

LEARNING OBJECTIVES

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

1. Articulate the criteria used by both the National Institutes of Health (NIH) and the Rotterdam criteria to define PCOS.
2. Differentiate the key features of each of these definitions that lead to possible under- or over-diagnosis of the condition.
3. Develop a set of definitional criteria that are appropriate for the practitioner's practice.

Debate: Have the Rotterdam Criteria Simplified the Diagnosis of PCOS?

Pro: Richard Legro, M.D.

Con: Kathleen Hoeger, M.D.

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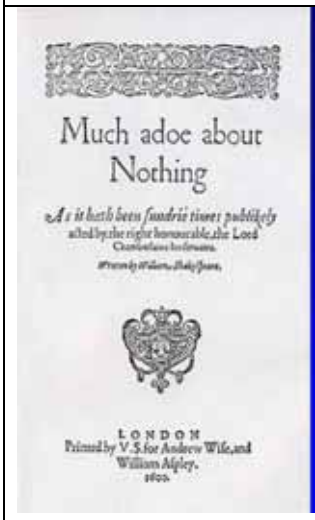
Debate: The Rotterdam Criteria HAVE Simplified the Diagnosis of PCOS

Richard S. Legro, M.D.
Department of Obstetrics and Gynecology
Penn State College of Medicine
M.S. Hershey Medical Center
Hershey, PA

Disclosures

- Study Investigator-Solvay Pharmaceuticals
- Consultant- Merck-Serono


Much adoe about Nothing

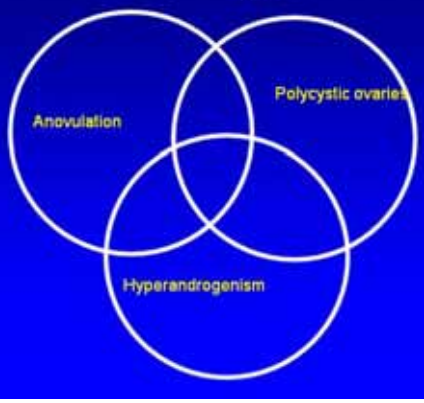
As it hath been sundrie times publikely acted by the right honourable, the Lord Chamberlaine his seruants.

Written by William Shakespeare.

LONDON
Printed by V.S. for Andrew Wise, and William Aspley.
1600.

- Nothing/Noting
  - Elizabethan homophones

What Is the PCOS Phenotype?



All Diagnostic Criteria for PCOS Have a Common Theme:

It Is an Ovarian Disorder!

Diagnosis of PCOS (National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Conference, 1990)

- Ovulatory dysfunction
- Clinical hyperandrogenism and/or hyperandrogenemia
- Exclusion of other disorders:
  - Non-classic adrenal hyperplasia
  - Androgen-secreting tumors
  - Hyperprolactinemia/thyroid disorder

Zawadski & Dunaif, 1992

Diagnosis of PCOS

(The 2003 Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop)

- At least 2 of the following 3 features:
  - Oligo- and/or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries
- Exclusion of other etiologies

The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Fertil Steril 81:19-25, 2004; & Hum Reprod 19:41-7, 2004

The 2003 Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Sonographic Criteria

- Definition:
  - ◆Presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or
  - ◆Increased ovarian volume (> 10 mL)
- Only one ovary fitting this definition is sufficient to define PCO.
- Does not apply to women taking oral contraceptive pills (OCPs)
- If evidence of a dominant follicle (> 10 mm) or a corpus luteum, scan should be repeated next cycle

The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Fertil Steril 81:19-25, 2004; & Hum Reprod 19:41-7, 2004

Androgen Excess Society Diagnostic Recommendations

1- Hyperandrogenism: *Hirsutism and/or hyperandrogenemia*

and

2 – Ovarian Dysfunction: *Oligo-anovulation and/or polycystic ovaries*

and

3 - Exclusion of other androgen excess or related disorders*

Azziz et al, JCEM, 2006

Potential Phenotypes in PCOS

	Potential phenotypes														
Features	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligoanovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	✓	✓	✓	✓	✓	✓										
Rotterdam 2003 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
AES 2006 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓							

+, Presence; -, absence.

Azziz et al, JCEM, 2006

Prevalence of PCOS

Greek Island, Lesbos 17-45 years	192	NIH 6.8%	Diamanti, JCEM 99
Caucasian, reproductive age Blood donors, Spain	154	NIH 6.5%	Asuncion, JCEM 00
Preemployment physical, US 18-45 years (223 black, 166 white)	400	NIH 6.6%	Azziz, JCEM 04 Knochenhauer, JCEM 98
WHO type II anovulation	847	Rotterdam 50% more common than NIH	Broekmans, BJOG 06

	NIH Criteria 1990 (both)	Rotterdam 2003 (2 of 3)	Androgen Excess Society 2006 (HA plus 1 out of remaining 2)
Hyperandro-genism (HA)	■		
Oligo- or amenorrhea	■		
Polycystic ovaries			■

■ = mandatory

Diagnostic Criteria for PCOS

- All allow for a clinical diagnosis with the same criteria.
- All exclude the diagnosis based on one criterion (for example, polycystic ovaries alone).
- The prevalence of PCOS will vary according to the criteria utilized.
- None are sufficient without further clarification for a clinical trial or clinical study - they define only a minimum expectation.

Debate: The Rotterdam Criteria Have NOT Simplified the Diagnosis of PCOS

Kathleen Hoeger, M.D.
University of Rochester Medical Center

Disclosure

No commercial or financial interests to disclose

Two definitions of PCOS

- NIH consensus conference, 1990
  - Hyperandrogenism or hyperandrogenemia
  - Oligo-ovulation
  - Exclusion of related disorders
- ESHRE/ASRM sponsored Rotterdam consensus conference, 2003
  - The presence of 2 out of 3 criteria
    - Oligo- or anovulation
    - Clinical or biochemical evidence of hyperandrogenism
    - Polycystic ovaries on ultrasound

Simplicity in Medicine

- It is immensely important that the diagnosis be accurate.
  - Medical perspective
  - Research perspective
  - Patient perspective
- Implications of a diagnosis and long-term prognosis depend on a straightforward definition of the disease.

Added diagnostic criteria

- The Rotterdam consensus includes those who would have been classified as PCOS using the NIH criteria.
- Adds expanded criteria and hence new phenotypes defined as PCOS

Defining the syndrome

- The precise etiology of PCOS is unknown.
- Since a common underlying etiology cannot be stated for PCOS, the syndrome can be defined by its consequences or a specific phenotype.

Simplicity?

★ = ✦ = ♥ ?

PCOS Phenotypes Possible with the 2003 Rotterdam Criteria

Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasound	polycystic	normal	polycystic	polycystic
Androgen concentration	high	high	high	normal

Are the Long-term Consequences the Same for All 4 Phenotypes?

- Known consequences of PCOS that present morbidity to the patient include:
  - Infertility
  - Menstrual dysfunction
  - Type 2 diabetes mellitus (DM) and other metabolic disorders
  - Hirsutism

Based on Available Data

- Phenotype 3:

Irregular menses with hyperandrogenism with or without polycystic ovaries—increased risk of:

- √ Infertility
- √ Type 2 DM
- √ Hirsutism

Based on Available Data

- Phenotype 3:

Regular menses with hyperandrogenism with polycystic ovaries—increased risk of:

- ? Infertility
- ? Type 2 DM
- √ Hirsutism

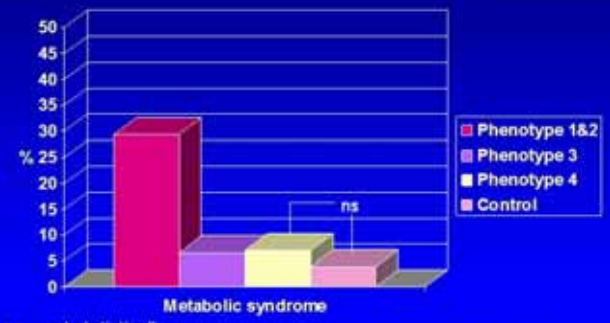
Based on Available Data

- Phenotype 4:

Irregular menses without hyperandrogenism with polycystic ovaries—increased risk of:

- √ Infertility
- ? Type 2 DM
- - Hirsutism

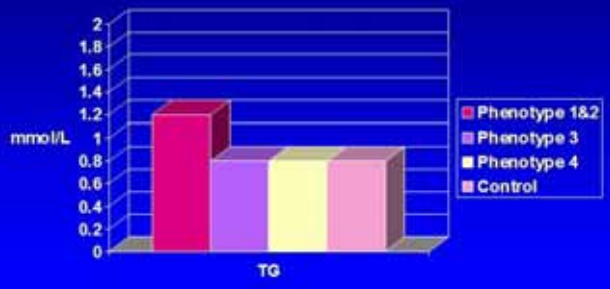
Metabolic Consequences of the Different Phenotypes



ns = not statistically significant

Barber et al Clin Endocrinol 66: 513, 2007

Metabolic Consequences of the Different Phenotypes



TG = triglycerides

Barber et al Clin Endocrinol 66: 513, 2007

Conclusion

- While the Rotterdam criteria add information regarding ovarian morphology, the physician is left with a more confusing picture.
- Do the other phenotypes identified have the same risk over the long term?
- Literature must be interpreted in light of the phenotype studied rather than the diagnosis of PCOS.

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NOTES

NOTES

PREVENTING THE LONG-TERM SEQUELAE OF INSULIN RESISTANCE IN POLYCYSTIC OVARY SYNDROME (PCOS)

Richard S. Legro, M.D.
Department of Obstetrics and Gynecology
Penn State College of Medicine
M.S. Hershey Medical Center
Hershey, Pennsylvania

LEARNING OBJECTIVES

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

1. Identify the components of the metabolic syndrome.
2. Discuss the benefits of metformin in treating PCOS.
3. Identify risks of thiazolidinediones.
4. List the approved medications for the treatment of obesity.
5. Assess the role of statins in the management of PCOS.

Preventing the Long-Term Sequelae of Insulin Resistance in Polycystic Ovary Syndrome (PCOS)

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- List approved medications for the treatment of obesity.
- Assess the role of statins in the management of PCOS.

Disclosures

- Study Investigator-Solvay Pharmaceuticals
- Consultant- Merck-Serono

- Labelled drug use: sibutramine, orlistat

- Off -label drug Use: metformin, rosiglitazone, pioglitazone, atorvastatin

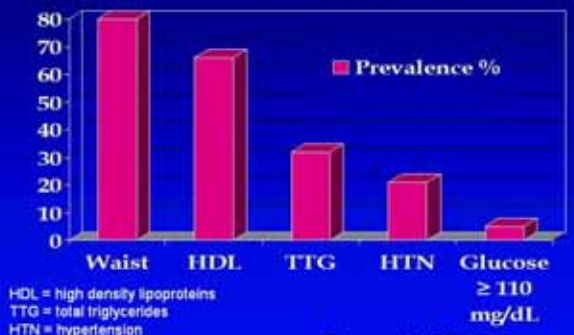
Metabolic Syndrome (MBS) in Women

3 of 5

Risk Factor	Abnormal Cutoff
1. Abdominal obesity (waist circumference)	> 88 cm (> 35 in)
2. Triglycerides	≥ 150 mg/dL
3. High-density lipoprotein cholesterol (HDL-C)	< 50 mg/dL
4. Blood pressure	≥ 130/ 85
5. Fasting glucose	100-126 mg/dL

Ford et al JAMA 2002

Prevalence of Individual Components of the MBS in PCOS



HDL = high density lipoproteins
TTG = total triglycerides
HTN = hypertension

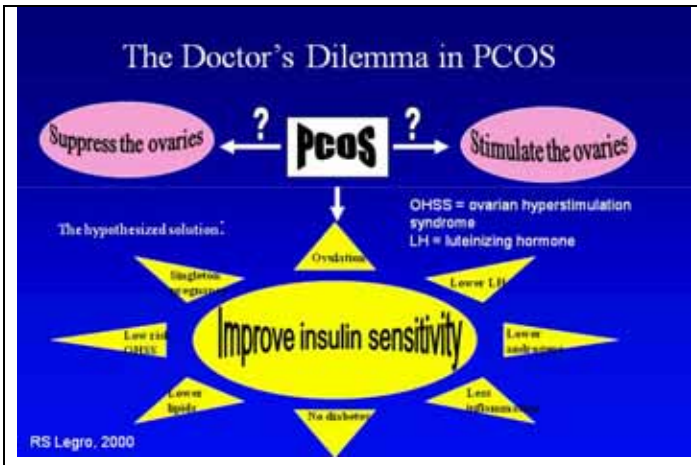
Ehrmann et al, JCEM, 2006

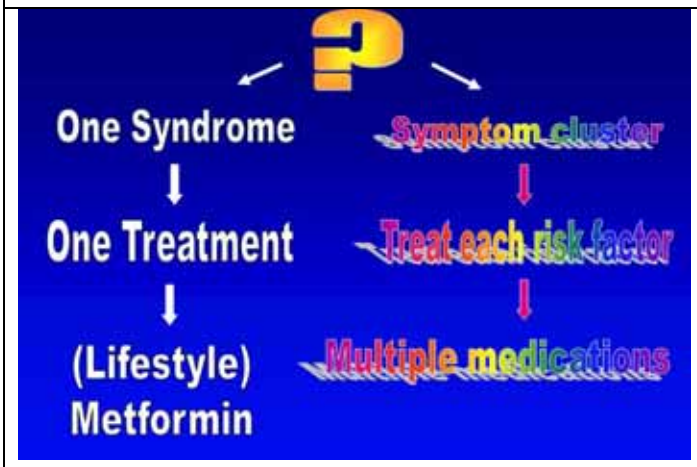
Syndrome XX- Female Metabolic Syndrome-PCOS

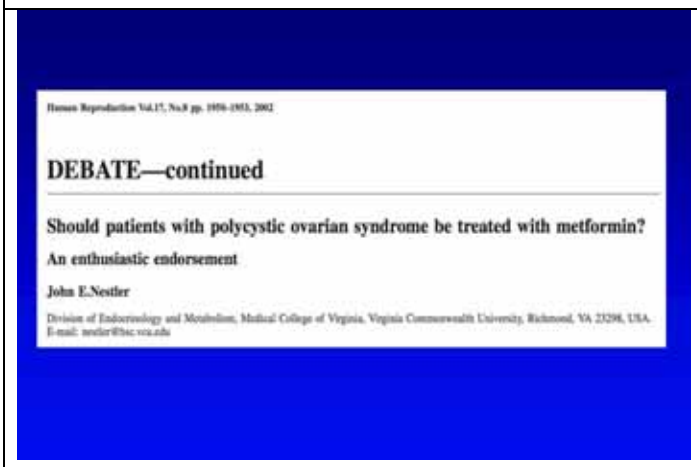
- Centripetal obesity
- Hyperglycemia
- Hypertension
- Dyslipidemia
- Anovulation

DM = diabetes mellitus
CVD = cardiovascular disease

All are risks factors for type 2 DM, CVD and endometrial cancer






Human Reproduction Vol.17, No.8 pp. 1956–1963, 2002

DEBATE—continued

Should patients with polycystic ovarian syndrome be treated with metformin?

An enthusiastic endorsement

John E.Nestler

Division of Endocrinology and Metabolism, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, USA.

Metformin - Favorable Pharmacology

- Circulates unbound
- Excreted unchanged from the kidney
- Half-life of 1.3-4.5 hours
- Does not induce hypoglycemia, no counter-regulatory responses with no effect on glucagons, cortisol, growth hormone, or somatostatin.

Metformin: Adverse Effects

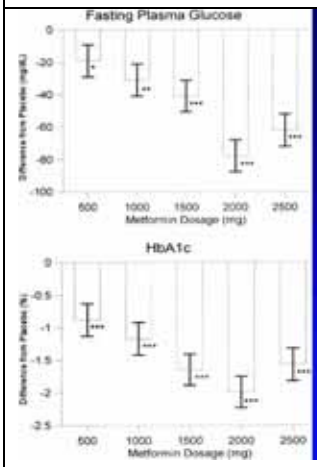
- Contraindications
  - renal impairment, hepatic disease, chronic obstructive pulmonary disease (COPD), cardiac failure, past history of lactic acidosis, hypersensitivity
- Side effects
  - up to 20% with nausea, diarrhea, abdominal discomfort and anorexia
- Pregnancy category B
- Extended-release XR version with more favorable side-effect profile

Pregnancy in PCOS (PPCOS): Adverse Events on Study Medication Pre-pregnancy

	Clomiphene (CL) (N = 209)	Metformin (Met) (N = 208)
Diarrhea	48/209 (23.0%)	135/208 (64.9%)
Nausea	82/209 (39.2%)	128/208 (61.5%)
Vomiting	28/209 (13.4%)	62/208 (29.8%)
Decreased appetite	17/209 (8.1%)	27/208 (13.0%)
Anovulatory bleeding	6/209 (2.9%)	18/208 (8.7%)

NEJM, 2007

Dose Ranging Metformin Study in Type 2 DM



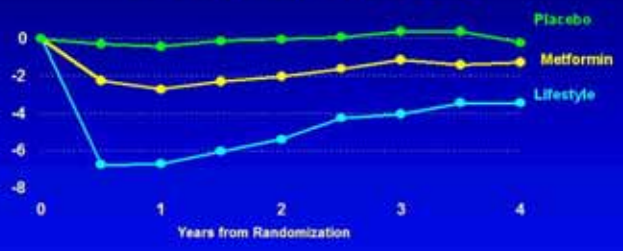
451 patients - 14 weeks

multicenter trial

Best dose=2000 mg/day

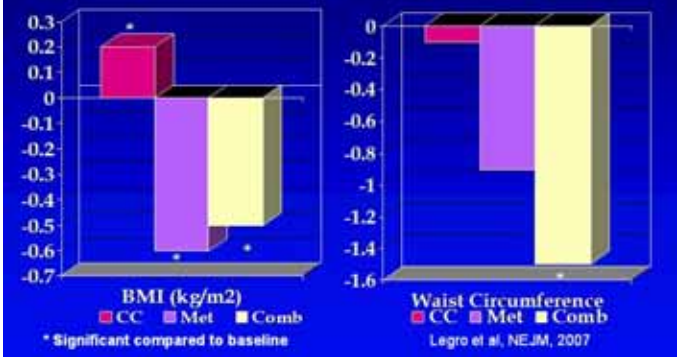
Garber et al, Am J Med, 1997

Mean Weight Change in Diabetes Prevention Program



The DPP Research Group, NEJM 2002

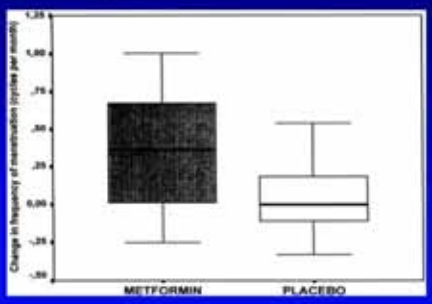
Effect on BMI and Waist Circumference in PPCOS



* Significant compared to baseline

Legro et al, NEJM, 2007

% Increase in Menstrual Frequency on Metformin in PCOS

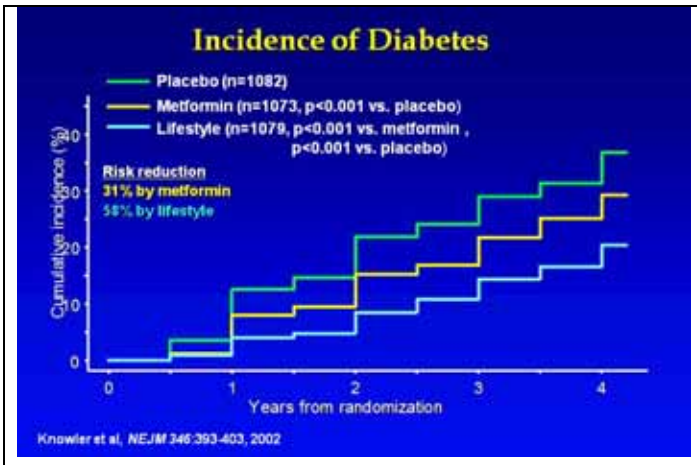


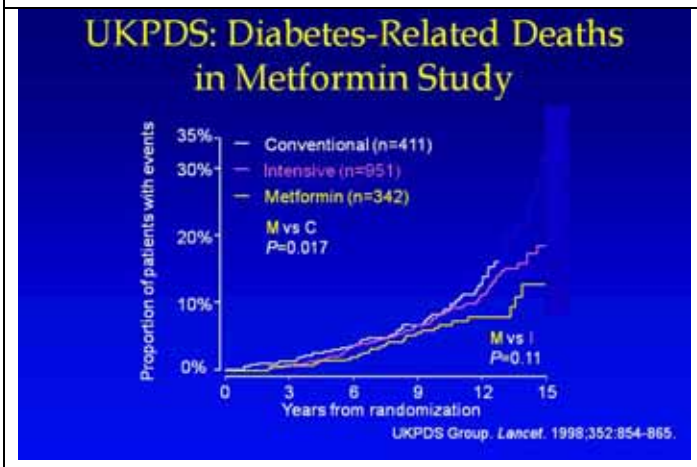
Moghetti et al, JCEM, 2000

No Consistent Effect of Metformin on Circulating Lipids and Blood Pressure

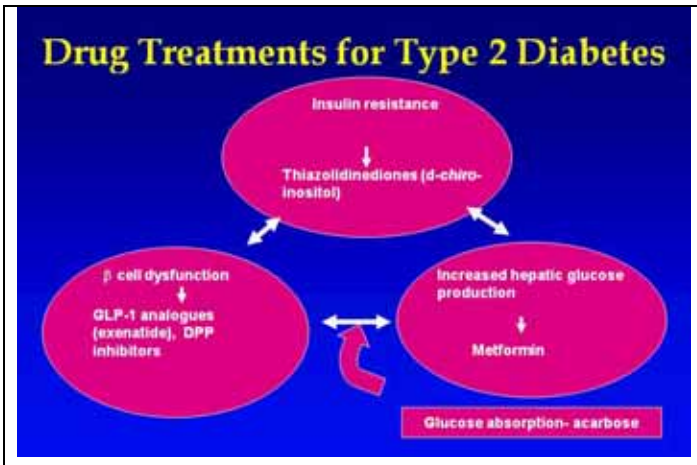
-Lord et al., 2003, Costello et al., 2007
Cochrane Systematic Reviews

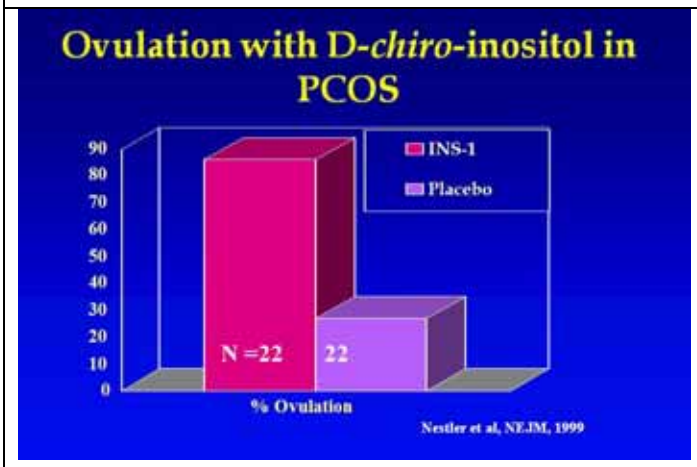
However, in other populations metformin is associated with clear benefit in preventing major morbidity and mortality.


Incidence of Diabetes
Placebo (n=1082)
Metformin (n=1073, p<0.001 vs. placebo)
Lifestyle (n=1079, p<0.001 vs. metformin , p<0.001 vs. placebo)
Risk reduction
31% by metformin
58% by lifestyle
Cumulative incidence (%)
0
10
20
30
40
0
1
2
3
4
Years from randomization
Knowler et al, NEJM 346:393-403, 2002


UKPDS: Diabetes-Related Deaths in Metformin Study
Conventional (n=411)
Intensive (n=951)
Metformin (n=342)
M vs C
P=0.017
M vs I
P=0.11
Proportion of patients with events
35%
30%
20%
10%
0%
0
3
6
9
12
15
Years from randomization
UKPDS Group. Lancet. 1998;352:854-865.


Metformin and PCOS
F.D.A.
No approved indication to treat PCOS, anovulation, or hirsutism in the U.S.


Drug Treatments for Type 2 Diabetes
Insulin resistance
Thiazolidinediones (d-chiro-inositol)
β cell dysfunction
GLP-1 analogues (exenatide), DPP inhibitors
Increased hepatic glucose production
Metformin
Glucose absorption– acarbose


Ovulation with D-chiro-inositol in PCOS
90
80
70
60
50
40
30
20
10
0
INS-1
Placebo
N =22
22
% Ovulation
Nestler et al, NEJM, 1999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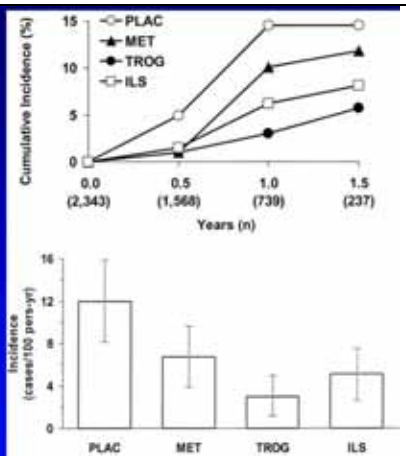
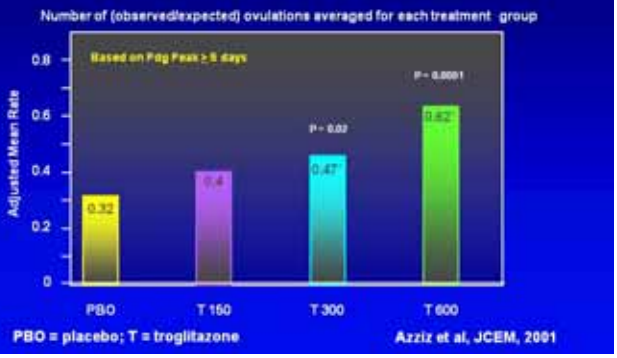
NEWS CENTER
Insmed Incorporated (ticker: INSM, exchange: NASDAQ) News Release - 10-Sep-2002
Insmed Discontinues Internal Development of INS-1 for Diabetes and Polycystic Ovary Syndrome - PCOS -
RICHMOND, Va., Sep 10, 2002 (BUSINESS WIRE) -- Insmed Incorporated (Nasdaq:INSM)
Decision Follows Results of Phase II Clinical Trials
Company Will Direct Resources Toward Most Promising Clinical Drug Candidates
Insmed Continues Its Commitment to Develop Drugs for Diabetes and PCOS
Insmed Incorporated today announced that it has discontinued its internal development of INS-1, one of its investigational drug candidates for type 2 diabetes and polycystic ovary syndrome (PCOS). The decision not to proceed was based on the results of recently completed Phase II clinical trials.
In a recently completed clinical trial in patients with type 2 diabetes, INS-1 was safe and well tolerated but did not achieve statistical significance on its primary efficacy measures. These efficacy results failed to corroborate those reported in several previous studies.

Thiazolidine-diones (TZD) Better than Lifestyle and Metformin in Preventing Diabetes



Knowler et al, Diabetes, 2005

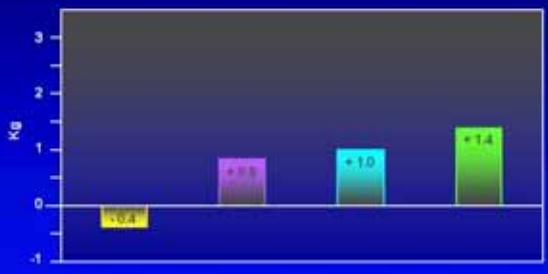
Incidence Rate of Ovulation with Troglitazone



PBO = placebo; T = troglitazone

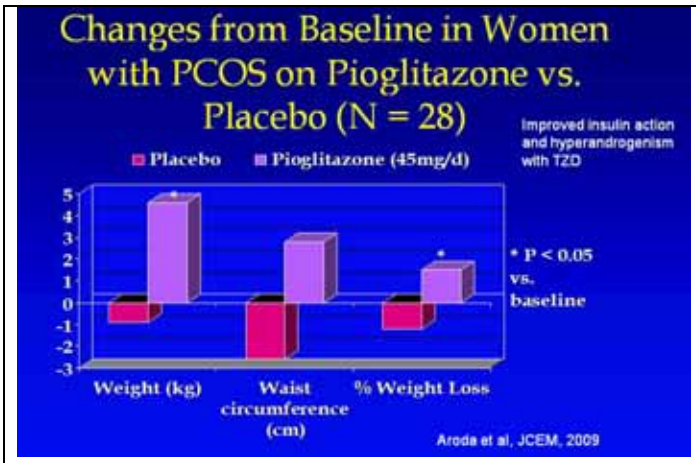
Azziz et al, JCEM, 2001

Changes in Body Weight at Week 44 with TGZ in PCOS

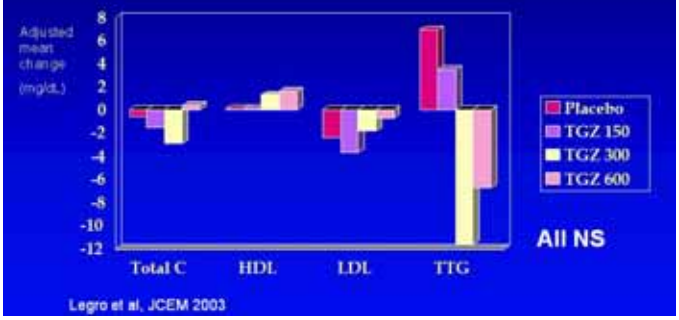


Azziz et al, JCEM, 2001

Changes from Baseline in Women with PCOS on Pioglitazone vs. Placebo (N = 28)



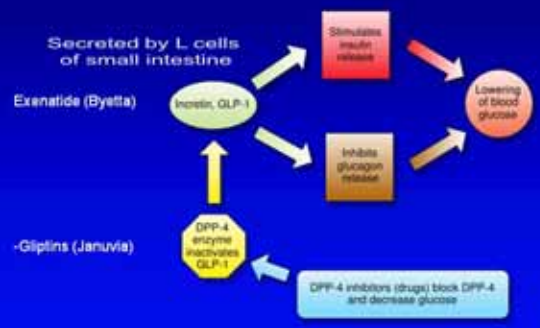
No Effect of Troglitazone on Serum Lipids in PCOS



Thiazolidinediones in PCOS

- Troglitazone-
  - Removed from the market due to hepatoxicity
- Rosiglitazone-
  - Concerns about increased risk of myocardial infarction
  - American Diabetes Association (ADA) recommends against its use!
- Pioglitazone
- Class Effects
  - Category C - ? fetal toxicity
  - Weight gain
  - Increased adiposity

Incretins: The Next Frontier of Treatment of PCOS??



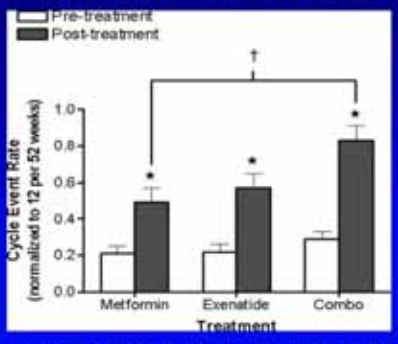
ORIGINAL ARTICLE

Endocrine Care

Comparison of Single and Combined Treatment with Exenatide and Metformin on Menstrual Cyclicity in Overweight Women with Polycystic Ovary Syndrome

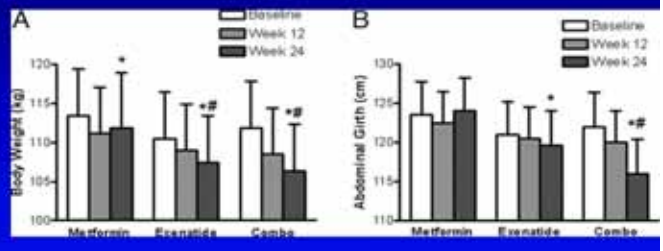
July 2008 JCEM

Menstrual Frequency at Baseline and after 24 Weeks



Eikind-Hirsch, K. et al. J Clin Endocrinol Metab 2008;93:2670-2678

Change in Body Weight and Waist During Treatment



Elkind-Hirsch, K. et al. J Clin Endocrinol Metab 2008;93:2670-2678

Side Effects: Exenatide

- Common
  - Nausea, vomiting, heartburn, diarrhea
  - Hypoglycemia
  - Local injection effects
- Serious
  - Pancreatitis
  - Systemic allergic reactions

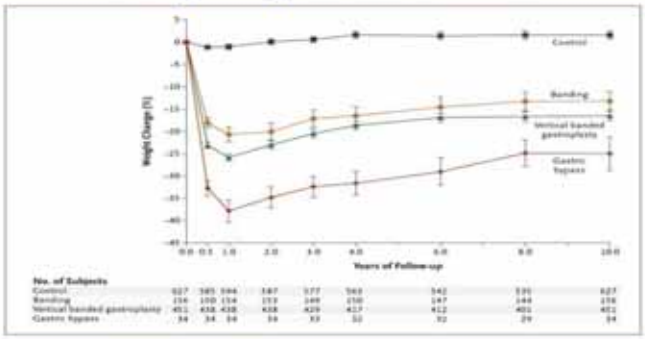
TZDs, d-chiro Inositol, Exenatide and PCOS

No approved indication to treat PCOS, anovulation, or hirsutism in the U.S.

Should We Target Aspects of the Metabolic Syndrome Other than Hyperglycemia?

i.e., centripetal obesity, dyslipidemia

Weight Changes among Subjects in the Swedish Obesity Study over a 10-Year Period

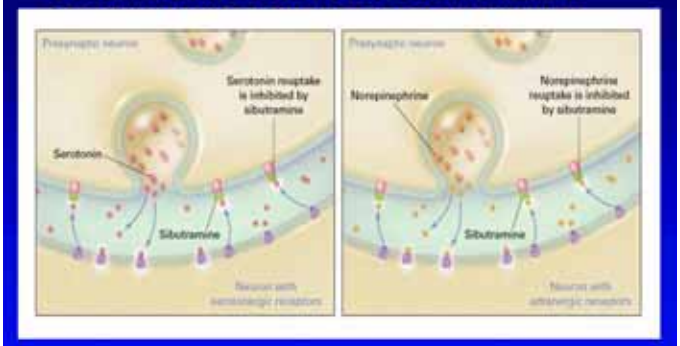


Sjostrom, L. et al. N Engl J Med 2004

Pharmacologic Treatment of Obesity

- Sibutramine
  - Short term,
  - Potential adverse CVD risk profile
- Orlistat
  - Steatorrhea
  - Poor compliance with diet
- Rimonabant
  - Not approved by the U.S. Food and Drug Administration (FDA)
  - Concerns about effects on mood (depression and suicide)

Mechanisms of Action of Sibutramine

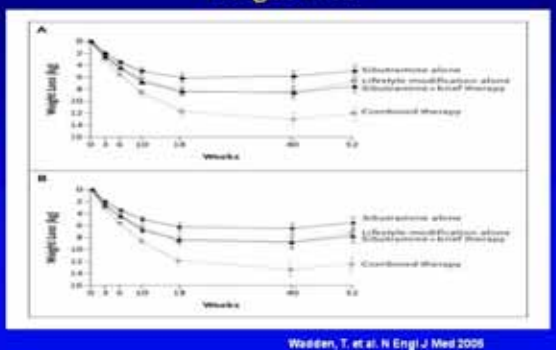


Yanovski, S. Z. et al. N Engl J Med 2002

Side Effects and Interactions: Sibutramine

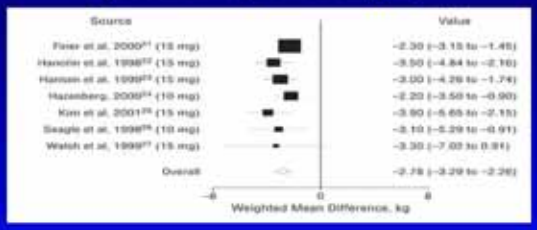
- 15 mg/day
- Tachycardia, hypertension, seizures
- Headache, dry mouth, insomnia
- Avoid with coronary artery disease (CAD), arrhythmia, hypertension
- Interactions: check for individual drugs

Combination Therapy (Lifestyle/Medication/Behavior) Achieves Best Weight Loss



Wadden, T. et al. N Engl J Med 2005

Pooled Analysis of 8- to 12-Week Trials of Sibutramine Hydrochloride, 10 to 15 mg/day

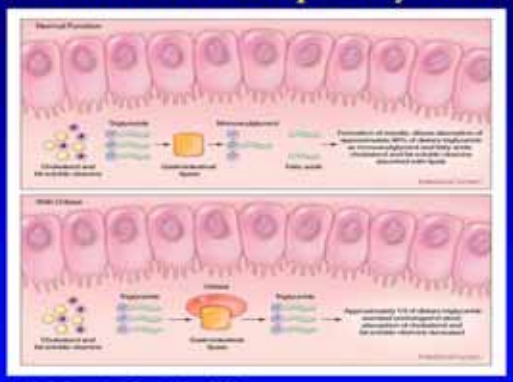


Arterburn, D. E. et al. Arch Intern Med 2004

6-month placebo-controlled trial in PCOS: 7.8 kg weight loss on sibutramine vs .2.8 kg with placebo

Lindholm et al, Fertil Steril, 2008

Inhibition of Fat Absorption by Orlistat



Yanovski, S. Z. et al. N Engl J Med 2002

Differences in Mean Weight Loss between Orlistat and Control Groups at 12 Months

- Meta-analysis of 22 studies
- Mean weight loss: 2.9 kg
- 95% CI (-3.7 to -2.3)

Li et al, Ann Intern Med, 2005

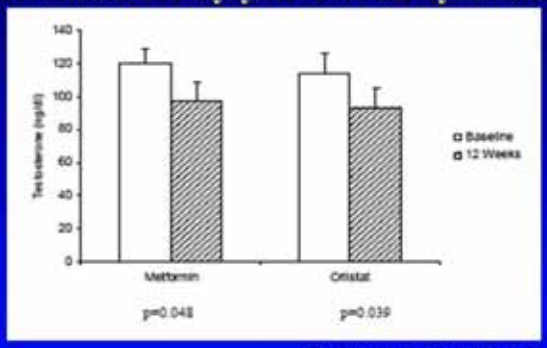
In PCOS, 5.6 kg weight loss at 24 weeks

Panidis et al, Fertil Steril, 2008

Side Effect and Interactions: Orlistat

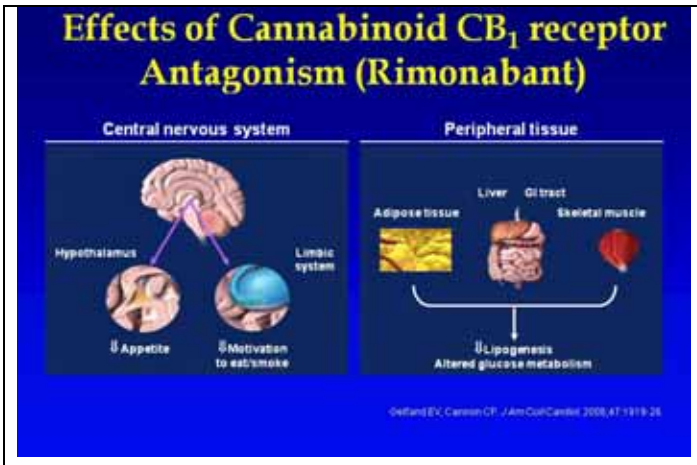
- 120 mg three times a day with meals (non-prescription Abilify 60 mg now available in the U.S.)
- Gastrointestinal: Steatorrhea, flatulence, cramps
  - Avoid with fatty meals
- Drug interaction: warfarin
  - Decreased vitamin K absorption
- Vitamin supplement recommended

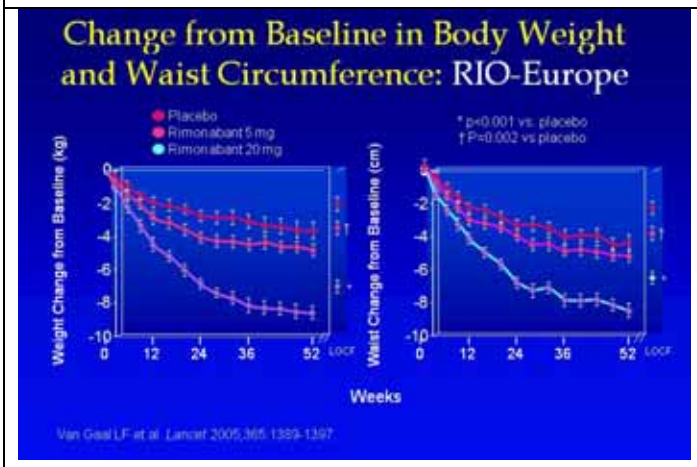
Orlistat Is as Beneficial as Metformin in the Treatment of Polycystic Ovarian Syndrome

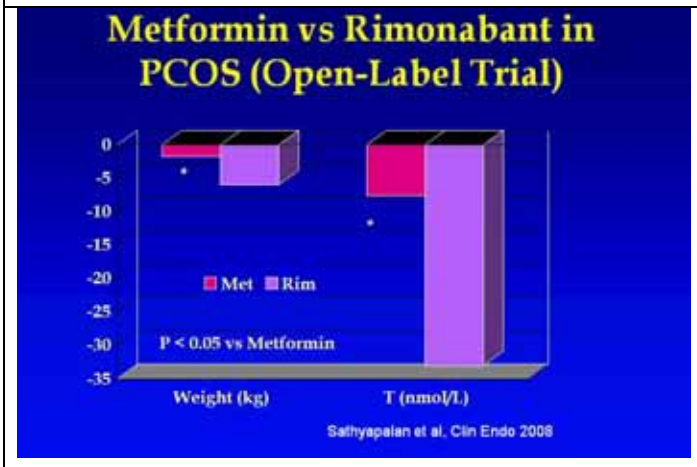


Jayagopal V, J Clin Endocrinol Metab 2004

Available Over-the-Counter as Alli (60 mg)


Effects of Cannabinoid CB_1 receptor Antagonism (Rimonabant)
Central nervous system
Peripheral tissue
Hypothalamus
Limbic system
Liver
GI tract
Adipose tissue
Skeletal muscle
⇩Appetite
⇩Motivation to eat/smoke
⇩Lipogenesis
Altered glucose metabolism


Change from Baseline in Body Weight and Waist Circumference: RIO-Europe
Placebo
Rimonabant 5 mg
Rimonabant 20 mg
* p<0.001 vs. placebo
† P=0.002 vs placebo
Weight Change from Baseline (kg)
Waist Change from Baseline (cm)
0
-2
-4
-6
-8
-10
0
12
24
36
52
LOCF
Weeks
Van Gaal LF et al. Lancet 2005;365:1389-1397


Metformin vs Rimonabant in PCOS (Open-Label Trial)
0
-5
-10
-15
-20
-25
-30
-35
Met
Rim
P < 0.05 vs Metformin
Weight (kg)
T (nmol/L)
Sathyapalan et al. Clin Endo 2008

Side Effects and Interactions- Rimonabant

- Not approved in the U.S.
- Psychiatric: depression (? increased suicidal ideation), anxiety, sleep disturbance
- Gastrointestinal: Nausea/vomiting
- Drug interaction: Hepatically metabolized, activity increased with so-called CYP3A4 inhibitors
  - Ketoconazole, clarithromycin

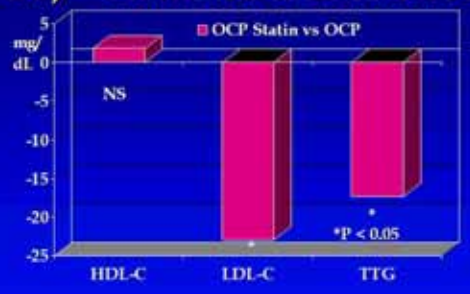
Anti-Obesity Drugs and PCOS

- Weight loss is modest
- Long-term return to baseline
- Limited studies in women with PCOS
  - Short time frame
  - Underpowered
- Unknown effects on pregnancy

Benefits of Statins in PCOS

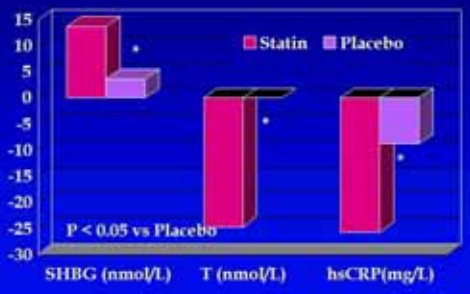
- Decreased ovarian steroidogenesis
  - Decreased availability of cholesterol, the precursor for testosterone production.
  - Statins may also decrease the expression of several key enzymes involved in testosterone production (SCC, 3B-HSD,17B-HSD)
  - Finally, statins may reduce ovarian testosterone output by inhibiting the proliferation of the testosterone-producing theca-interstitial cells.
- Improved lipid profile
  - Decreased LDL-C and triglycerides

Effects of Oral Contraceptive Pills (OCP) + Statin vs. OCP Alone in PCOS



Banaszewska et al, JCEM, 2007

Effects of Atorvastatin: Placebo RCT



No change in cycle length- both greater than 50d

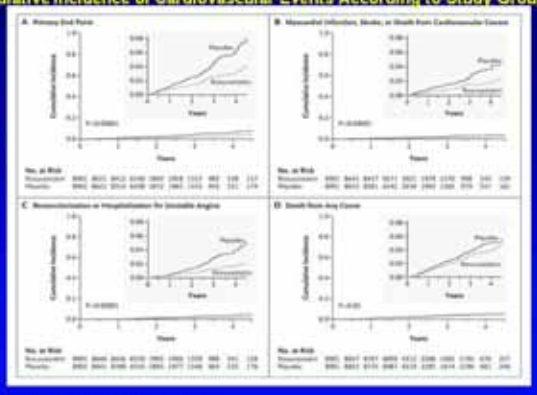
Sathyapalan et al, JCEM, 2009

Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Study

- Randomized controlled study of primary prevention of cardiovascular disease with rosuvastatin
- 17,802 apparently healthy men and women with LDL-C < 130 mg/dL and high-sensitivity C-reactive protein (hsCRP) levels ≥ 2.0 mg/L
- Combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Ridker P et al. N Engl J Med 2008;10.1056

Cumulative Incidence of Cardiovascular Events According to Study Group



Ridker P et al. N Engl J Med 2008;10.1056/NEJMoa0807646

Potential Risks of Statin Therapy

- Common adverse events associated with statins include constipation, flatulence, dyspepsia, abdominal pain, headaches, and rash.
- More severe side effects include
  - Myopathy (0.2% of patients)
  - Can lead to rhabdomyolysis and acute renal failure (0.1%)
  - Abnormal liver function (0.7%)
- Pregnancy category X
  - Based on its mechanism of action

Statins and PCOS

No approved indication to treat PCOS, anovulation, or hirsutism in the U.S.

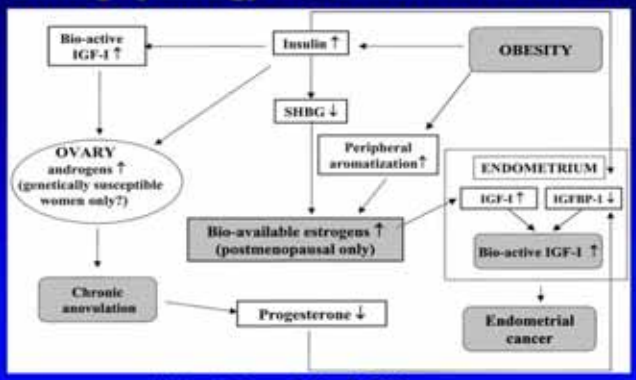
Syndrome XX- Female Metabolic Syndrome-PCOS

- Centripetal obesity
- Hyperglycemia
- Hypertension
- Dyslipidemia
- Anovulation

DM = diabetes mellitus
CVD = cardiovascular disease

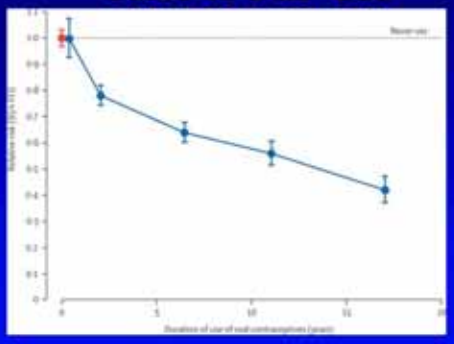
All are risks factors for Type 2 DM, CVD, and endometrial cancer

Pathophysiology of Endometrial Cancer



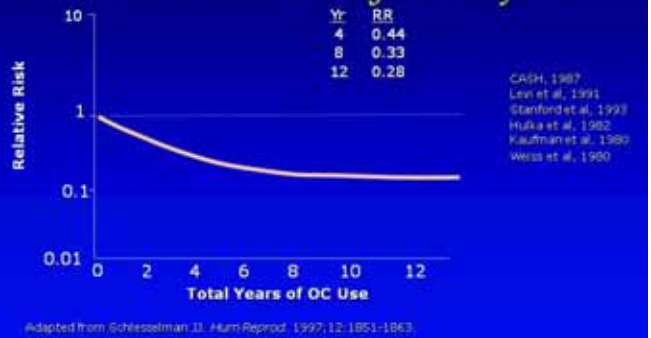
Kaaks et al, Cancer Epidem Bio 2002

Risk of Ovarian Cancer by Years of OCP Use



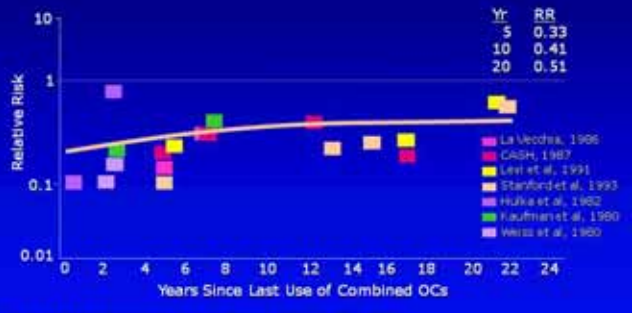
Collaborative Group on Epidemiological Studies of Ovarian Cancer, Lancet 2008

Oral Contraceptives Reduce Risk of Endometrial Cancer *By Years of Use*



Adapted from Schlesselman JJ. Hum Reprod. 1997;12:1851-1863.

OCs Protect Against Endometrial Cancer After Discontinuation



Adapted from Schlesselman JJ. Hum Reprod. 1997;12:1851-1863.

OCP Contraindications Likely Overrepresented in Women with PCOS

- Hypertension
- Obesity
- Smoking
- Diabetes/vascular involvement

Intrauterine Device (IUD) Protective against Endometrial Cancer

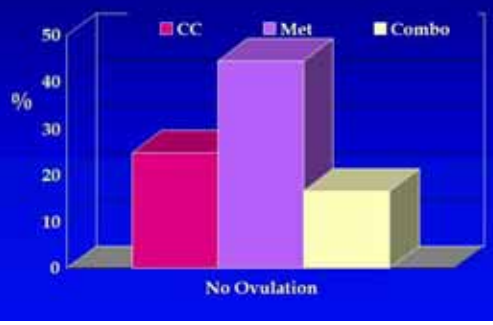
- Based on the random effects model, a protective association between IUD use and endometrial cancer was observed (odds ratio [OR] = 0.39; 95% confidence interval [CI] = 0.29-0.51)
- A decreased risk of endometrial cancer also was seen for increased years of IUD use .

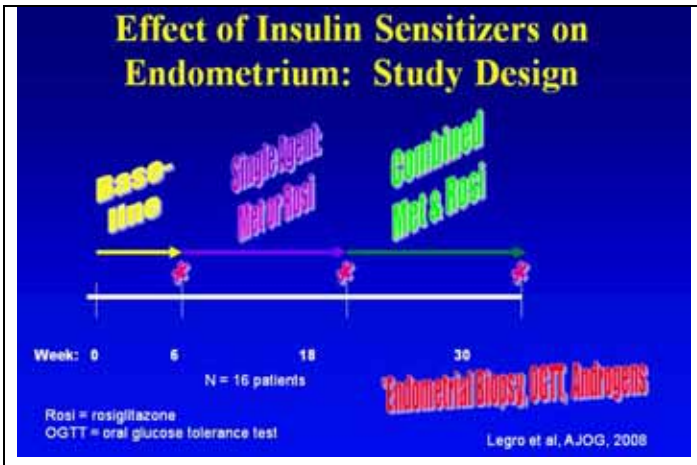
Beining, Ann Epidemiol, 2008

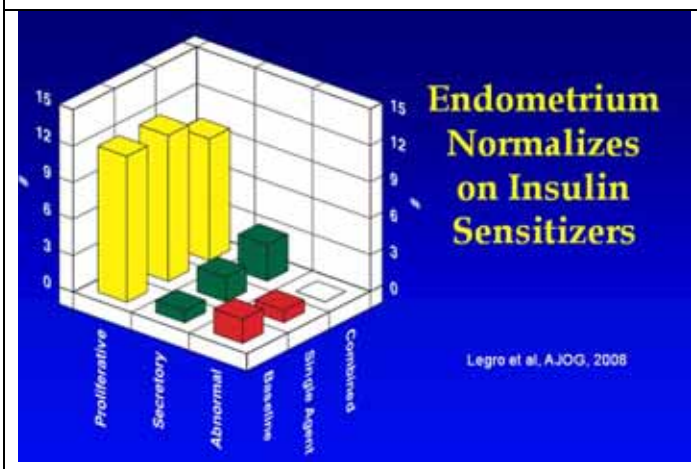
How Best to Prevent Endometrial Cancer with Progestin Therapy:

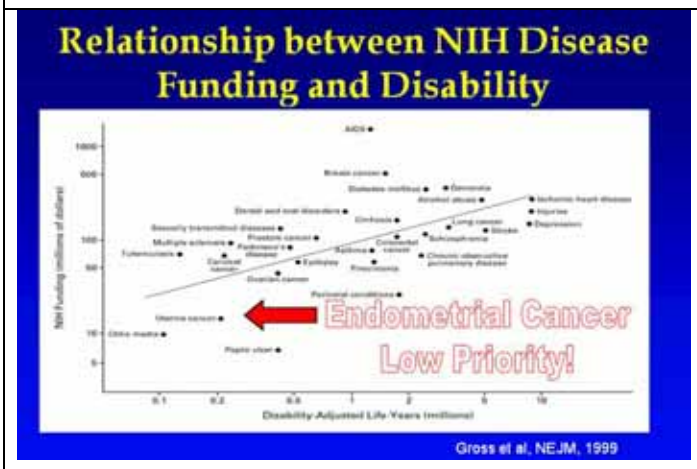
Dose?
Frequency?
Type of progestin?

Prevalence of No Ovulations During Study Participation in PPCOS




Effect of Insulin Sensitizers on Endometrium: Study Design
Base-line
Single Agent: Met or Rosi
Combined Met & Rosi
Week: 0
6
18
30
N = 16 patients
Endometrial Biopsy, OGTT, Androgens
Rosi = rosiglitazone
OGTT = oral glucose tolerance test
Legro et al, AJOG, 2008


Endometrium Normalizes on Insulin Sensitizers
15
12
9
6
3
0
Proliferative
Secretory
Abnormal
Baseline
Single Agent
Combined
Legro et al, AJOG, 2008


Relationship between NIH Disease Funding and Disability
Endometrial Cancer
Low Priority!
Disability-Adjusted Life-Years (millions)
Gross et al, NEJM, 1999

SUMMARY

There is no one ***pharmaceutical*** that will address all the metabolic abnormalities in PCOS.

Polypharmacy is needed to prevent long-term complications.

The Unbundled Pharmacologic Treatment of Syndrome XX in PCOS

Abnormality	Treatment
Centripetal obesity	Metformin, bariatric surgery, orlistat vs. sibutramine?
Dyslipidemia (assuming increased LDL-C)	Statin therapy
Hypertension	Spironolactone ??
Hyperglycemia (impaired fasting or glucose tolerance)	Metformin
Anovulation	Progestin therapy (micronized progesterone)

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- **Penn State REI Research Team**
  - Bill Dodson, M.D.
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  - Jan McAllister, Ph.D.
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  - Anuja Dokras, M.D., Ph.D.
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NOTES

PREVENTION OF HIRSUTISM

Daniel A. Dumesic, M.D.
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Department of Obstetrics and Gynecology
University of Wisconsin, Madison
Affiliated Scientist, National Primate Research Center
University of Wisconsin, Madison

LEARNING OBJECTIVES

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

1. State two endocrine factors that influence the growth of hair.
2. Indicate when testing for hyperandrogenism is recommended for hirsutism.
3. Define permanent hair removal.
4. Formulate a medical therapy for patient-important hirsutism despite cosmetic measures.

PREVENTION OF HIRSUTISM

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Ferring Pharmaceuticals

The Hair Follicle

- Types: terminal, vellus, sebaceous
- Cycle: growth (anagen), transition (catagen), resting (telogen)
- Anagen: basal hair bulb initiates hair growth
  - epithelial cells (keratinocytes) in hair matrix divide to cause growth of hair, which acquires pigment from melanocytes
  - Mesenchymal cells in the dermal papilla mediate the action of androgen action through the androgen receptor (AR).
- Steroid enzymes: 3β- and17β-HSD, 5α-reductase, aromatase.
- Androgens transform vellus to terminal follicles; prolong anagen
- Insulin and IGF-I also may regulate the hair cycle.

Thiboutot D 1997; Randall V 1997

Hirsutism

- Defined as excessive terminal hair appearing in a male pattern (modified Ferriman-Gallwey score ≥ 8).
- Depends on circulating androgen levels and response of the hair follicle to the local androgen milieu.
- Influenced by local conversion of testosterone (T) to dihydrotestosterone (DHT) by 5α-reductase and subsequent binding of these molecules to the AR.
- May be associated with underlying disorders, including neoplasms and various endocrinopathies, of which polycystic ovary syndrome (PCOS) is the most common.

Dumesic D et al. 1997; Martin K et al. 2008; Hatch R et al. 1981

Endocrine Society Clinical Practice Guidelines

- Task Force was selected by the Clinical Guidelines Subcommittee (CGS) of the Endocrine Society.
- Consensus was guided by systematic reviews of evidence and group discussions.
- Task Force recommendations were reviewed by the Endocrine Society's CGS, Clinical Affairs Core Committee, and Council.
- Revisions were placed on the Endocrine Society's Web site for comments by members.

Martin K et al. 2008

Endocrine Society Clinical Practice Guidelines Diagnosis: Testing for Hyperandrogenism

- Not recommended for isolated hirsutism
  - Because the likelihood of identifying a disorder that would change management or outcome is low.
- Recommended for hirsutism that is
  - Moderate to severe
  - Sudden in onset and rapidly progressive, or
  - Associated with menstrual dysfunction, obesity, acanthosis nigricans or clitoromegaly.

Martin K et al. 2008

Testing for Hyperandrogenism

- Plasma total T should be measured in the early morning on cycle day 4-10 in a regularly cycling women.
  - T levels are low during menses and vary by 25% during the follicular phase, with highest levels in the early morning.
- Total T should be rechecked in a reliable laboratory, along with a free T, if it is normal in the presence of risk factors or progression of hirsutism on therapy.
  - Lab interpretation is complicated by excessively broad normal ranges and no uniform laboratory standard.

Martin K et al. 2008

Testing for Hyperandrogenism (continued)

- 17-hydroxyprogesterone also should be obtained in women at risk for late-onset congenital adrenal hyperplasia
  - Ashkenazi Jews, prevalence 3.7%; Hispanics, 1.9%; Yugoslavs, 1.6%; Italians, 0.3%; diverse Caucasian population, 0.1%.
- Although dehydroepiandrosterone (DHEAS) levels are elevated in 16% of women with normal T levels, such mild elevations are unlikely to affect therapy.

Martin K et al. 2008; Dumesic D 1997; Azziz R et al. 2004; Speiser P et al. 1985

Therapy for Patient-Important Hirsutism Despite Cosmetic Measures

- Depends on patient preferences, the extent to which the affected area is amenable to direct hair removal and access to and affordability of alternatives.
- Pharmacological therapy is usually oral contraceptives, with addition of an antiandrogen after 6 months if the response is suboptimal.
- Laser photoepilation can be used for direct hair removal
  - With pharmacological therapy continued in women with hyperandrogenemia to minimize hair regrowth.

Martin K et al. 2008

Oral Contraceptive (OC) Therapy

- Drospirenone: a progestin with weak anti-androgenic properties. Three mg drospirenone = 25 mg spironolactone = 1 mg cyproterone acetate (CPA)
- Norgestimate and desogestrel: progestins with low androgenicity
- Levonorgestrel; the most androgenic progestin
- No clinical advantage of using one OC over another
- Six-month trial is recommended before adding another medication, given a 4-month anagen phase for facial hair.

Martin K et al. 2008; Breitkopf D et al. 2003

Antiandrogen Therapy

- Steroidal: block AR and have antigonadotropic actions
  - Spironolactone (100-200 mg/day): aldosterone antagonist
    - inhibits AR and 17α-hydroxylase/17-20 lyase
    - Side effects: polyuria, polydipsia, menstrual dysfunction, hyperkalemia, hypotension, risk of fetal male pseudohermaphroditism (if used in pregnancy)
  - Cyproterone acetate (2-100 mg/day): 17OHP$_4$ derivative
    - inhibits AR and 5α-reductase.
    - Side effects: asthenia, loss of libido and mastalgia

Martin K et al. 2008; Ibáñez L et al. 2002; Calaf J et al. 2007; Fruzzetti F 1997

Antiandrogen Therapy (continued)

- Nonsteroidal (pure): block AR only
  - Flutamide (250-500 mg/day; low dose: 62.5-250 mg/day
  - Side effect: dry skin, dose-related risk of hepatotoxicity
  - Finasteride (2.5-5.0 mg/day): blocks type 2 5α-reductase
  - Partial response may occur due to type 1 5α-reductase

Martin K et al. 2008; Ibáñez L et al. 2002; Calaf J et al. 2007; Fruzzetti F 1997; Legro R 2007

Insulin Sensitizers (Meta-analysis of 16 Randomized Controlled Trials)

- Insulin sensitizers provide limited benefit for women with hirsutism and no significant benefit over OCPs or antiandrogens.
- Small decrease in Ferriman-Gallwey scores with insulin sensitizers *vs.* placebo (weighted mean difference [WMD] -1.5 [95% CI -2.8 to -0.2]).
- No significant difference between insulin sensitizers and OCPs (WMD -0.5 [95% CI -5.0 to 3.9).
- Metformin was inferior to spironolactone (WMD 1.3 [95% CI 0.03 to 2.6]) and flutamide (WMD 5.0 [95% CI 3.0 to 7.0]).

Martin K et al. 2008; Cosma M et al. 2008

Effect of Dietary Restriction on Hirsutism in Overweight PCOS Women Receiving Placebo or Medical Therapy

	Diet + Placebo	Diet + Metformin	Diet + Flutamide	Diet + Metformin + Flutamide
Basal	9.3 ± 4.8	13.0 ± 8.9	14.6 ± 6.8	14.5 ± 6.5
0.5 yr	8.0 ± 5.1[a]	10.9 ± 8.6[b]	8.4 ± 4.0[c]	7.9 ± 4.3[c]
1.0 yr	8.0 ± 4.1[a]	10.4 ± 6.6[b]	5.7 ± 1.7[c,e]	6.5 ± 3.9[c,d]

Mean ± SD
a, $P<0.05$; b, $P<0.01$; c, $P<0.001$ *vs* basal
d, $P<0.05$; e, $P<0.01$ *vs.* 6 months

Gambineri A et al. 2006

Alternate Pharmacological Therapies

- Glucocorticoids may be used in women with nonclassical congenital adrenal hyperplasia (NCAH) who have a suboptimal response to previous medications, cannot tolerate them or seek ovulation.
  - Side effects include adrenal atrophy, hypertension, weight gain, abdominal striae and bone loss.
- Gonadotropin-releasing hormone (GnRH) analog has no therapeutic advantage over oral contraceptives or antiandrogens.
  - It is expensive, requires injections and causes severe hypoestrogenism and eventual bone loss.

Martin K et al. 2008; Cosma M et al. 2008; Legro R 2007; Spritzer P et al. 1990; Heiner JS et al. 1995

Temporary Methods of Hair Removal

- Cosmetic methods (bleaching): irritation, pruritis, discoloration
- Depilation: removes hair shafts from the skin surface
  - Shaving: leaves a blunt tip
  - Thioglycolates; unpleasant odor from sulfur, dermatitis
  - Epilation: extracts hair to above the bulb
  - Plucking, and/or waxing: discomfort, scarring, folliculitis, hyperpigmentation

Martin K et al. 2008

Permanent Methods of Hair Reduction

> 30% reduction in terminal hair numbers after treatment, that is stable for longer than the complete growth cycle of hair follicles

- Electrolysis
  - Painful, time-consuming, erythema, scarring
  - Good for small areas of sparse hair of any color
- Laser photoepilation (red-near/infrared); intense pulsed light (IPL)
  - Expensive but efficient
  - Scarring, dyspigmentation, IPL-related hypertrichosis
  - Longer wavelength lasers (Nd:YAG) needed in dark-skinned individuals to reduce burning.

Martin K et al. 2008; Gorgu M et al. 2000; Radmanesh M et al. 2008

Permanent Methods of Hair Reduction (continued)

Recommendation based on higher value of efficiency, convenience and pain relief over cost.

- Laser photoepilation
- Pharmacological therapy should be considered in women with hyperandrogenemia to minimize hair regrowth.
- Eflornithine hydrochloride cream 13.9%
  - Irreversible inhibitor of ornithine decarboxylase, which catalyzes the rate-limiting step for follicular polyamine synthesis necessary for hair growth
  - Can be applied topically during photoepilation to improve the initial response

Martin K et al. 2008

Hyperandrogenic Anovulation Among Women Requesting Electrolysis

- 652 premenopausal women attending one of 27 electrology clinics in the United States, Canada and Germany.
- 27.3% of these women had hirsutism with menstrual irregularity.
  - One half were also obese.
  - Two thirds were unaware of the reason for their hirsutism.

Dumesic D et al. 1997A

Prevention of Hirsutism

- Insulin and IGF-I may regulate the hair cycle.
- In 2003-2004, 17.1% of children and adolescents in the United States were overweight.
- An exaggerated decrease in SHBG during adolescence may be a cofactor in the development of hirsutism.
- Hyperinsulinemia occurs in children of PCOS women.
- Triglyceride and HDLcholesterol levels positively and negatively correlate with free testosterone levels in PCOS adolescents, respectively.

Thiboutot D 1997; Cross G et al. 2008; Fruzzetti F et al. 2008; Kent S et al. 2008; Ogden C et al. 2006

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NOTES

NOTES

POLYCYSTIC OVARY SYNDROME (PCOS) 101— FIRST-LINE OVULATION INDUCTION: WEIGHT LOSS, CLOMIPHENE AND ITS VARIATIONS

Richard S. Legro, M.D.
Department of Obstetrics and Gynecology
Penn State College of Medicine
M.S. Hershey Medical Center
Hershey, Pennsylvania

LEARNING OBJECTIVES

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

1. Assess preconception issues to discuss with patient.
2. Identify the clinical and biochemical factors that predict response.
3. Explain to patients approximate success rates of first-line therapies.
4. List varying strategies to treat obesity prior to ovulation induction.
5. Discuss adjuvant therapy for patients non-responsive to frontline therapy.

Polycystic Ovary Syndrome (PCOS) 101—First-Line Ovulation Induction: Weight Loss, Clomiphene and Its Variations

Richard S. Legro, M.D.
Penn State College of Medicine
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Hershey, PA

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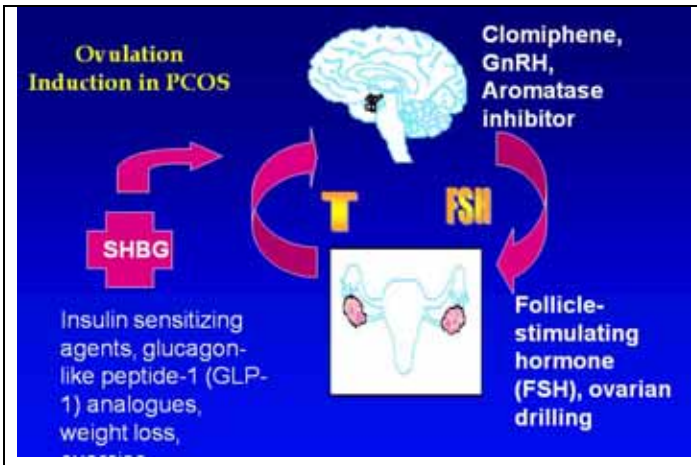
- Identify the clinical and biochemical factors that predict response
- Discuss with patients approximate success rates of first-line therapies
- List varying strategies to treat obesity prior to ovulation induction
- Discuss adjuvant therapy for patient non responsive to front line therapy

Disclosures

- Study Investigator-Solvay Pharmaceuticals
- Consultant- Merck-Serono

- Off-label drug use: metformin, letrozole, anastrazole
- Labelled drug use: sibutramine, orlistat



Preconception Issues in Women with PCOS

- Undiagnosed, untreated, or poorly controlled medical conditions
- Nutritional Issues
- Family history and genetic risk
- Tobacco and substance use
- Occupational and environmental exposures
- Mental health issues

Adapted from ACOG Committee Opinion #313, September 2005

Other Medical Conditions Among Pregnancy in PCOS (PPCOS) Subjects

Criteria among screened patients	Abnormal results/ Total number tested	Prevalence
Currently pregnant	20/968	2.0%
Diabetes mellitus	14/902	1.5%
Liver disease	8/822	0.9%
Criteria among randomized patients		
Hypertension	39/626	6.2%
History of psychiatric disease	110/626	17.6%

Legro et al, Fertil Steril, 2006; McGovern et al, Fertil Steril 2007

Smoking and ETOH Use is Common Among Women with PCOS

	All Patients n = 626
Patient had history of smoking	247/626 (39.5%)
Current smoker	107/626 (17.1%)
Stopped smoking	140/626 (22.4%)
Patient had history of alcohol use	416/626 (66.5%)
Currently using alcohol	226/626 (36.1%)
No current alcohol use	190/626 (30.4%)

Legro et al. Fertil Steril, 2006

Should We Screen the Patient and Couple for Infertility Factors Other than Chronic Anovulation?

Presence of Other Infertility Factors in PPCOS

Criteria	Abnormal test/number tested	Prevalence
Oligospermia (< 20 million/mL)	95/881	10.1%
Bilateral tubal occlusion	35/839	4.2%

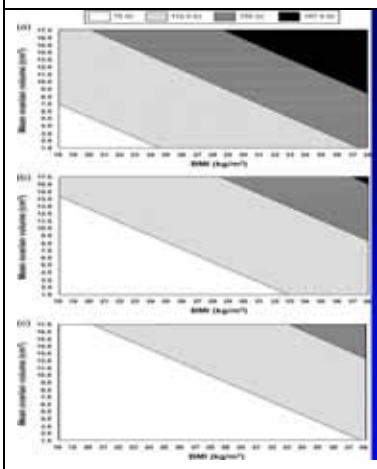
McGovern et al. Fertil Steril, 2007

Improving Hyperandrogenism, Not Insulin Resistance, Correlates with Live Birth

Multivariate Significant Predictors of FSH Threshold Dose in WHO Type II

	Odds Ratio (OR)	95% CI
Body mass index (BMI)	1.17	1.07-1.29
Menstrual Cycle		
Amenorrhea vs. normal length	11.9	(3.4-42.1)
Oligomorrhea vs. normal length	2.57	(0.97-1.37
Mean ovarian volume	1.22	(1.08-1.37)

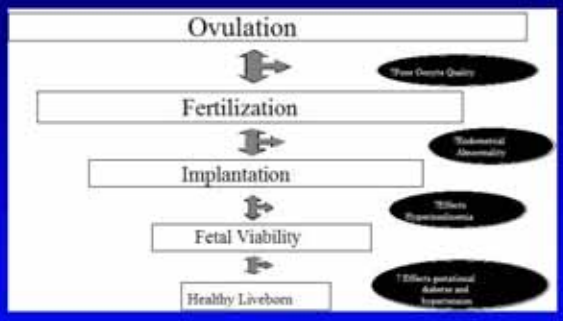
Andersen et al., Hum Reprod, 2008



Nomograms for Prediction of Individual FSH Threshold Dose in WHO II Patients

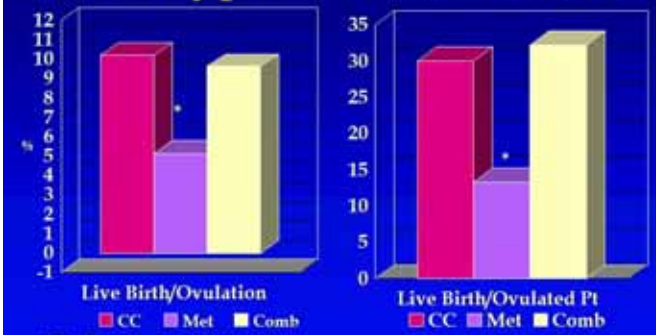
Nyboe Andersen, A. et al. Hum. Reprod. 2008 23:1424-1430

Does Ovulation = Live Birth?



Legro et al. Hum Reprod, 2004

Fecundity per Ovulation in PPCOS



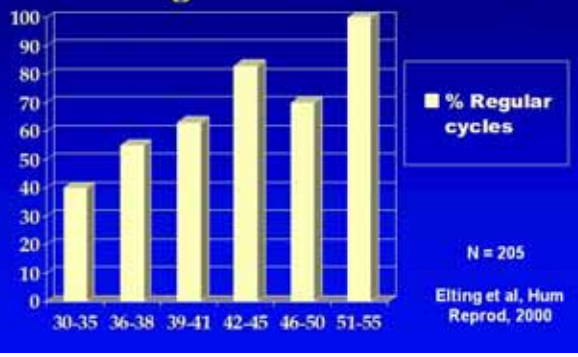
* Significant compared to baseline

Legro et al, NEJM, 2007

Be Suspicious of Models that Only Look at Ovulation!

Effect	Ovulation	Live Birth
Age (Yrs)		
>34 (Reference)	1.0	1.0
≤34	0.61[0.41,0.92]	5.05[1.46,17.52]

Improved Menstrual Regularity with Age in PCOS Women



N = 205

Elting et al, Hum Reprod, 2000

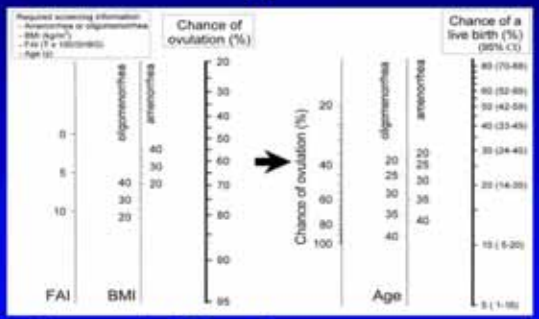
Multivariable Logistic Regression Model to Predict Pregnancy with rFSH treatment in PCOS

	Odds Ratio	95% confidence intervals
Oligomenorrhea vs. amenorrhea	2.34	1.11 to 5.38 P = 0.04
Duration of infertility	0.84	0.73 to 1.04 P = 0.13
Free androgen index	0.93	0.89 to 0.98 P = 0.003

57 pregnancies in 85 patients

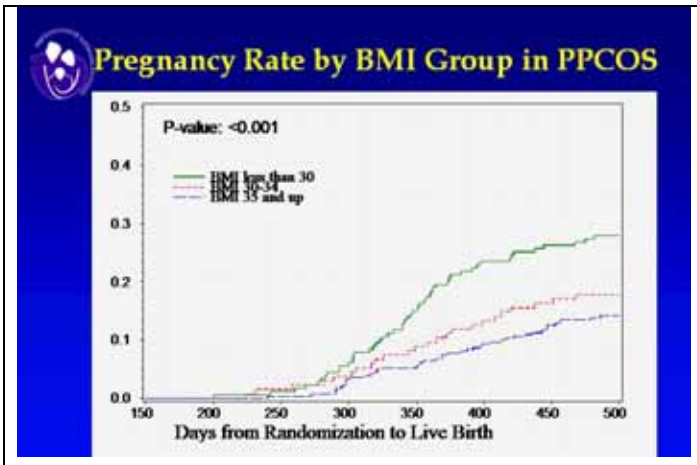
Van Wely et al, Hum Reprod, 2005

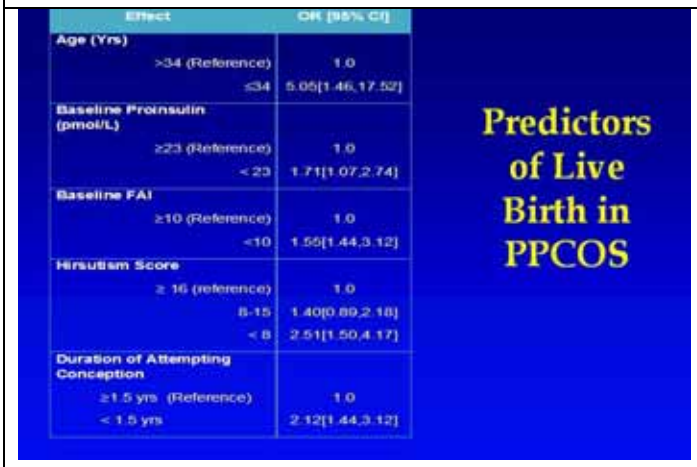
Nomogram to Predict Ovulation/Live Birth in WHO Type II Anovulation



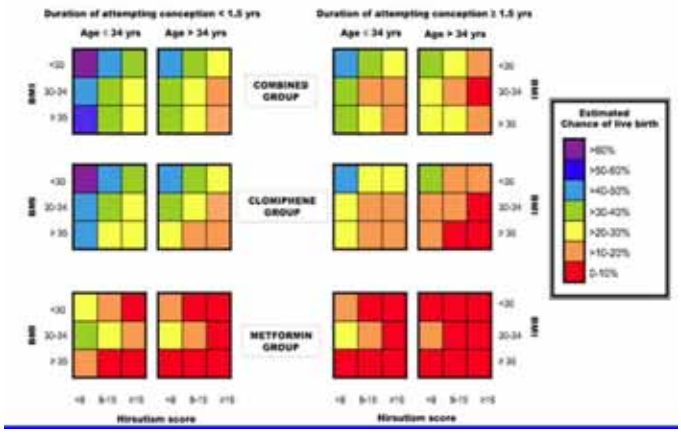
Retrospective case series of 259 couples

Imani et al, Fertil Steril 2002





Effect	OR [95% CI]
Age (Yrs)	
>34 (Reference)	1.0
≤34	5.05[1.46,17.52]
Baseline Proinsulin (pmol/L)	
≥23 (Reference)	1.0
< 23	1.71[1.07,2.74]
Baseline FAI	
≥10 (Reference)	1.0
<10	1.55[1.44,3.12]
Hirsutism Score	
≥ 16 (reference)	1.0
8-15	1.40[0.89,2.18]
< 8	2.51[1.50,4.17]
Duration of Attempting Conception	
≥1.5 yrs (Reference)	1.0
< 1.5 yrs	2.12[1.44,3.12]



What Is the Evidence-Based Schema for First-Line Infertility Therapy in Women with PCOS?

What Is Evidence?

Worst

- Expert opinion
- Case series
- Case/control studies
- Cohort studies
- Randomized controlled trials (RCTs)

Best

Answer: There Is No Evidence-Based Schema

SPECIAL CONTRIBUTIONS

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

Symposium supported by an unconditional grant from NV Organon and by European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM).

*Group members: B. C. Tarlatzis (Gr), B. C. J. M. Fauser (NL), R. S. Legro (USA), R. J. Norman (Aus), K. Hoeger (USA), R. Pasquali (It), S. Franks (UK), I. E. Messinis (Gr), R. F. Casper (Can), R. Homburg (Is), R. Lobo (USA), R. W. Rebar (USA), R. Fleming (UK), B. R. Carr (USA), Ph. Bouchard (Fr), J. Chang (USA), J. N. Hugues (Fr), R. Azziz (USA), E. M. Kolibianakis (Gr), G. Griesinger (Ger), K. Diedrich (G), A. Balen (UK), C. Farquhar (NZ), P. Devroey (B), P.C. Ho (HK), J. Collins (Can), D.G. Goulis (Gr), R. Eijkemans (NL), P. G. Crosignani (It), A. DeCherney (USA), A. van Steirteghem (B).

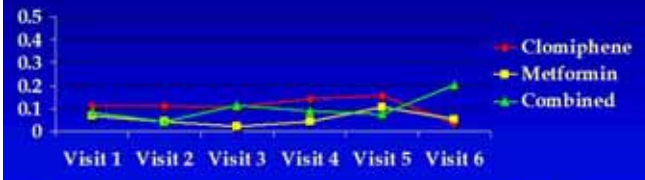
Hum Reprod. 2008 Mar;23(3):462-77 and Fertil Steril. 2008 Mar;89(3):505-22.

How Many Treatment Cycles?

Minimum of 6 ovulatory cycles

Fecundity (Live Birth/Ovulation) by Treatment Cycle in PPCOS

N = 626



Caveat: The best (pregnancy) and worst (anovulation) drop out over time

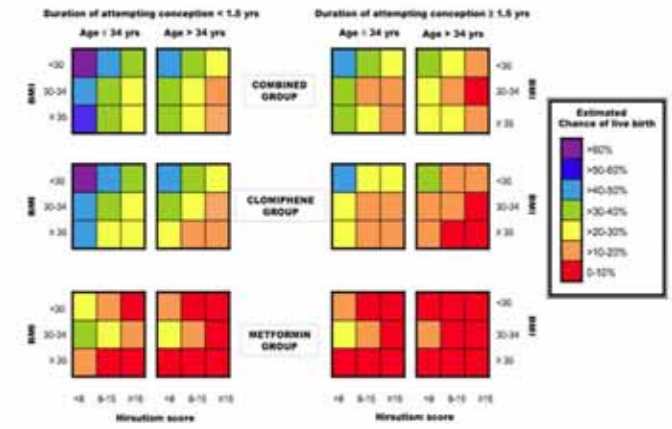
Extracted from Legro et al, NEJM, 2007

PCOS Case Presentation

	Yes	No
Old		
Obese		
Hirsute/ hyperandrogenic		

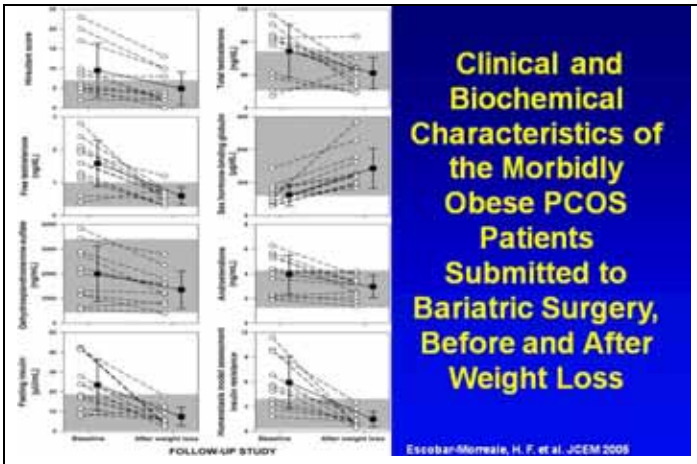
Patient #1

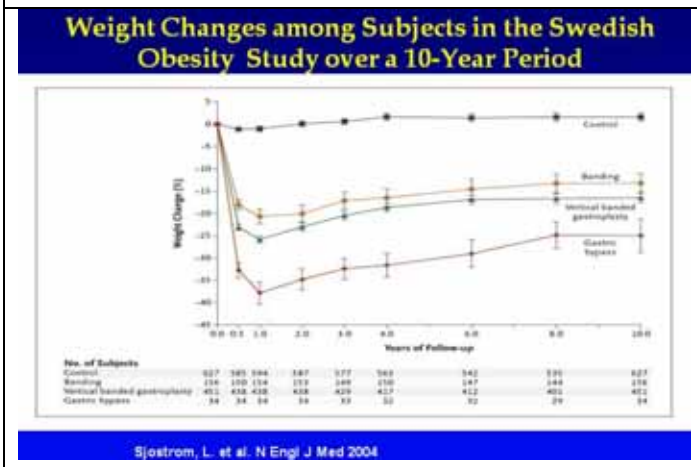
- 26-year-old woman with primary infertility
  - Amenorrhea
  - Ferriman -Gallwey (F-G) score 20
  - BMI 44
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - Oral glucose tolerance test (OGTT): normal

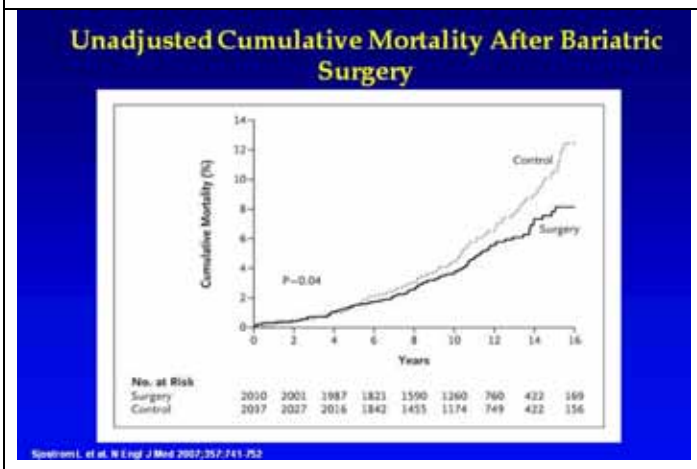


Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Lifestyle intervention
- D) Obesity medication
- E) Bypass surgery


Clinical and Biochemical Characteristics of the Morbidly Obese PCOS Patients Submitted to Bariatric Surgery, Before and After Weight Loss
FOLLOW-UP STUDY
Escobar-Morreale, H. F. et al. JCEM 2005


Weight Changes among Subjects in the Swedish Obesity Study over a 10-Year Period
Control
Banding
Vertical banded gastroplasty
Gastric bypass
Weight Change (%)
Years of Follow-up
No. of Subjects
Sjostrom, L. et al. N Engl J Med 2004


Unadjusted Cumulative Mortality After Bariatric Surgery
Cumulative Mortality (%)
Control
Surgery
P=0.04
Years
No. at Risk
Surgery 2010 2001 1987 1821 1590 1260 760 422 169
Control 2037 2027 2016 1842 1455 1174 749 422 156

Bariatric Surgery Pearls

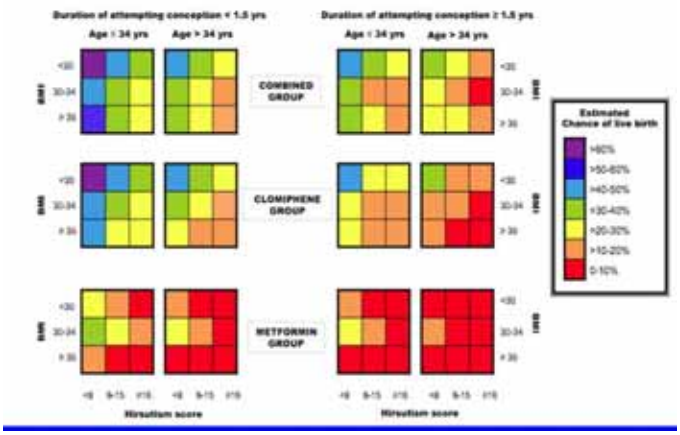
- In experienced hands, mortality is well under 1%.
- The best type of procedure for those seeking pregnancy is unknown.
  - Lap band vs. bypass
- Avoid pregnancy during 12-month period of rapid weight loss
- ? Extra folic acid/nutrient supplementation due to malabsorption

Patient #2

- 24-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 7, total testosterone 45 ng/dL (normal < 60 ng/dL)
  - BMI 30
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal

Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Lifestyle intervention
- D) Obesity medication
- E) Bypass surgery

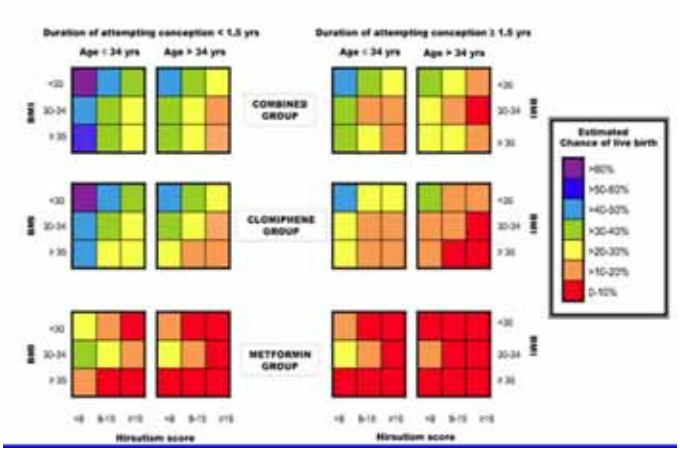


Patient #3

- 28-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 12, total testosterone 75 ng/dL (nl < 60 ng/dL)
  - BMI 33
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal

Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Lifestyle intervention
- D) Obesity medication
- E) Bypass surgery

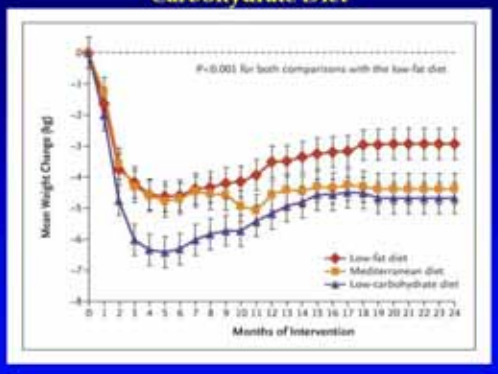


Lifestyle Modifications in PCOS

- Obesity adversely affects reproduction and is associated with anovulation, pregnancy loss, and late-pregnancy complications.
- Obesity within PCOS is associated with failure of infertility treatment.
- Weight loss prior to infertility treatment improves ovulation rates in women with PCOS, but there are limited data that it improves fecundity or lowers pregnancy complications.

Hum Reprod. 2008 Mar;23(3):462-77 and Fertil Steril. 2008 Mar;89(3):505-22

Best Short-Term and Long-Term Weight Loss with a Low Carbohydrate Diet



Shai I et al. N Engl J Med 2008;359:229-241

Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome[1-3]

Lisa J Moran, Manny Noakes, Peter M Clifton, Gary A Wittert, Gemma Williams, and Robert J Norman

Meal replacements; 2x per day

In 8 Weeks, Mean Weight Loss of 6 kg

Pearls on Office Lifestyle Recommendations

- Calorie restriction is the key.
  - ◆Limit portion size
- Dietary composition is irrelevant.
- Although exercise is facilitative, in and of itself it is unlikely to lead to significant weight loss.
- Exercise must be tailored to the weight and physical fitness of the individual.

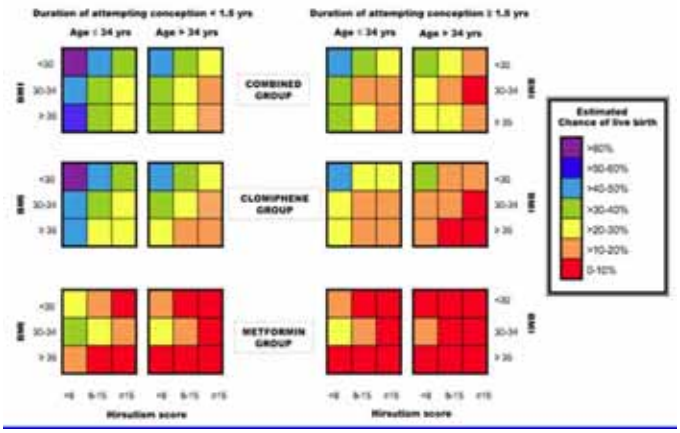
Avoid Conception During Weight Loss

Patient #4

- 32-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 15, total testosterone 72 ng/dL (nl < 60 ng/dL)
  - BMI 28
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal

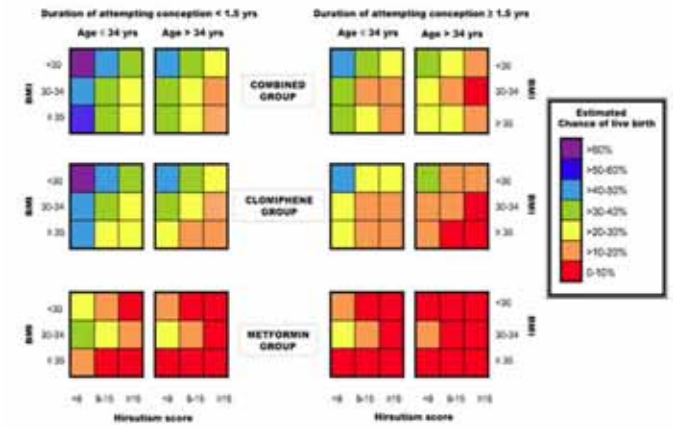
Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Lifestyle intervention
- D) Obesity medication
- E) Bypass surgery



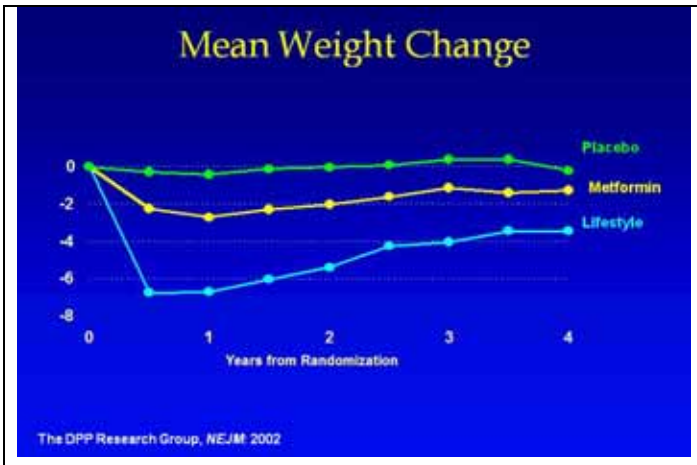
Patient #5

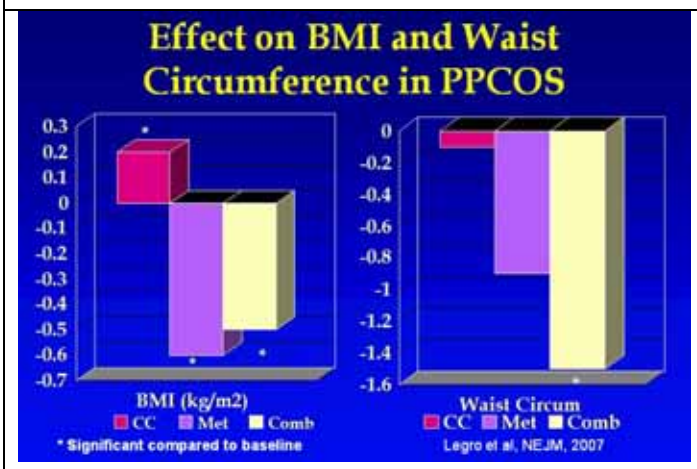
- 29-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 13, total testosterone 85 ng/dL (nl < 60 ng/dL)
  - BMI 35
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: 2hour 165 mg/dL (impaired glucose tolerance)

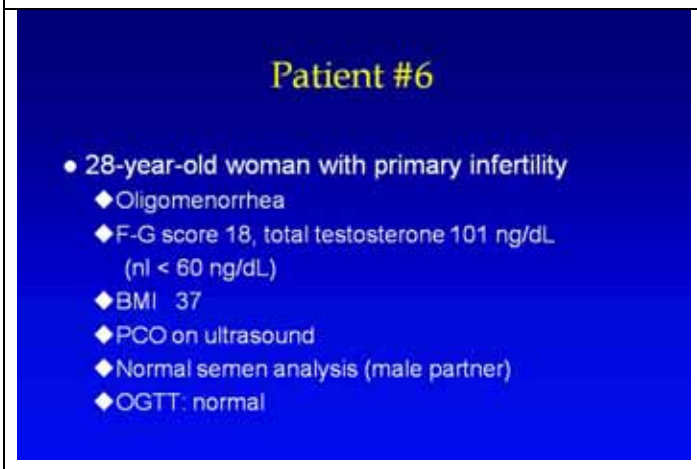


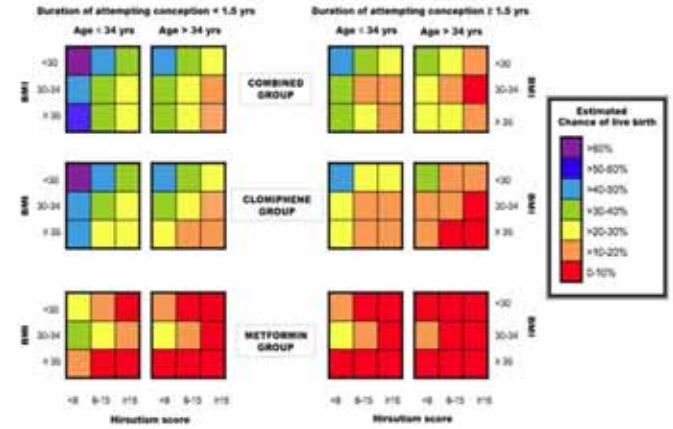
Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Lifestyle intervention
- D) Obesity medication
- E) Bypass surgery

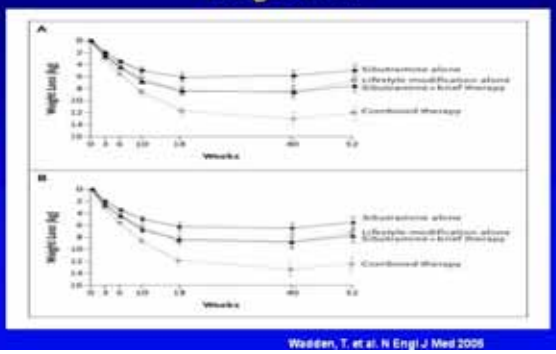

Mean Weight Change
Placebo
Metformin
Lifestyle
0
-2
-4
-6
-8
0
1
2
3
4
Years from Randomization
The DPP Research Group, NEJM 2002


Effect on BMI and Waist Circumference in PPCOS
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
BMI (kg/m2)
CC Met Comb
* Significant compared to baseline
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
Waist Circum
CC Met Comb
Legro et al, NEJM, 2007


Patient #6
• 28-year-old woman with primary infertility
◆Oligomenorrhea
◆F-G score 18, total testosterone 101 ng/dL (nl < 60 ng/dL)
◆BMI 37
◆PCO on ultrasound
◆Normal semen analysis (male partner)
◆OGTT: normal



Combination Therapy (Lifestyle/Medication/Behavior) Achieves Best Weight Loss



Wadden, T. et al. N Engl J Med 2006

Anti-Obesity Medications

Sibutramine

- Verify normal blood pressure (B/P)
- Start low (5 mg/day)
- Monitor B/P, pulse, symptoms 2-4 weeks later
- Increase as tolerated to 15 mg/day

Orlistat

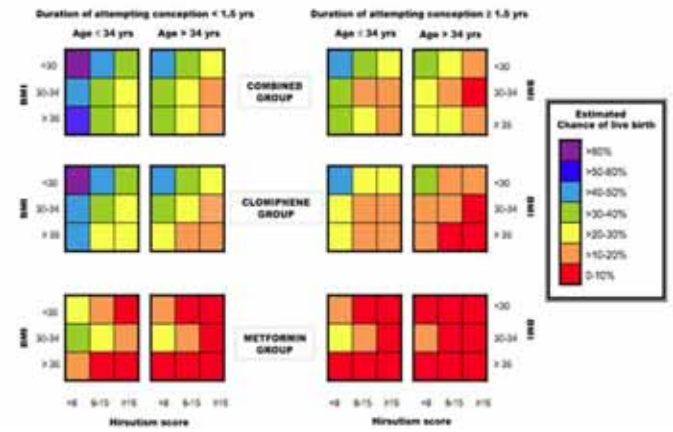
- Start at home, beware of steatorrhea
- ? Interaction with metformin
- Skip for breakfast (usually low fat)
- Low-fat threshold varies

PCOS Case Presentation

	Yes	No
Old		
Obese		
Hirsute/ Hyperandrogenic		

Patient #7

- 28-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 7, total testosterone 52 ng/dL (nl < 60 ng/dL)
  - BMI 23
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal



Recommendation

- A) Start metformin
- B) Start clomiphene
- C) Start letrozole
- D) Lifestyle intervention

Live Birth Results of Double-Blinded RCTs of Insulin Sensitization and Clomiphene (CC) (N = 100)

Study	N	Treatments	Results
Palumba et al, 2006, JCEM	100	Metformin vs. CC	Metformin superior to CC
Moll et al, 2006, BMJ	225	CC vs. Metformin/CC	No benefit of metformin/CC
Legro et al, 2007, NEJM	626*	CC vs. metformin vs. CC/metformin	No benefit of metformin/CC AND clomiphene superior to metformin
Mohd Zain et al, Fertil Steril 2008	125	CC vs. metformin vs. CC/metformin	No benefit of metformin/CC AND clomiphene superior to metformin

*Adequately powered and designed to detect differences in live birth rates

PCOS Case Presentation

	Yes	No
Old		
Obese		
Hirsute/ Hyperandrogenic		

Patient #8

- 38-year-old woman with primary infertility
  - Married with unprotected intercourse, attempting pregnancy for 2 years
  - Oligomenorrhea
  - F-G score 17, total testosterone 92 ng/dL (nl < 60 ng/dL)
  - BMI 43
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal

Recommendation

- A) Start metformin and clomiphene
- B) Gonadotropins
- C) IVF
- D) Obesity medication
- E) Bypass surgery

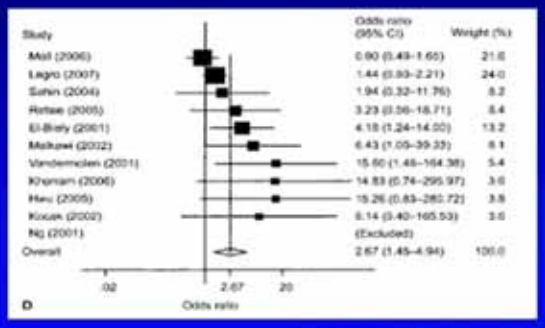
Live Birth by BMI Group

	BMI < 30 N = 179		
	CC n = 57	MET n = 57	COMB n = 65
Live Birth	21/57 (36.8%)	5/57 (8.8%)	24/65 (36.9%)

	BMI ≥ 35 N = 311		
	CC n = 110	MET n = 105	COMB n = 96
Live Birth	18/110 (16.4%)	4/105 (3.8%)	22/96 (22.9%)

Legro et al, NEJM, Supplemental online table, 2007

Meta-Analysis of Metformin/CC and Pregnancy in PCOS



Creanga et al, Obstet Gynecol, 2008

PCOS Case Presentation

	Yes	No
Old		
Obese		
Hirsute/ Hyperandrogenic		

Patient #9

- 28-year-old woman with primary infertility
  - Oligomenorrhea
  - F-G score 17, total testosterone 98 ng/dL (nl < 60 ng/dL)
  - BMI 26
  - PCO on ultrasound
  - Normal semen analysis (male partner)
  - OGTT: normal
  - 3 cycles of clomiphene: dose up to 150 mg/day, no ovulation

Recommendation

- A) Start metformin and clomiphene
- B) Give longer dose of 150 mg CC
- C) Add dexamethasone
- D) Add oral contraceptive pills (OCP)
- D) Use letrozole
- E) Lifestyle therapy

Live Birth by BMI Group

BMI <30 N=179	CC n = 57	MET n = 57	COMB n = 65
Live Birth	21/57 (36.8%)	5/57 (8.8%)	24/65 (36.9%)

BMI ≥ 35 N =311	CC n = 110	MET n = 105	COMB n = 96
Live Birth	18/110 (16.4%)	4/105 (3.8%)	22/96 (22.9%)

Legro et al, NEJM, Supplemental online table, 2007

Extended Cycle CC

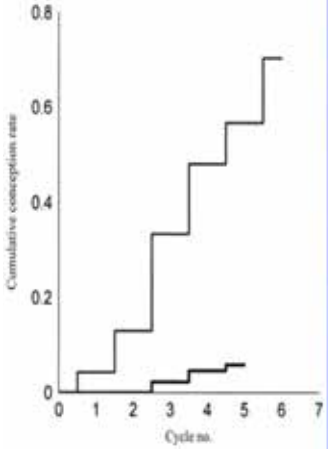
- N = 30, CC-resistant at 150 mg/day
- Fourteen patients (47%) ovulated during 31 of their 48 cycles (65%). Five women (17%) conceived a total of seven singleton pregnancies.
- Side effects were similar to those reported during standard CC treatment.

Fluker et al, Fertil Steril, 1996

RCT of Dexamethasone in CC-Resistant Women with PCOS

- 230 women failed to ovulate on 250 mg CC, normal DHEAS levels
- 119 randomized to 2 mg dexamethasone (DEX)/CC vs. 111 placebo/CC
- DEX 2 mg day 5-14, CC 200 mg day 5-9
- Follicular monitoring with human chorionic gonadotropin (hCG) 10,000 U to trigger ovulation

Parsanezhad ME, Fertil Steril, 2002



Improved Cumulative Conception Rate on Dexamethasone/CC vs Placebo/CC

Parsanezhad ME, Fertil Steril, 2002

Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study

Aboubakr Elnashar[1], Emad Abdelmageed, Mahmod Fayed and Magdy Sharaf

Department of Obstetrics and Gynecology, Benha University Hospital, Benha, Egypt

N = 80 women, CC 100 mg/DEX 2 mg day 3-12,

Higher pregnancy rate in DEX group 40% vs. 5%

(P < 0.05)

OCP Pretreatment in CC-Resistant Anovulation

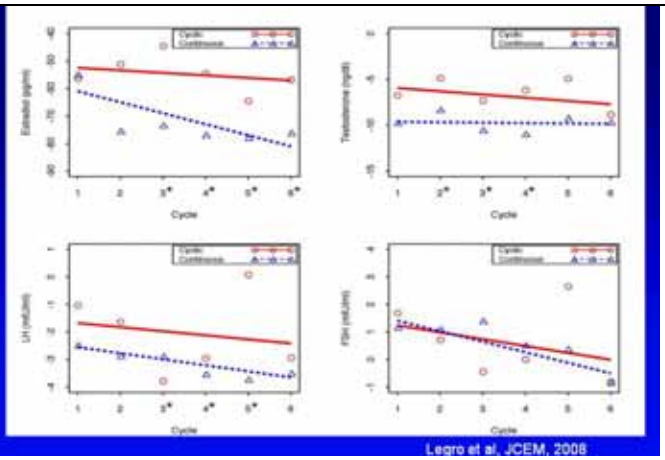
- 48 anovulatory women with PCOS at 150 mg/day of clomiphene
- Randomized to OCP (desogen) for 42 – 50 days or no treatment for 48 – 56 days.

Branigan et al, AJOG, 2003

Effects of Pretreatment with OCP on Outcomes

	OCP	No pre-treatment	P Value
Ovulation	17/24 (71%)	2/24 (8%)	.001
Ovulatory cycles	40/62 (64.5%)	3/27 (11%)	.001
Pregnancy	13/24 (54%)	1/24 (4%)	.001

Branigan et al, AJOG, 2003



Legro et al, JCEM, 2008

Rationale for Letrozole in Ovulation Induction

- Interferes with inappropriate estrogen feedback at the hypothalamus similar to clomiphene
- Shorter half-life than clomiphene
  - ◆Less potential teratogenicity
- No adverse endometrial effects
  - ◆Higher implantation rates
- Lower multiple ovulation
  - ◆Fewer multiple pregnancies

RCTs of Letrozole and Clomiphene for PCOS

Author	Type	Total Subjects	Duration	Conception Rate (Letrozole Group)	Conception Rate (CC group)
Bayar et al., 2006	openlabel,	N = 46 (anovulatory infertility)	Multiple, (mean = 2.6 cycles)	9% (5/52)	12% (9/67)
Atay et al., 2006	open label	N = 106 (PCOS)	Not stated	21.6% (11/51)	9% (5/55)
Badawy et al., 2007	open label, .	N = 220 (PCOS)	Multiple (mean = 2.3 cycles)	37.6% (82/208)	43% (94/220)
Begum et al., 2008	open label	N = 64 (PCOS)	Up to 6 cycles	40.3% (13/32)	19% (6/32)

PUBLIC COMMUNICATION
Health Canada Endorsed Important Safety Information on
Femara®(letrozole)

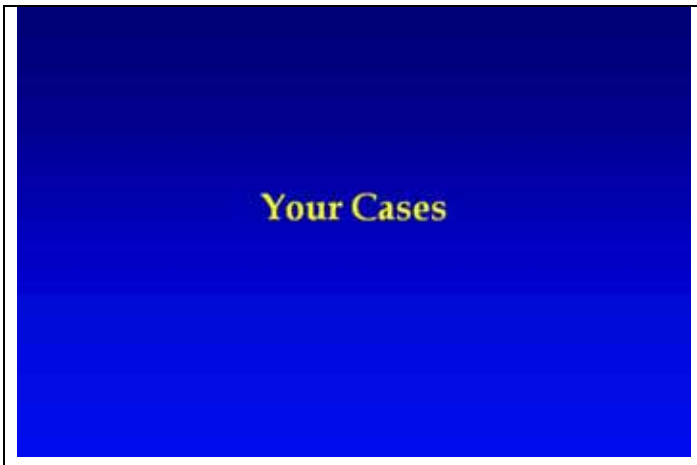
NOVARTIS

November 24, 2005

Subject: Femara® (letrozole) should not be used in women who may become pregnant

of becoming pregnant. Novartis believes it is our responsibility to remind physicians treating infertility and their patients that:

- Femara® is authorized for use in post-menopausal women with breast cancer only.
- The use of Femara® for the purpose of inducing ovulation and increasing the chance of pregnancy is **not** an authorized use of this drug.


Your Cases

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NOTES

GONADOTROPIN REGIMENS FOR ART

Daniel A. Dumesic, M.D.
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Department of Obstetrics and Gynecology
University of Wisconsin, Madison
Affiliated Scientist, National Primate Research Center
University of Wisconsin, Madison

LEARNING OBJECTIVES

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

1. State a potential risk for using a GnRH analog trigger to induce oocyte maturation in IVF patients at risk for ovarian hyperstimulation syndrome (OHSS).
2. Formulate a medical strategy to reduce the risk of OHSS in polycystic ovary syndrome (PCOS) women with exaggerated ovarian responsiveness to gonadotropin therapy for IVF.
3. Describe one intrafollicular abnormality in terminally differentiated PCOS follicles that could impair oocyte developmental competence.

GONADOTROPIN REGIMENS FOR ART

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University of Wisconsin, Madison

Learning Objectives

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

- State a potential risk of using a gonadotropin-releasing hormone (GnRH) analog trigger to induce oocyte maturation in IVF patients at risk for ovarian hyperstimulation syndrome (OHSS).
- Formulate a medical strategy to reduce the risk of OHSS in polycystic ovary syndrom (PCOS) women with exaggerated ovarian responsiveness to gonadotropin therapy for IVF.
- Describe one intrafollicular abnormality in terminally differentiated PCOS follicles that could impair oocyte developmental competence.

Disclosure

Grant Support:
Schering-Plough Pharmaceuticals
Ferring Pharmaceuticals

IVF and PCOS

- With an increased risk of high-order multiple birth from gonadotropin therapy, IVF might be a reasonable option for PCOS women who fail clomiphene therapy because such a risk can be reduced by transferring one or two embryos.
- The major risk ovarian stimulation for IVF in PCOS women is ovarian hyperstimulation syndrome (OHSS).

Eijkemans et al. 2005

OHSS Prevention

- Oral contraceptives/GnRH analog dual suppression
- Coasting before hCG administration
- Reduced dose of administered human chorionic gonadotropin (hCG)
- Embryo cryopreservation
- Cabergoline
- GnRH antagonist/gonadotropin therapy with GnRH analog trigger for final oocyte maturation
- Metformin

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008; Damewood M et al. 1989; Engmann L et al. 2008; Alvares C et al. 2007; Damario M et al. 1997; Shapiro B et al. 2005

Dopamine Agonists for OHSS Prevention

- Vascular endothelial growth factor (VEGF) induces angiogenesis and vascular hyperpermeability by interacting with its VEGF receptor-2 (VEGFR-2).
- In animal studies, dopamine agonist blocks VEGF-mediated vascular permeability without altering angiogenesis.
- Carbergoline has high affinity for the dopamine receptor 2 and also causes VEGFR-2 dephosphorylation.
- Prospective, randomized, double-blind study of oocyte donors showed a significant decrease in moderate OHSS from 44% to 20%.

Alvarez C et al. 2007
Gomez R et al. 2006

Dopamine Agonists for OHSS Prevention

- Enrolled oocyte donors undergoing ovarian stimulation were at increased risk for OHSS, defined as:
  - Development of ≥ 20 follicles >12 mm in size, and
  - Retrieval of > 20 oocytes.
- On day of hCG administration, patients were randomized to carbergoline (0.5 mg orally daily for 8 days) or placebo.
- Serial blood sampling for hematologic, renal and hepatic function, as well as transvaginal ultrasound (TVUS) monitoring, was performed every 2 days from day of hCG administration for 8 days.

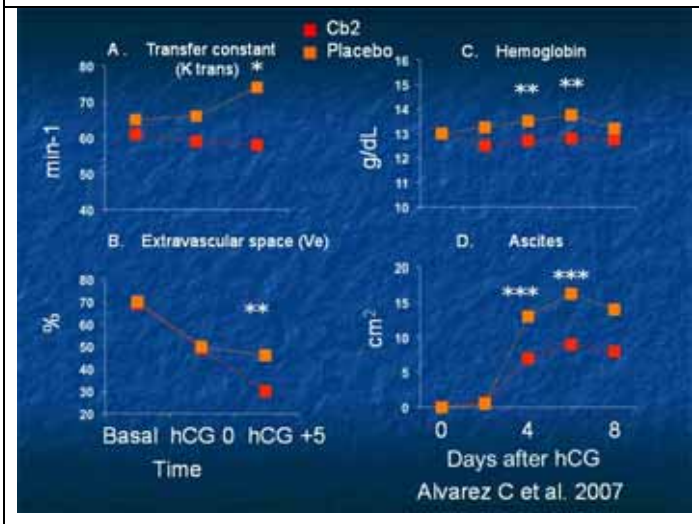
Alvarez C et al. 2007

Signs and Symptoms of OHSS in 82 Oocyte Donors Undergoing IVF

	Cb2	Placebo	*P*
Ascites > 9 cm^2 (%)	25.7	59.4	0.005
Moderate OHSS (%)	20.0	43.8	0.04
Severe OHSS (%)	11.4	18.8	NS

Cb2 = carbergoline

Alvarez C et al. 2007



Alvarez C et al. 2007

Retrospective Analysis of IVF Outcomes By Cabergoline Use

	Cb2 N=35	Placebo N=35	*P*
Implantation rate (%)	38.6	41.4	NS
Clinical pregnancy rate (%)	48.6	51.4	NS
Live birth per cycle	40.0	40.0	NS

Alvarez C et al. 2007

GnRH Agonist Trigger in OHSS Prevention

- An endogenous LH surge has a shorter half-life than hCG but subsequent pituitary suppression causes early luteolysis and reduces luteal steroidogenesis .
- Final oocyte maturation can occur using a GnRH agonist trigger but impaired embryo implantation may represent inadequate luteal phase steroid support.

Chan C et al. 2003; Fauser B et al. 2002; Humaidan P et al. 2005; Engmann L et al. 2008; Kolibianakis E. et al. 2005

GnRH Agonist Trigger in OHSS Prevention

- Enrolled patients had PCOS, polycystic ovarian morphology or hyperresponsiveness to previous ovarian stimulation for IVF.
- Patients were randomized:
  - Oral contraceptives (OC)/GnRH analog-recombinant human follicle-stimulating hormone (rhFSH) therapy - hCG adminstration (3300-10,000 IU), or
  - OC/GnRH antagonist - rhFSH therapy - 1 mg leuprolide.
- Patients received:
  - Intramuscular (IM) progesterone (50 mg), and
  - Study patients also received 0.1 mg transdermal estradiol (E_2) patches (3-4, every other day).
- Serum progesterone (P_4)/E_2 levels maintained > 25 ng/mL/200 pg/mL.
- Hormone supplementation continued for 10 weeks.

Engmann L et al. 2008

GnRH Agonist Trigger in OHSS Prevention

	Study group N = 30	Control N = 29	*P*
Number of oocytes	20.2±9.9	18.8±10.4	NS
Proportion of MII oocytes	81.0±16.3	83.8±13.2	NS
Fertilization (%)	71.6±14.1	74.9±17.3	NS
Serum E_2 pg/mL (at ET)	485±219	1320±695	<0.01
Serum P_4 ng/mL (at ET)	25±14	117±61	<0.01
Serum E_2 pg/mL (midluteal)	283±216	663±556	0.01
Serum P_4 ng/mL (midluteal)	28±8	46±50	NS

Engmann L et al. 2008

GnRH Agonist Trigger in OHSS Prevention

	Study group N = 30	Control N = 29	*P*
Mid-luteal ovarian volume (cm^3)	37 ± 22	129 ± 77	<0.01
OHSS (total)	0	31.3	<0.01
OHSS (moderate/severe)	0	15.6	<0.03
Implantation rate (%)	36	31	0.7
Clinical pregnancy rate (%)	56.7	51.7	0.45
Ongoing pregnancy rate (%)	53.3	48.3	0.45

Engmann L et al. 2008

Metformin-Gonadotropin Coadministration for IVF in Women with PCOS

- Meta-analysis of 5 randomized clinical trials (RCTs) shows that metformin-gonadotropin therapy:
  - Does not affect duration of FSH therapy, maximum serum E_2 levels, numbers of oocytes collected, or pregnancy/live-birth rates.
  - Reduces total amounts of FSH administered (OR = -290 [-450 to -131]) and lowers the risk of OHSS (OR=0.21 [0.11 to 0.41]).
- Metformin-gonadotropin therapy may be useful to reduce OHSS risk in IVF patients with PCOS.

Costello M et al. 2006; Tang T et al. 2006;
Kjotrod S et al. 2004; Moll E et al. 2007; Palomba S et al. 2009

Outcomes in PCOS Patients Randomized to Metformin or Placebo during IVF

Metformin increases clinical pregnancy and live birth rates and lowers the risk of severe OHSS.

Outcome	Metformin	Placebo	P
Ongoing pregnancy per transfer (%)	44.4	19.1	0.02
Live birth per transfer (%)	37.8	14.3	0.03
Severe OHSS (%)	3.8	20.4	0.02
Side effects (%)	45.1	8.2	0.001

Tang T et al. 2006

Metformin Treatment Before IVF in PCOS Women: IVF Stimulation Data

Metformin does not affect ovarian responsiveness to FSH nor improve pregnancy outcome.

		BMI < 28 kg/m²			BMI ≥ 28 kg/m²		
Treatment Group		Mean	CI	P	Mean	CI	P
Estradiol on hCG day (nmol/l)	Placebo	5.7	2.9-8.4	0.3	9.1	6.3-11.8	0.4
	Metformin	5.8	4.1-7.5		7.5	5.2-9.6	
FSH stimulation (days)	Placebo	14.2	11.5-16.8	0.2	14.6	12.4-16.8	0.3
	Metformin	15.8	13.7-17.9		13.4	11.7-14.8	
Total FSH dose (IU)	Placebo	1483	1049-1917	0.5	2463	1643-3283	0.2
	Metformin	1671	1253-2089		1981	1584-2279	

Kjotrod S et al. 2004

Metformin Treatment Before IVF in PCOS Women: Pregnancy Rates

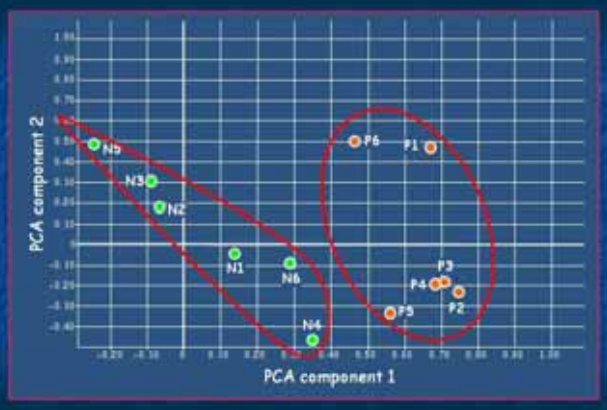
		BMI < 28 kg/m²			BMI ≥ 28 kg/m²		
Treatment Group		Mean	CI	P	Mean	CI	P
Ova (no.)	Placebo	9.8	6.8-12.7	0.3	15.2	11.9-18.5	0.9
	Metformin	13.1	8.9-17.3		14.6	10.4-18.9	
Fertilization rate	Placebo	0.54	0.36-0.72	0.4	0.55	0.45-0.66	0.8
	Metformin	0.50	0.40-0.61		0.54	0.42-0.67	
Pregnancy rate	Placebo	0.23	0.15-0.31	0.04	0.63	0.55-0.71	0.6
	Metformin	0.71	0.63-0.79		0.47	0.39-0.55	
Clinical pregnancy rate	Placebo	0.23	0.15-0.31	0.12	0.58	0.50-0.66	0.5
	Metformin	0.57	0.49-0.65		0.41	0.33-0.49	
Live birth rate	Placebo	0.15	0.07-0.23	0.12	0.47	0.39-0.55	0.5
	Metformin	0.43	0.35-0.51		0.35	0.27-0.43	

Kjotrod et al. 2004

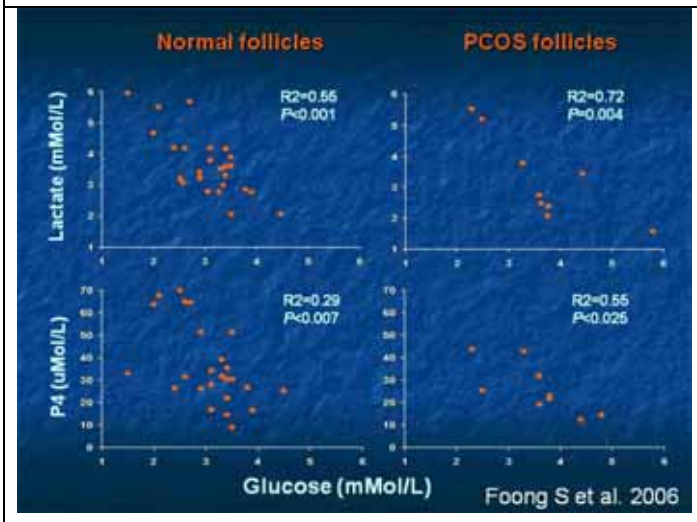
PCOS and IVF Pregnancy Outcome

- Impaired fertilization of PCOS oocytes occurs without gross chromosomal abnormalities or nuclear immaturity.
- After IVF with ICSI, increased miscarriage rate can occur in lean PCOS patients.
- Insulin resistance increases the risk for miscarriage after IVF, controlling for PCOS.
- High miscarriage rate in obese PCOS patients follows transfer of normal-appearing embryos into a surrogate uterus.

Heijnen E et al. 2006; Cano F et al. 1997; Tian L et al. 2007 Ludwig M et al. 1999; Sengoku K et al. 1997



Wood J et al. 2007



Foong S et al. 2006

Metabolic Abnormalities in Human Follicular Fluid

- Intrafollicular insulin levels are positively correlated with body mass index (BMI) and fasting serum insulin levels on the day of oocyte retrieval.
- Follicle fluid insulin levels are elevated in women with impaired glucose tolerance.
- Total free fatty acid levels in follicular fluid vary inversely with follicle development and oocyte quality.

Phy J et al. 2004; Dumesic D et al. 2007; Jungheim E et al. 2009

Effect of Preconceptional Metformin on Miscarriage Risk (Meta-Analysis of 17 RCTs)

- PCOS was defined by both the National Institutes of Health (NIH) and Rotterdam criteria.
- No significant effect of metformin was detected on miscarriage rate for:
  - The entire PCOS population (OR 0.89 [95% CI 0.65-1.21], P = 0.5), or
  - PCOS patients undergoing IVF (OR 0.96 [95% CI 0.40-2.34], P = 0.9).
- "Metformin has no effect on the abortion risk in PCOS patients when administered before pregnancy."

Palomba S et al. in press

Intrafollicular Hormone Levels in Normal Women and PCOS Patients Undergoing IVF

	Normal (N=30)	PCOS (N=11)	P
bioLH (ng/mg)	0.5±0.3	0.4±0.2	0.7
17OHP$_4$ (ng/mg)	11.4±4.0	12.2±4.1	0.6
DHEA (ng/mg)	0.03±0.02	0.07±0.1	0.06
A$_4$ (ng/mg)	0.2±0.07	0.9±1.7	0.006
T (pg/mg)	26.8±12.3	65.1±65.4	0.001
DHT (pg/mg)	21.9±17.7	30.1±24.1	0.2
E$_2$ (ng/mg)	3.5±2.0	5.0±2.6	0.1
iFSH (ng/mg)	4.0±2.0	2.7±1.0	0.004

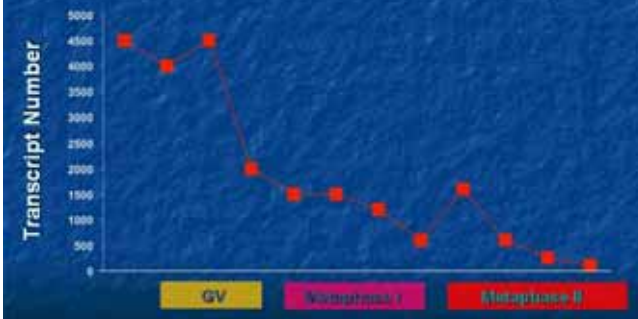
Foong S et al. 2006

Steroid Effects on the Human Germinal Vesicle (GV) Oocyte

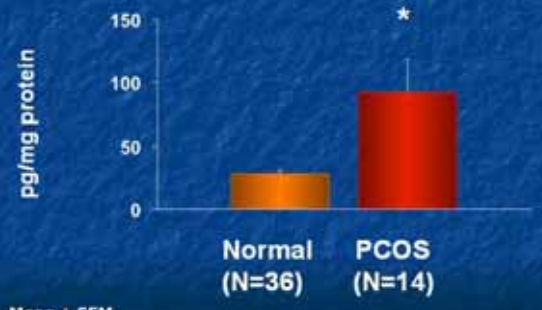
- E_2 supports a nongenomic, calcium-mediated mechanism of cytoplasmic maturation in the immature oocyte.
- The E_2/androgen ratio to which oocytes are exposed during follicle growth affects the quality of mature human oocytes obtained through IVF.
- Pregnancy outcome by IVF is related more to the E_2/androgen ratio than to the absolute amount of E_2 in the follicle.
- Oocytes obtained from hyperandrogenic PCOS follicles and matured *in vitro* have impaired embryonic development.

Revelli A et al. 1998; Tesarik J et al. 1997
Barnes F et al. 1996; Yding Andersen C 1993

Transcription Repression of Growth Differentiation Factor (GDF)-9 mRNA Expression in 12 Human Oocytes



Intrafollicular anti-müllerian hormone (AMH) Levels in Normal Women and PCOS Patients Undergoing GnRH analog/rhFSH therapy for IVF



Mean ± SEM
* P <5 X 10^{-4} versus normal

Dumesic D et al. 2007A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NOTES

NOTES

LONG-TERM CARDIOVASCULAR ISSUES AND THEIR PREVENTION

Kathleen Hoeger, M.D.
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LEARNING OBJECTIVES

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

1. List and evaluate the cardiometabolic risks present in polycystic ovary syndrome (PCOS).
2. Discuss metabolic syndrome, its evaluation and the relationship to PCOS.
3. Review the options for prevention of cardiovascular disease in this population.

Long-term Cardiovascular Issues and Their Prevention

Kathleen Hoeger, M.D.
Associate Professor of Obstetrics and Gynecology
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Disclosures

- The author has no commercial or financial relationships to disclose.
- The lecture may include a discussion of the use of agents for indications that are not FDA approved.

Metabolic Consequences Cardiovascular risk

- Since the mid 1980s, women with PCOS have been observed to have increased risk factors for cardiovascular disease when compared with women of similar age.
- Dyslipidemia
- Hypertension

PCOS and Cardiovascular Disease

- Dahlgren et al. published long-term follow-up of 30 women who had received wedge resection.
- They showed an increased incidence of hypertension in this cohort, as well as increased incidence of diabetes.

Dahlgren, et al. Acta Obstet Gynecol Scand, 1992

Metabolic Consequences: Lipids

- Several case-control studies suggest increased total cholesterol and low-density lipoprotein (LDL) with low high-density lipoprotein (HDL) in PCOS compared to controls.
- This finding is not consistent across all studies, and despite the elevation in younger PCOS women compared with controls, the levels often remain in an acceptable range.

Cardiovascular Risk

- 1992, Talbott et al. inititated a large-scale case-control study of coronary heart disease (CHD) risk factors in women with PCOS.
- Mean age of cases was 35.5 years
- After adjusting for body mass index (BMI), hormone use and insulin, PCOS women had significantly higher LDL cholesterol and total cholesterol at a younger age.

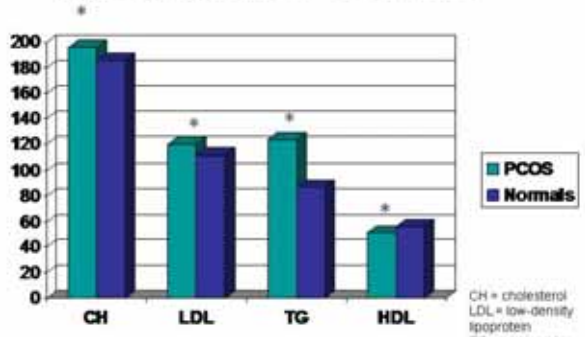
Talbott et al, J Clin Epidemiology 1998

Cardiovascular Risk

- In the follow-up reported to year 1999, they noted a 23% incidence of hypertension, compared with 6.9% in controls.
- Additionally, there was a 32% increase in plasminogen activator inhibitor- 1 (PAI-1) adjusted for age and BMI

Talbott et al, Arterioscler Thromb Vasc Biol , 2000

Lipid Profiles from Cases and Age-Matched Controls



Talbott et al J Clin Epidemiol 1998

Lipid Profiles and PCOS

- Looking at the Finnish Birth Cohort from 1966 to age 31
- 1005 controls with no menstrual irregularity or hirsutism vs. 75 cases with both.
- Women with both hirsutism and oligo-/amenorrhea had increased TG, decreased HDL.
- They also had increased BMI, C-reactive protein (CRP) and systolic blood pressure (SBP)/diastolic blood pressure (DBP) compared with controls.
- Lipid changes persisted when controlled for BMI.

Taponen, et al. JCEM 2004

Inflammatory Markers and PCOS

- Investigators studied 17 women with PCOS with a mean BMI of 31 compared to age and weight-matched controls
- PCOS women had increased levels of CRP
- Correlated directly with BMI and inversely with insulin sensitivity

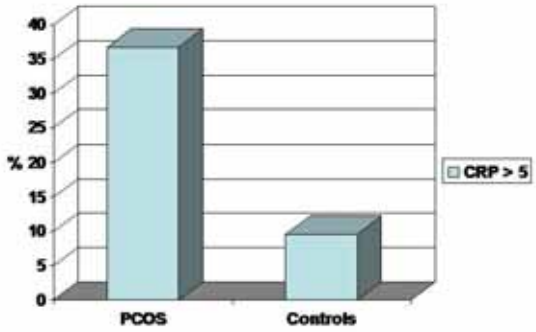
Kelly CC, et al, JCEM, 2001

CRP and PCOS

- Boulman et al. studied 116 women with PCOS and 94 BMI-matched controls
- PCOS was defined by menstrual irregularity and hyperandrogenism
- Means ages were 27.5 and 30.4 years
- 41.4% of cases and 42.5% of controls were overweight or obese.

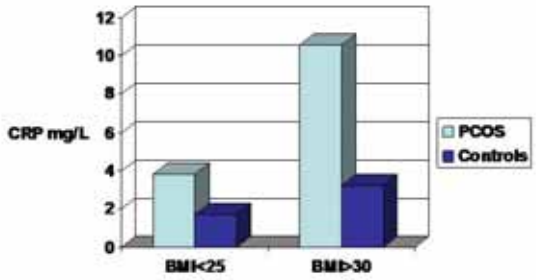
Boulman et al JCEM 2004

CRP and PCOS



Boulman et al JCEM 2004

CRP and PCOS



Boulman et al JCEM 2004

Cardiovascular Risk: Pre-clinical Disease

- Overall, despite the possible abnormal lipid and inflammatory marker profiles, it is unclear whether there are increased cardiovascular events in this population.
- There is demonstrated evidence, however, of pre-clinical disease.

Vascular Reactivity and PCOS

- There is a suggestion that women with PCOS may have early evidence of vascular changes associated with cardiovascular risk.
- Kelly et al. studied 19 women with PCOS and mean BMI of 33 compared with weight-matched controls by pulse-wave velocity (PWV).
- Measurement of pulse transit time between brachial and radial arteries.

Kelly CJ, et al. JCEM, 2002

Vascular Reactivity and PCOS

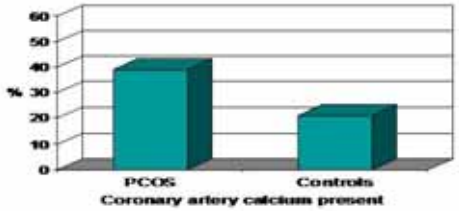
- Elevated PWV at the brachial artery was noted in the PCOS group, suggesting reduced vascular compliance.
- The control population, although weight matched, was significantly younger than the PCOS group.

Kelly CJ, et al. JCEM, 2002

Coronary Artery Calcification

- Coronary artery calcification may be an early sign of significant cardiovascular disease.
- This can be measured non-invasively by electron beam computed tomography (EBCT)
- Women 30 to 45 years old with PCOS were compared to BMI-matched controls by EBCT.

Coronary Artery Calcification (CAC)



Waist circumference, BMI, total cholesterol and LDL predicted presence of CAC.

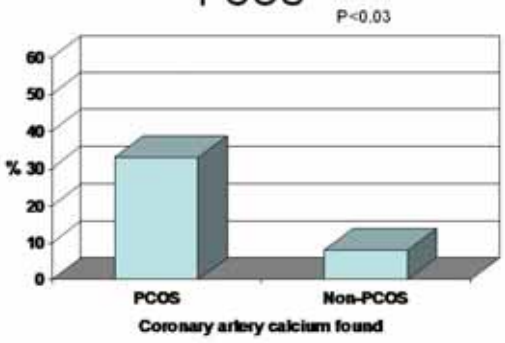
Christian et al, JCEM 2003

Coronary Artery Calcium and PCOS

- 24 women with mean age of 32 years and BMI of 36 with PCOS were compared with 24 control women with mean age of 36 years and BMI of 35.
- Coronary artery calcium measured by multislice CT.

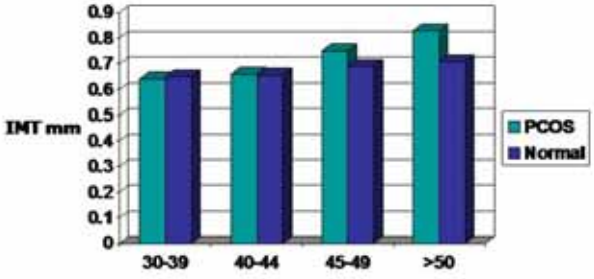
Shroff et al JCEM 2007

Coronary Artery Calcium and PCOS



Shroff et al JCEM 2007

Carotid Intima-Media Thickness (IMT) and Age



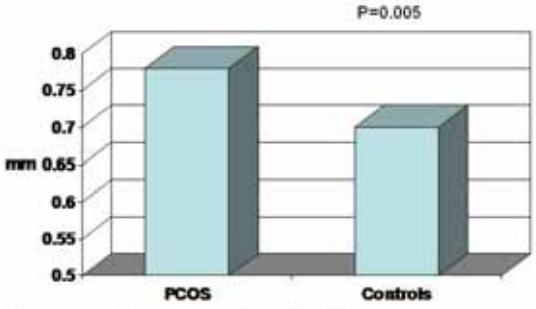
Talbott et al. Arterioscler Thromb Vasc Biol 2000

Carotid Intima-Media Thickness

- Talbott et al. studied 47 women with PCOS and 59 age-matched controls with a mean age of 49 years.
- Carotid artery intima-media thickness was measured.
- Mean BMI was 32 in PCOS women and 26 in controls.

Talbott et al. JCEM 2004

Carotid Intima-Media Thickness



In a multi-linear regression model, controlling for BMI, PCOS is still associated with increased IMT, although the effect is mediated.

Talbott et al JCEM 2004

PCOS and Cardiac Function

- 30 women with PCOS and 30 weight-matched controls with a mean age of 24 years were studied with echocardiography.
- Mean BMI was 28.7 in the PCOS women and 27.3 in the controls.
- PCOS women demonstrated greater fasting insulin levels, HOMA scores and lipid parameters.
- Diastolic blood pressure (BP) was 5 points (72 vs. 67) higher, but no difference was seen in SBP.

Orio et al JCEM, 2004

PCOS and Cardiac Function

	PCOS	Controls
Left ventricle (LV) systolic diameter	26.6*	23.0
Interventricular (IV) septum thickness (mm)	8.3*	6.7
LV posterior wall thickness	8.1*	6.6
LV mass index (g/m^2)	80.5*	56.1
Left atrium size	32*	27.4
Left ventricular ejection fraction (LVEF) (%)	64.4*	67.1

Orio et al JCEM, 2004 *$p<0.01$

PCOS and Cardiac Function

- In contrast, Kosmala et al. studied 52 women with PCOS and 54 women without PCOS or insulin resistance with BMIs of 38 and 36 kg/m^2, respectively.
- They did not find any differences between LV size, mass index, ejection fraction or IV septum thickness.
- Women were all non-smokers and were excluded for any pre-existing cardiovascular risk factor, such as hypertension or diabetes.

Kosmala et al JCEM 2008

PCOS and Cardiac Function

- They did find, however, that peak systolic strain rate, as well as peak early diastolic strain rate, was impaired in the PCOS women.
- There was no relationship with androgens in this study, but rather any differences were primarily associated with BMI and fasting insulin.

Kosmala et al JCEM 2008

Metabolic Syndrome

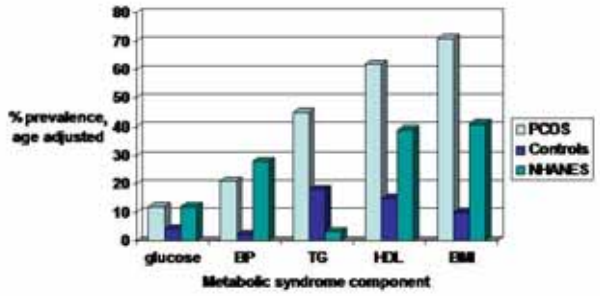
- Metabolic syndrome is characterized by central adiposity, low HDL cholesterol, increased triglycerides, hypertension and central adiposity.
- Several reports indicate that up to 43% of non-diabetic women with PCOS have metabolic syndrome, characterized by at least 3 abnormal findings.
- This prevalence is influenced by obesity.

Metabolic Syndrome (MS)

- Dokras et al. reported a retrospective review of women with PCOS compared with controls and a national database
- The age-adjusted prevalence of MS was 47.3% in PCOS, 4.3% in controls and 23.4% in the National Health and Nutrition Examination Survey (NHANES).

Dokras, et al Obstet Gynecol 2005

Metabolic Syndrome and PCOS



Dokras, et al Obstet Gynecol 2005

Metabolic Syndrome in Adolescent Women with PCOS

- 43 obese adolescent women with PCOS and 37 control adolescents who were age- and weight-matched were compared for metabolic markers.
- All were overweight, with a BMI percentile of 97.7 and 97.5, respectively.
- Mean age was 15.6 and 14.8 years, respectively.

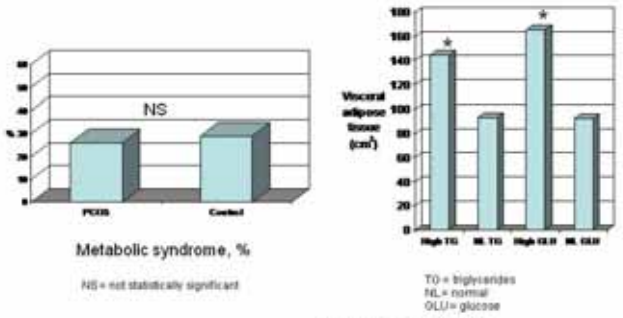
Rossi et al JCEM 2008

Metabolic Markers

	PCOS	Controls
Waist circumference (cm)	108	105
CRP (mg/L)	5.3	3.5
Total CH (mg/dL)	164	154
LDL	114	107
HDL	39	40
TG	90	90
PAI-1(ng/mL)	52.4*	37.1

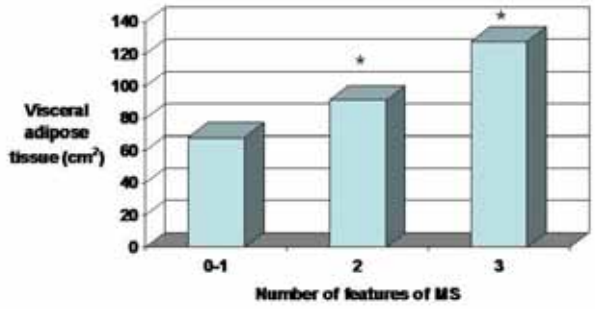
Rossi et al JCEM 2008

Metabolic Syndrome Prevalence



Rossi et al JCEM 2008

Metabolic Syndrome Features and Visceral Adipose Tissue



Rossi et al JCEM 2008

Metabolic Syndrome and PCOS

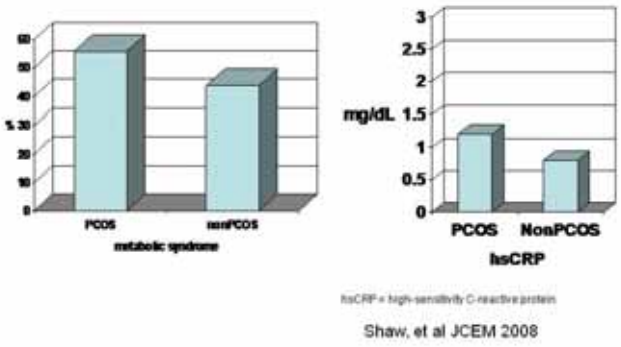
- Coviello et al. studied 49 PCOS adolescents, with a mean age of 17 years and BMI of 32, and compared them to 165 adolescents matched from the NHANES III database (mean age 15 years and BMI 23).
- Metabolic syndrome was detected in 37% of adolescents with PCOS and 5% in the NHANES set, using criteria of Cook, et al.

Coviello, et al JCEM 2006

PCOS and Cardiovascular Disease

- What do these findings of adverse cardiovascular risk parameters indicate for risk of cardiovascular **events**?
- Despite the increased prevalence of these risk factors and early preclinical disease, there is yet little data to support an increase in cardiovascular morbidity/mortality.
- This is in part because the population studies are conducted in a younger age group than that at which the disease typically presents.

Metabolic Syndrome and CRP



hsCRP = high-sensitivity C-reactive protein

Shaw, et al JCEM 2008

Treatment of Cardiovascular Risk Factors in PCOS

- Obesity is a major contributor to cardiovascular disease risk in PCOS.
- Lifestyle modification has been shown to be beneficial in the management of diabetes risk (Diabetes Prevention Program).
- Lifestyle modification with modest weight reduction may improve ovulation rates in PCOS.
- There are no prospective trials looking specifically at cardiovascular disease prevention in PCOS.

Diabetes Prevention Program (DPP) Model

- The progression rate to diabetes from impaired glucose tolerance (IGT) was significantly improved with both lifestyle intervention and metformin therapy in the DPP.
- Improvement in cardiovascular risk factors (primarily lipid profile) was also noted in the lifestyle treatment arm only if reversion to normal glucose tolerance was seen ($p<0.001$).

Goldberg et al, Diabetes Prevention Program Research group, Diabetes Care, 2009

Lifestyle Modification: Impact on Cardiovascular Risk Factors

- In addition to improvement in lipid profiles and decrease in conversion to diabetes, the lifestyle intervention program of the DPP was also demonstrated to reverse the presence of metabolic syndrome by 41%, particularly with respect to blood pressure and triglyceride levels.

Orchard et al Ann Int Med, 2005

Pre-clinical Disease

- In a study of 30 obese premenopausal women, an intensive weight management program resulted in a 16% reduction in overall weight.
- Improvement in all cardiovascular parameters was noted, including BP and lipids.
- In women with a sustained weight reduction at 5 months, a 13% reduction in carotid intima-media thickness was noted over baseline.

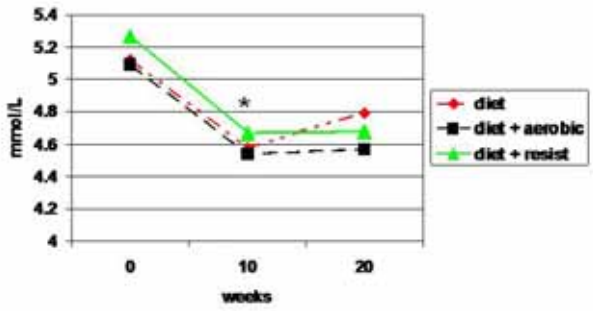
Mavri, et al Obesity Research, 2001

Lifestyle Interventions in PCOS

- Most trials measuring weight reduction in PCOS have not focused on cardiovascular risk parameters.
- Lipid profiles improve in a majority of (but not all) trials, which are generally small
- A recent randomized trial of diet, diet and aerobic exercise, and diet and resistance training in PCOS suggested dietary efforts were the main factor in improvement.

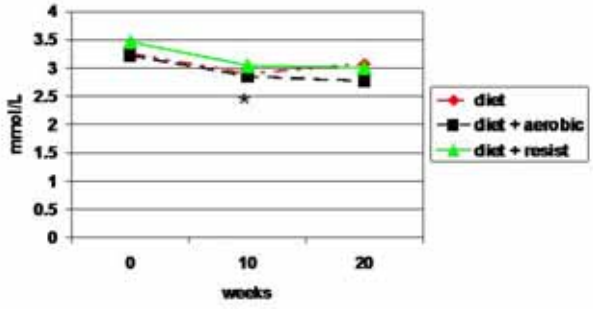
Thompson et al JCEM 2008

Change in Total Cholesterol



Thompson et al JCEM 2008

Change in LDL Cholesterol

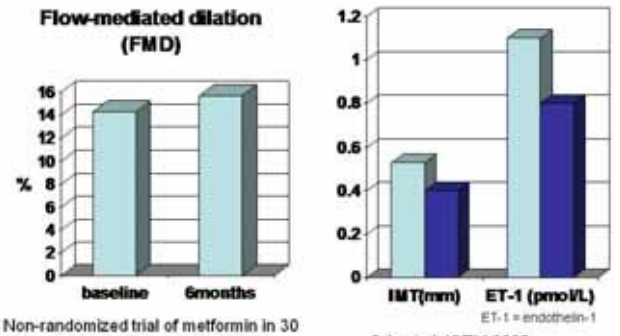


Thompson et al JCEM 2008

Insulin Sensitizers

- No large-scale trials of metformin have been published to address the cardiovascular risk factors in PCOS.
- A meta-analysis of 13 smaller studies suggested improvement in BP and LDL cholesterol, independent of weight loss (Lord et al BMJ, 2003).

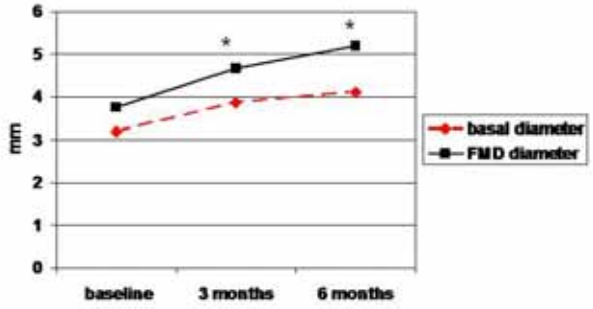
Insulin Sensitizers
Metformin and Endothelial Function



Non-randomized trial of metformin in 30 normal-weight women for 6 months

Orio et al JCEM 2005

Metformin in PCOS
Endothelial Function



13 normal-weight women treated with metformin for 6 months

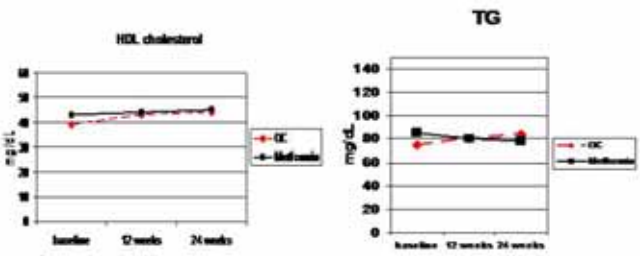
Romualdi et al Hum Reprod 2008

Oral Contraceptives versus Metformin

- Randomized trial of oral contraceptive (OC) with cyproterone acetate or metformin, 1700 mg for 24 weeks
- 34 overweight women with PCOS were studied.
- Lipid profiles were compared.

Luque-Ramirez et al JCEM 2007

OC versus Metformin



No significant negative impact of OC seen and no difference with metformin noted

Luque-Ramirez et al JCEM 2007

PCOS and Risk of Cardiovascular Disease

- In most studies, women with PCOS demonstrate higher incidences of:
  - Obesity
  - Diabetes
  - Abnormal lipid profiles
  - Hypertension
  - Inflammatory markers of cardiovascular disease
  - Pre-clinical disease

Conclusions

- Conclusive evidence of increased risk of cardiovascular events is not yet available; however, current evidence suggests this may be the case.
- Treatment of cardiovascular risk factors improves the overall cardiometabolic risk in PCOS.

Conclusions

- No long-term, large-scale trial of treatment for cardiovascular risk endpoint exists in PCOS.
- Data available from small trials in PCOS, as well as general population studies, indicate lifestyle modification is most effective for women with obesity.
- Oral contraceptives may not significantly worsen risk in normal-weight women.
- Unclear role of metformin.

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NOTES

MENOPAUSE: IT'S DIFFERENT IF YOU HAVE PCOS

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

1. Describe the general pattern of the menopausal transition in women with polycystic ovary syndrome (PCOS).
2. Examine the relationship between PCOS and cardiovascular disease risk.
3. Develop a strategy for clinical management of the menopausal woman with PCOS.

Nanette Santoro, MD
Professor and Director, REI
Albert Einstein College of Medicine

Menopause: It's Different If You Have PCOS

Learning Objectives

- At the conclusion of this presentation, participants should be able to:
  - Describe the general pattern of the menopausal transition in women with polycystic ovary syndrome (PCOS).
  - Examine the relationship between PCOS and cardiovascular disease risk.
  - Develop a strategy for clinical management of the menopausal woman with PCOS.

Disclosure

QuatRx: Consultant
Ferring: Grant support

PCOS: Definitions

- Oligo-/amenorrhea (<6 menses/yr)
- Hyperandrogenism
- Rule out other causes

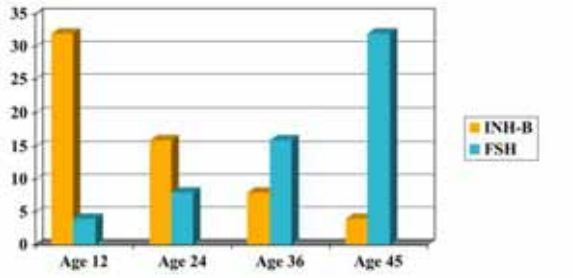
+/-

- Polycystic appearance of ovaries
- Definitions may not be useful as women approach menopause

Hypotheses for the Genesis of PCOS

- Increased complement of ovarian follicles compared with normally cycling women
  - Concomitant increase in inhibin
  - Increased müllerian inhibiting substance (MIS)
  - Can these lead to failure of follicle growth through inhibitory pathways?

The Inhibin Hypothesis



INH-B = inhibin B
FSH = follicle-stimulating hormone

Does Perimenopause Correct the FSH Deficit in PCOS?

If PCOS women have more follicles, and part of their anovulation is due to chronic FSH suppression, the inhibin hypothesis predicts a return of menstrual cyclicity when ovarian reserve reaches a low enough level.

Dahlgren et al., F/S1992; 57:505

- 33 wedge-resection (pathology-proven) PCOS
- Aged 40-59 years
- 'Considerable spontaneous restitution of cycle length over time'
- More hysterectomies than population controls
- Later menopause than population controls
- Role of wedge resection?

Elting et al., Human Reproduction 2000; 15:24

- 205 PCOS, not on oral contraceptive pill (OCPs), age >30 years
- Menses less frequent than every 6 weeks
- History of diagnosis of PCOS
- Questionnaires re: menstrual cycle length
  - Linear trend to shorter intermenstrual interval (IMI) with age
  - ***Independent of body mass index (BMI)***

Winters, F/S 2000; 73:724

- 84 women with PCOS ages 20-57 years
- 37 age-matched controls
- Testosterone (T) decreased by 50% across menopausal transition
- T did not differ from controls ages 42-47 years.

Elting F/S 2003; 79:1154

- Sample size = 24 women with PCOS
- Of those who became more regular:
  - Inhibin B was lower
  - Androgens were reduced
  - Less responsive to exogenous follicle-stimulating hormone ovarian reserve test (EFFORT)
  - Lower follicle count

PCOS and Ovarian Reserve: Summary

- Evidence exists for a beneficial effect of low ovarian reserve on menstrual cyclicity in PCOS.
- Expect regular cycles.
- Beware late-life pregnancies in women who believe they cannot conceive.
- ***Effect independent of obesity and linked to ovarian reserve markers.***

What Happens to CVD Risk After Menopause in Women with PCOS?

- Azziz, JCEM 2004; 89:2745
- 400 pre-employment physicals at the University of Alabama at Birmingham (UAB)
- 6.6% of women met criteria for PCOS

BUT

- Risk pool for cardiovascular disease (CVD) is much larger than 6.6% of the population.
- What drives CVD risk in PCOS?

Hormonal Associations in Obesity and the Metabolic Syndrome

- Increased free and total T
- Decreased sex hormone-binding globulin (SHBG) [increased free androgen index (FAI)]
- Insulin resistance [homeostasis model assessment (HOMA)]
- Increased blood pressure (BP)
- Increased waist circumference (>88 cm)
- Dyslipidemia
- Reproductive hormonal changes similar in obesity and PCOS

Does PCOS Lead to Excess Cardiovascular Risk After Menopause?

- Premature acceleration of risk
  - Dyslipidemia (Wild)
  - Type 2 diabetes mellitus (DM) and insulin resistance (IR) (Dunaif, Ehrmann, Legro)
  - Dahlgren: ***predicted*** (but did not observe) 7.4 RR of CVD in PCOS women based on risk factors
  - Obesity—not a universal feature of PCOS, may be an effect modifier
  - Follow-up studies of strictly defined PCOS do not find more coronary death (Pierpoint, Wild).

Irregular Cycles Predict CVD

- Kaplan (Menopause 2008; 15:768)
  - Precocious acceleration of CVD
  - Linked to all types of cycle dysfunction
  - Subclinical disease may be present in many more women and increase risk.

Precocious Acceleration of Plaque

Author	N	Outcome
Guzick 1996	16	CIMT 63.1% vs. 41%
Cibula 2000	28	Type2 DM 32% vs. 8%
Talbott, 2008	149	CAC > 10 63% PCOS vs. 41% non-PCOS

CIMT = carotid intima-media thickness
CAC = coronary artery calcium
DM = diabetes mellitus

Evidence for Increased Risk

- Many studies come from mixed age populations with small samples truly menopausal.
- Many studies do not control for BMI or findings become not statistically significant (NS) after controlling for BMI.
- Many epidemiological studies diagnose elevated T and irregular self-reported menses as PCOS.

Elting, Clin Endo 2001; 55:767

- N = 346 women with PCOS aged 17-56 years; phone interview
  - Type 2 DM 2.3%
  - High blood pressure (HBP) 9%
  - CVD 0.9%
  - All higher than Dutch population controls
  - Median BMI, 24.4 kg/m²

Krentz, Menopause 2007; 14:284

- 713 post-menopausal white women
- Mean BMI 24 +/-3.5 kg/m²
- Definition of PCOS
  - History of irregular menses
  - Increased androgens
  - Infertility or miscarriage
  - Obesity
  - Insulin resistance
- 9.3% of women 'defined' with PCOS
- CVD risk similar in PCOS vs non-PCOS, but increased with more features of PCOS

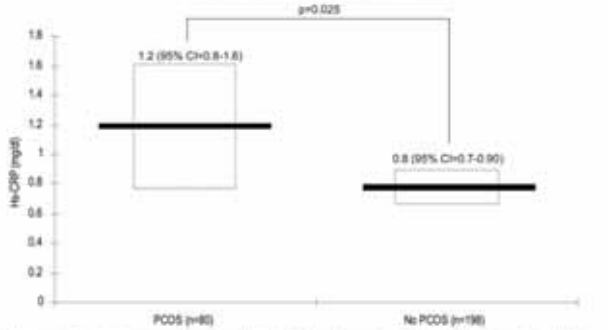
Korhonen, F/S 2003; 79:1327

- N = 543 women 34-54years old
- 63 with metabolic syndrome (MS)
  - Increased FAI
  - Increased BP
  - Decreased insulin sensitivity
  - All in the absence of PCOS

Obesity, Increased T and Irregular Menses Do NOT Equal PCOS

- Shaw: Women's Ischemia Syndrome Evaluation (WISE) study (n=390 pre-menopausal women; 104 with PCOS)
  - Increased T associated with irregular menses
  - 5-year CVD survival 78.9% vs. 88.7%
  - Hazard ratio (HR) of 3.3 unadjusted
  - HR decreased to 1.6 when adjusted for age and BMI
  - PCOS defined by elevated current T and irregular menses by history.

FIG. 1. Average hs-CRP Values (95% CI) for Women With and Without Clinical Features of PCOS



*p value was calculated using a general linear model controlling for statin use, LDL cholesterol, hypertension, metabolic syndrome, history of smoking, and angiographic coronary artery disease severity.

Shaw, L. J. et al. J Clin Endocrinol Metab 2008;93:1276-1284

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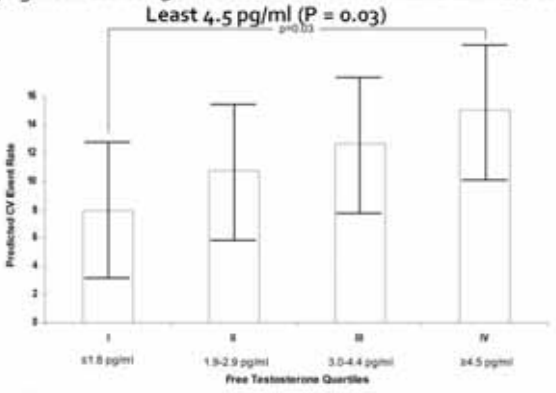
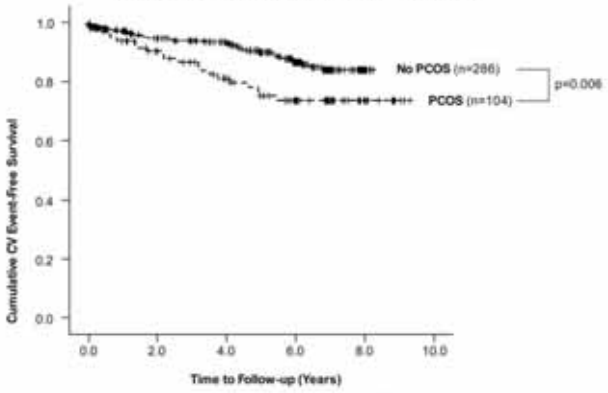
FIG. 2. Predicted CV Event Rates by Quartile of Free Testosterone Ranging from 8.0 to 15.1% for Levels from No More than 1.8 to at Least 4.5 pg/ml (P = 0.03)



*Predicted CV Event Rate is based on a multivariable Cox model including HOMA, waist circumference, and a history of diabetes.

Shaw, L. J. et al. J Clin Endocrinol Metab 2008;93:1276-1284

FIG. 3. Cumulative Unadjusted CV Death or Myocardial Infarction (MI)-free Survival in Postmenopausal Women With or Without Clinical Features of PCOS (P = 0.006)



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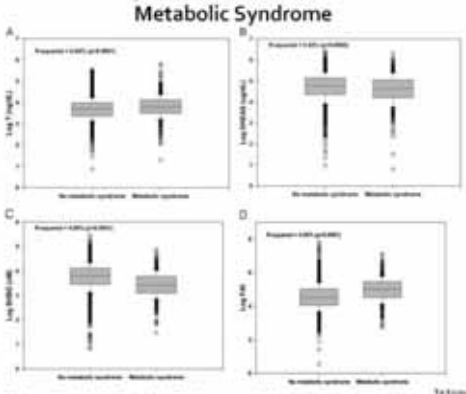
Enter the Study of Women's Health Across the Nation (SWAN)

- Cohort study of 3,302 perimenopausal women aged 42-54 years at baseline
- Criteria included at least one menstrual period within past 3 months
- No assessment for hirsutism or polycystic ovaries by ultrasound (U/S)
- Severe PCOS unlikely to be included

FIG. 2. The Relationship of Individual Hormone Parameters to the Metabolic Syndrome



Santoro, N., et al. J Clin Endocrinol Metab 2005;90:4836-4845

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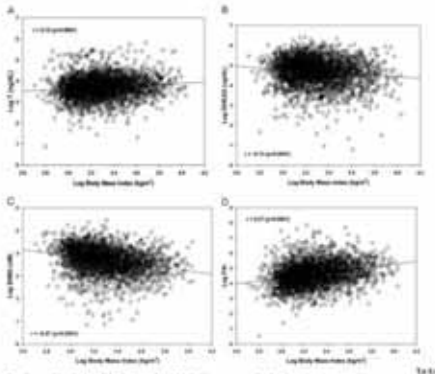
FIG. 1. Scatterplots Depicting the Relationship of Androgens to BMI



Santoro, N., et al. J Clin Endocrinol Metab 2005;90(8):4636–4644

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Disentangling PCOS from Obesity

- Does central obesity drive the CVD phenotype?
- Similar risk profile without PCOS and with metabolic syndrome
- Do non-PCOS women 'catch up' to PCOS women after menopause?
- Estrogen may mitigate PCOS adverse effects on endothelium in reproductive years

The Role of Testosterone

- Increased in obesity
  - 17-beta-hydroxysteroid dehydrogenase (HSD) in adipoctyes favors androgen production
  - Reduced metabolic clearance may occur
- Reduces insulin sensitivity
- Increases BP
- May adversely affect endothelial function

Evidence Against PCOS as a Distinct Risk for Postmenopausal Cardiovascular Disease

- Wild: 3.7 OR for positive cardiac catheterization when hirsutism present
  - Effect of hirsutism not statistically significant after multivariate adjustment
- Birdsall: Coronary artery disease (CAD) predicted PCOS
  - But 43% of sample had PCOS!
  - Androgens and anovulation not used to define PCOS

Current Models

- Do not explain the relationship between obesity and T in the absence of PCOS
- Do not account for the decrease in T with menopause in PCOS

Management of the Perimenopausal Woman with PCOS

- Weight control
- Maintain physical activity
- Address nutritional deficiency (Vitamin D; Thys-Jacobs)
- Address insulin resistance aggressively!

Weight Control

- Caloric restriction
- Physical activity
- Consider weight loss surgery when:
  - BMI>35
  - BMI<35 but other risk factors (type 2 DM)

Address Insulin Resistance

- DPP, 2006
- Metformin as effective as weight loss and exercise in women >40 years old
- PCOS = 'pre-diabetic condition'
- Indicated use for metformin

Summary

- PCOS appears to be characterized by a return to normal cyclicity in the twilight of reproductive life.
- Regularity is related to ovarian reserve.
- A temporary window of ovulation and normal cyclicity results.

Summary

- PCOS, as well as other irregularly cycling women, appear to be at increased risk of CVD.
- Obesity seems to drive this phenotype.
- Obesity is linked to increased androgens in the absence of PCOS.
- PCOS and non-PCOS related obesity are currently commingled conditions in the medical literature.

Summary

- Insulin resistance at any age is a predictor of CVD risk.
- Aggressive treatment of IR in the aging woman with PCOS may help avert future risk.

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NOTES

Course #13 Test Questions

1. A 21-year-old woman presents with concerns about irregular menses. She reports menarche at age 15 with irregular menses since then. She has menstrual cycles every 3-4 months and has been given progestin therapy in the past with positive withdrawal menses. She has no evidence of hirsutism or acne on exam. Her BMI is 22 kg/m2 with a normal body habitus. The hormonal pattern reveals normal TSH, and prolactin and androgen levels are in the normal range. A pelvic ultrasound is ordered and a multifollicular pattern with 12 follicles is noted in a single field. Ovarian volume averages 12 mL. She should be advised of which one of the following?
    a. By the NIH criteria as well as Rotterdam criteria, her findings are consistent with a polycystic ovary syndrome (PCOS) diagnosis.
    b. She does not meet the diagnostic criteria for PCOS.
    c. She meets a diagnosis of PCOS by Rotterdam criteria, but her risk of metabolic consequences is uncertain.
    d. She would benefit from metformin therapy for her irregular cycles.
    e. Results of a two-hour glucose tolerance test are needed for Rotterdam criteria assessment.

2. All diagnostic criteria agree that polycystic ovary syndrome is which one of the following?

    a. An autosomal dominant genetic disorder.
    b. Caused by hypothalamic pituitary dysfunction.
    c. A result of insulin resistance.
    d. An ovarian disorder.
    e. A diagnosis that requires the presence of polycystic ovaries.

3. A 40-year-old woman, G2P2, with polycystic ovary syndrome (PCOS), presents to the office to discuss management. She was diagnosed with PCOS as a young adult and has completed her childbearing. She has been using oral contraceptives for management of her menstrual cycles and has generally tolerated this well. Her body mass index (BMI) at the visit is 26.7 kg/m^2 with a recent weight gain of 10 lbs. Her blood pressure is 130/86. She would like to know her long-term risk of health problems and whether she should be on other therapeutic regimens. She should be advised of which one of the following?
    a. Her current management with oral contraceptives is adequate, as she is desirous of contraception and her menstrual cycles are well-controlled with this regimen.
    b. Risk of cardiovascular disease is increased in women with PCOS and treatment with insulin sensitizers should be started.
    c. Her use of oral contraceptives is contraindicated at this time due to her increased risk for cardiovascular complications.
    d. Cardiometabolic risk is increased in PCOS, and a current lipid panel and oral glucose tolerance test are indicated.
    e. Use of statin therapy is indicated due to her increased risk for cardiovascular disease.

(continued)

4. A 28-year-old nulliparous woman with polycystic ovary syndrome is undergoing GnRH antagonist/follicle-stimulating hormone (FSH) therapy for in vitro fertilization. Her baseline pelvic ultrasound shows bilateral polycystic ovaries and she is experiencing hyperresponsiveness to the ovarian stimulation. You use the GnRH trigger to induce ovulation in an attempt to reduce the risk of ovarian hyperstimulation syndrome. Which one of the following regarding use of the GnRH trigger to induce ovulation is true?
    a. There is an increase in the total numbers of oocytes retrieved.
    b. There is a decrease in the fertilization rate of oocytes.
    c. There is an increase in the proportion of mature oocytes.
    d. There is a decrease in endogenous progesterone production.
    e. There is an increase in endogenous estrogen production.

5. A 30-year-old nulliparous Caucasian woman complains of moderate hirsutism. Her menstrual cycles occur every 3 months. She is obese with coarse terminal hairs over her upper lip, chin, sternum and lower abdomen. Serum testosterone is mildly elevated and thyroid function studies, as well as prolactin, 17-hydroxyprogestone and dehydroepiandrosteone sulfate are normal. Which one of the following is MOST likely to provide the most rapid benefit for this woman's hirsutism?
    a. Eflornithine
    b. Combination oral contraceptive
    c. Spironolactone
    d. Electrolysis
    e. Flutamide

6. A 20-year-old nulliparous Caucasian woman complains of facial hirsutism. Menarche occurred at 12 years of age and her menstrual cycles occur every 50-60 days. Past medical history is significant for a congenital adrenal virilizing tumor that was completely removed by surgery after birth. Vital signs are normal and physical examination shows hirsutism. Pelvic examination shows clitoromegaly without genital ambiguity. Which one of the following hormone abnormalities is most likely to exist?
    a. Elevated cortisol
    b. Elevated dehydroepiandrosterone sulfate
    c. Elevated luteinizing hormone
    d. Reduced androstenedione
    e. Reduced antimüllerian hormone

7. For an overweight woman with polycystic ovary syndrome and no other infertility factors, the first-line therapy for ovulation induction to treat infertility is which one of the following?

    a. Clomiphene citrate
    b. Metformin
    c. Clomiphene citrate and metformin
    d. Letrozole
    e. Lifestyle therapy

8. Assuming no contraindications, which one of the following drugs has the best evidence to support a favorable risk-benefit ratio for use in the long-term treatment of polycystic ovary syndrome?
    a. Metformin
    b. Rosiglitazone
    c. Atorvastatin

(continued)

d. Orlistat
e. Exenatide

9. Which one of the following reproductive hormonal changes is MOST LIKELY to be associated with the menopausal transition in women with polycystic ovary syndrome?
    a. More frequent menstrual cycles
    b. Decreased follicle-stimulating hormone (FSH)
    c. Temporarily increased inhibin B
    d. A sudden decrease in müllerian-inhibiting substance (MIS)
    e. Increased hirsutism

10. By the time of menopause, the prevalence of type 2 diabetes mellitus in women with polycystic ovary syndrome is:

    a. 10%
    b. 20%
    c. 30%
    d. 40%
    e. 50%

11. Which one of the following markers of cardiovascular disease risk is MOST likely to be increased in a woman with polycystic ovary syndrome?
    a. Glucose to insulin ratio
    b. Coronary artery calcification
    c. Carotid intimal medial thickness
    d. Homocysteine
    e. Serum amyloid A

12. One potential drawback of a genome-wide association study is:
    a. Bias in selection of genetic markers.
    b. A study design that mandates replication.
    c. Matching for population stratification.
    d. False positives due to multiple testing.
    e. Identification of non-candidate genes.