

# Menopause in PCOS



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# Duality of Interest

- **Paid Lecture from Serono**
- **Travel Expense Reimbursement (multiple)**
- **Grantee: National Institute of Health, Pennsylvania Tobacco Settlement Funds**
- **Committee Member: American Society of Reproductive Medicine, Endocrine Society**
- **Associate Editor: Fertility and Sterility, Human Reproduction, Seminars in Reproductive Endocrinology**

# Talk Outline

- **1. What happens to the phenotype of women with PCOS as they age?**
- **2. Is there prolonged ovarian function in women with PCOS**
- **3. Is there a menopausal PCOS Phenotype?**
- **4. Where should research go in this area?**

# Life Cycle of PCOS

*In utero*

*Peripuberty*

*Adolescence  
Adulthood*

*Aging*

Small for Gestational Age/IUGR	Exaggerated Adrenarche	PCOS	Diabetes, CVD, Endometrial Cancer
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**? Reproductive**



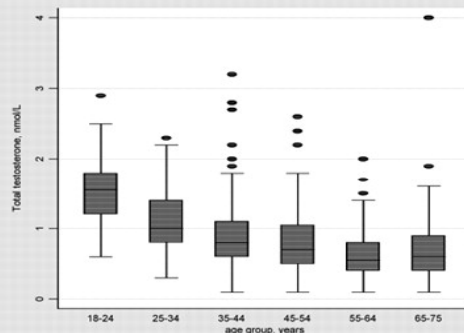
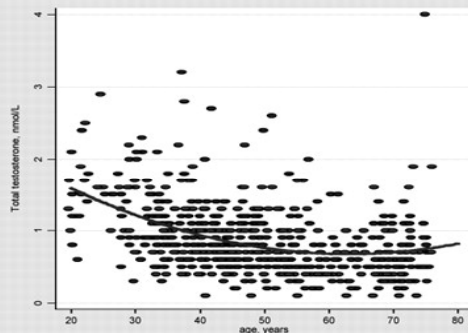
# Diagnostic Criteria: No Menopausal Phenotype

	NIH (1992)	Rotterdam (ASRM/ESHRE 2004) 2 of 3	Androgen Excess Society (2006) HA + 1
Oligomenorrhea	Yes	Maybe	Maybe
Hyperandrogenism (Biochemical and/or Clinical)	Yes	Maybe	Yes
Polycystic ovaries	No	Maybe	Maybe

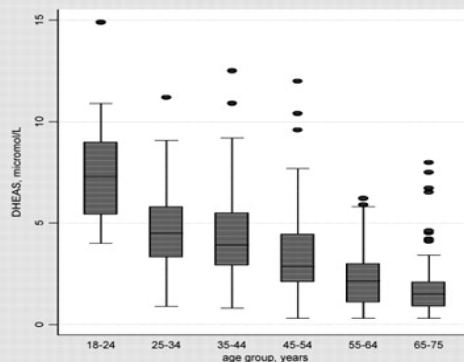
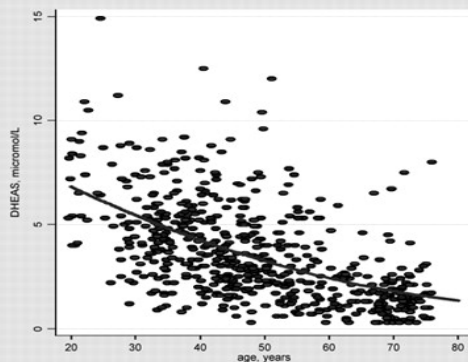
# Aging and Androgen Levels in Females

- Progressive, substantial, age-related decline in DHEAS.
- Minimal evidence to support a decline in testosterone associated with the menopause transition *per se*;
  - ◆ However T does decline substantially from the mid-reproductive years
  - ◆ women in their forties have an approximately 50% reduction in plasma testosterone from their 20'a

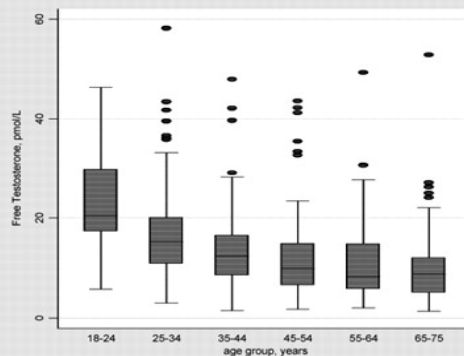
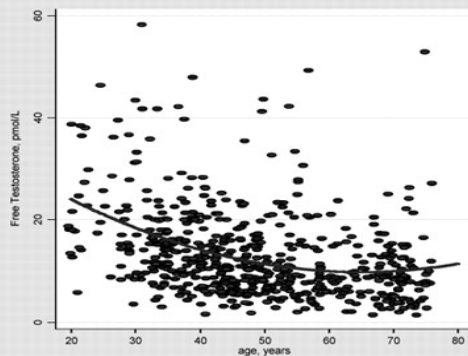
## Total Testosterone



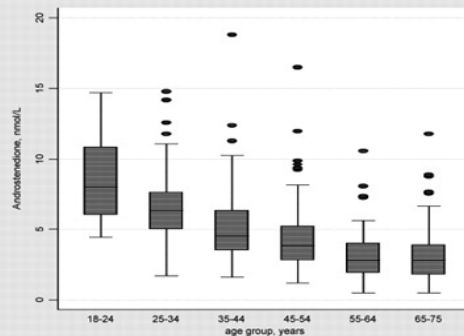
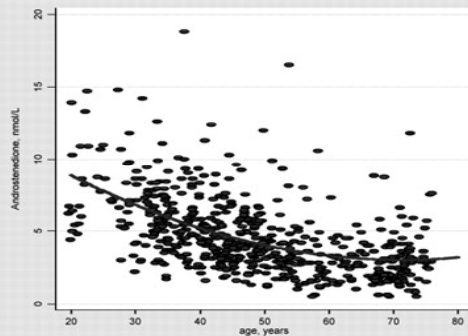
## DHEAS



## Free Testosterone



## Androstenedione



**Relationship between age and individual androgens for the reference group (N =1572 Australian Women)**

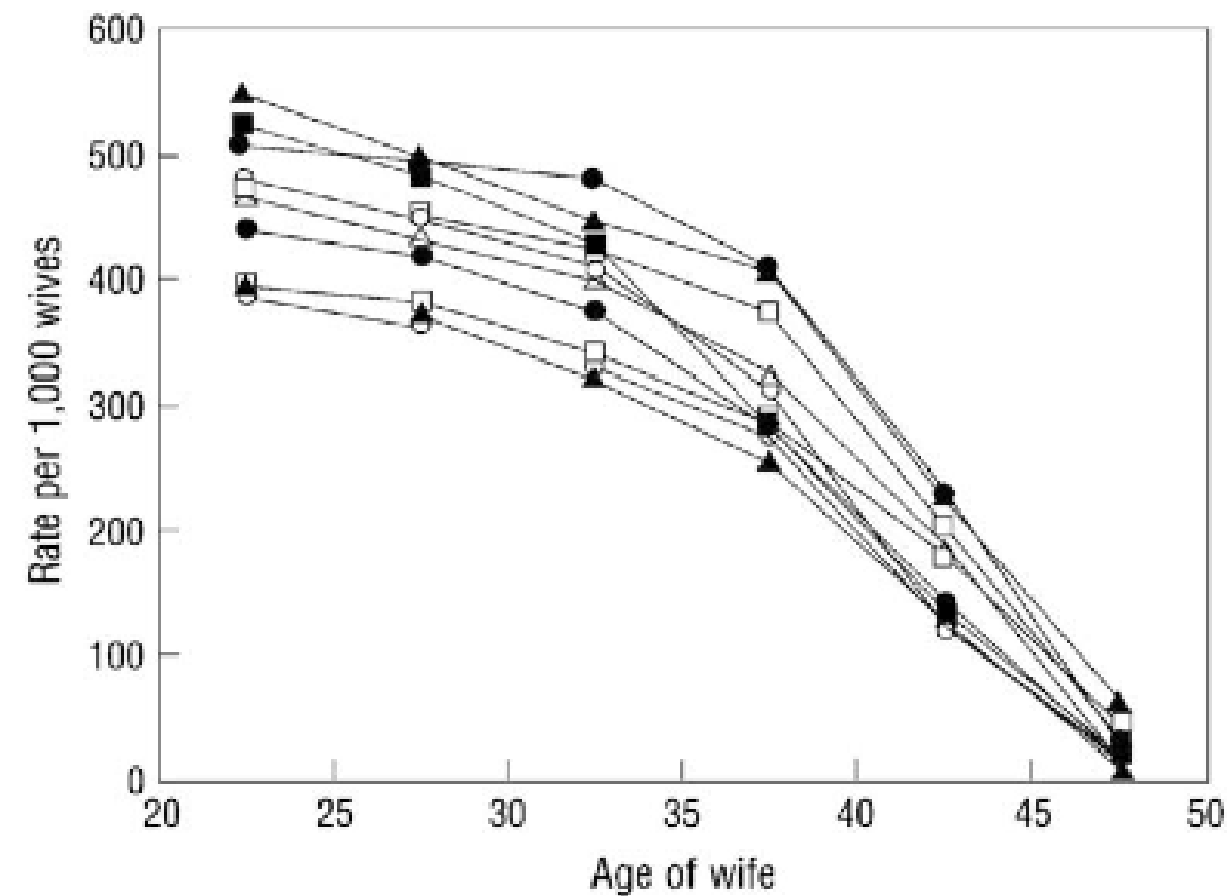
Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853

THE JOURNAL OF  
**CLINICAL  
ENDOCRINOLOGY  
& METABOLISM**

**If circulating hormones are meaningful indicators of biological activity, then the natural menopause cannot be conceptualized as an ovarian androgen-deficiency state.**



# Age and Fecundity



ACOG and ASRM. Age-related fertility decline. *Fertil Steril* 2008.

Marital fertility rates by 5-years age group. The ten population (in descending order at age 20–24 years) are Hutterites, marriages from 1921–30 (▲); Geneva bourgeoisie, husbands born in 1600–49 (■); Canada, marriages 1700–30 (●); Normandy, marriages 1760–90(○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840–59(△) Normandy, marriages 1674–1742 (●); Norway, marriages 1874–76 (□); Iran, village marriages, 1940–50 (▲); Geneva bourgeoisie, husbands born before 1600 (○); From Menken J, Trussel J, Larsen U, *Age and Science* 1986;233;1389–94 Reprinted with permission from AAAS.

# Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve

**M. Hudecova<sup>1</sup>, J. Holte, M. Olovsson, and I. Sundström Poromaa**

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<sup>1</sup>Correspondence address. Tel: +46 18 611 57 87; E-mail: miriam.hudecova@kbh.uu.se

Among women who had attempted a pregnancy, 86.7% of PCOS patients and 91.6% of controls had given birth to at least one child. Among PCOS patients who had given birth, 73.6% had done so following a spontaneous conception.

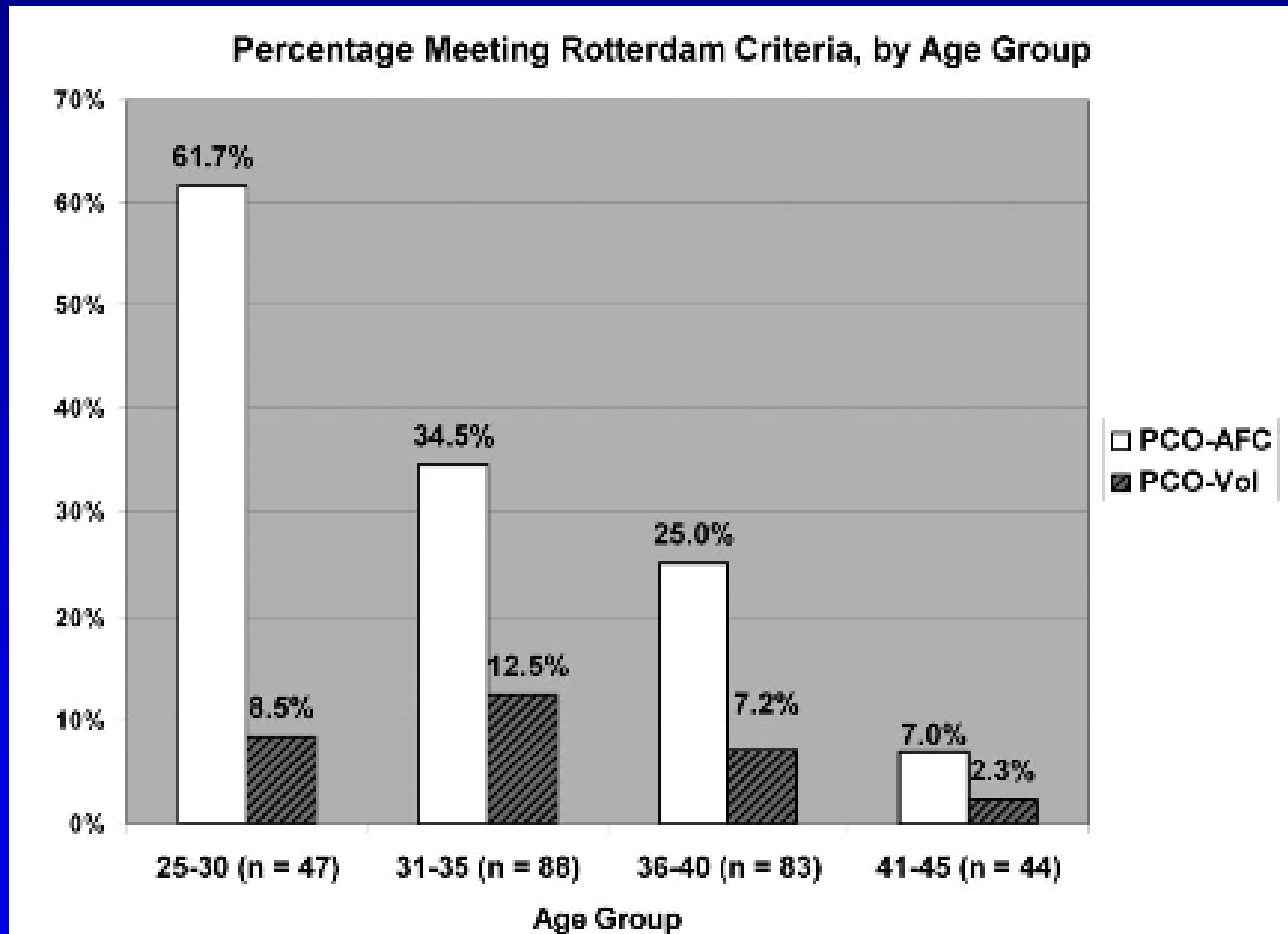
## **The Polycystic Ovary Post-Rotterdam: A Common, Age-Dependent Finding in Ovulatory Women without Metabolic Significance**

Erica B. Johnstone, Mitchell P. Rosen, Rebecca Neril, Deborah Trevithick, Barbara Sternfeld, Rosemary Murphy, Carolyne Addauan-Andersen, Daniel McConnell, Renee Reijo Pera, and Marcelle I. Cedars

Department of Obstetrics, Gynecology, and Reproductive Sciences (E.B.J., M.P.R., R.N., D.T., C.A.-A., M.I.C.), University of California, San Francisco, San Francisco, California 94115; Division of Research (B.S., R.M.), Kaiser Permanente, Oakland, California 94611; Department of Epidemiology (D.M.), University of Michigan School of Public Health, Ann Arbor, Michigan 48109; and Institute for Stem Cell Biology and Regenerative Medicine (R.R.P.), Stanford University, Palo Alto, California 94305

262 Caucasian women with normal menses  
22-45 days, off confounding medications in  
good health

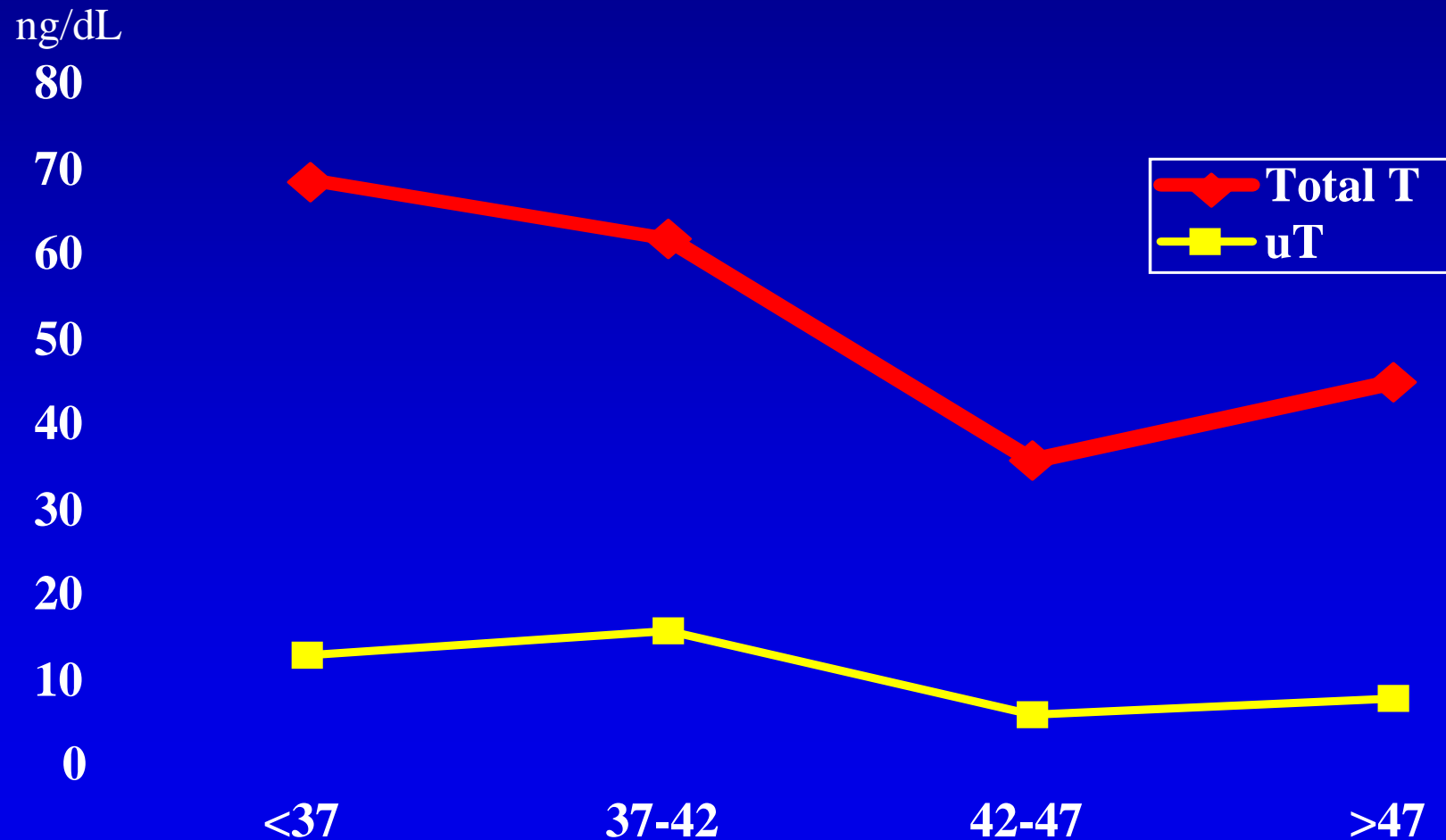
# In an Unselected Normal Female Population, PCOS Stigmata Resolve with Age



**FIG. 1.** Percentage of subjects meeting each portion of the Rotterdam Criteria, by age group.

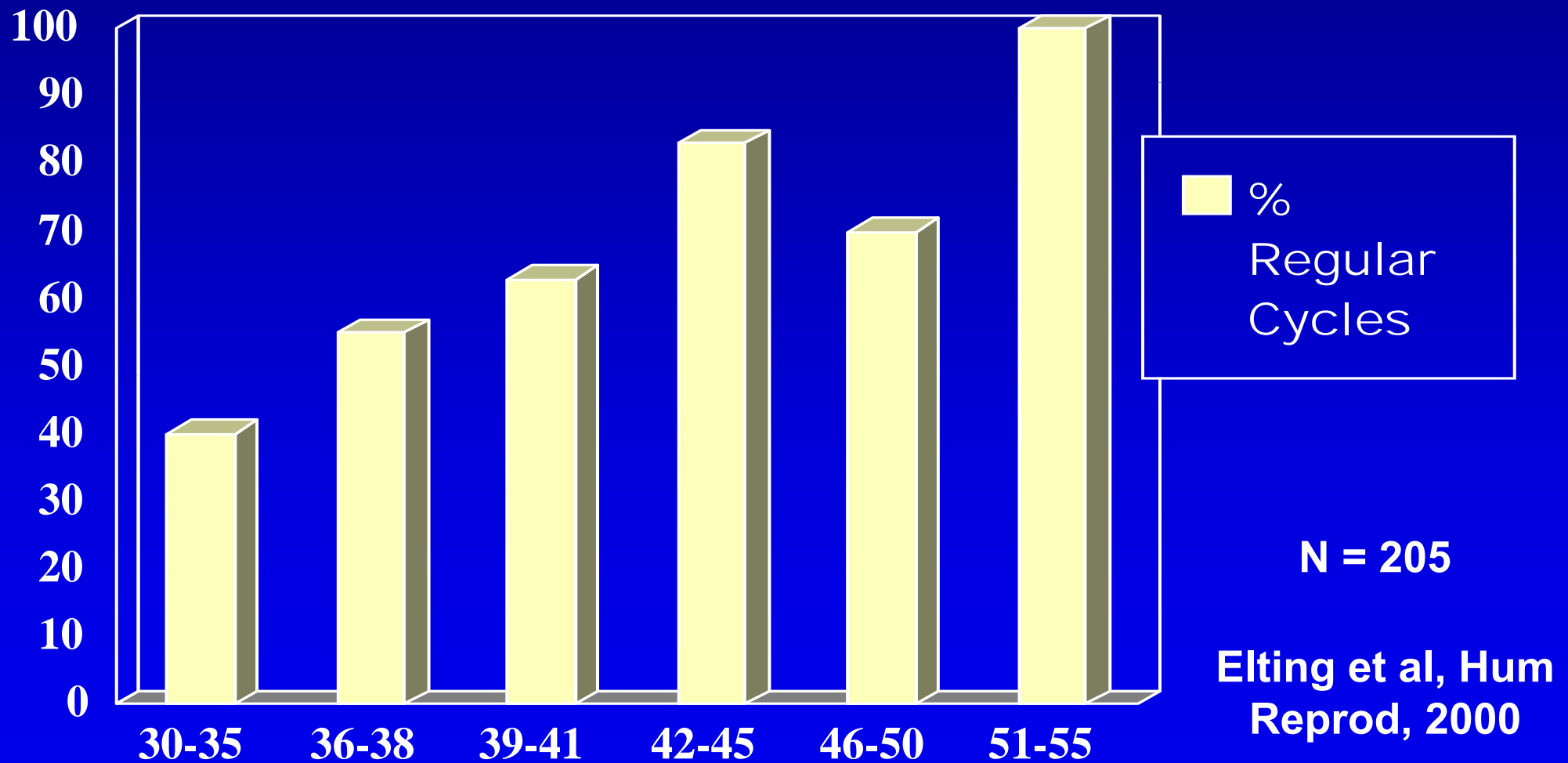
Johnstone et al,  
JCEM, Epub 2010

# Decreasing Testosterone Levels with Age in PCOS





# Improved Menstrual Regularity with Age in PCOS Women



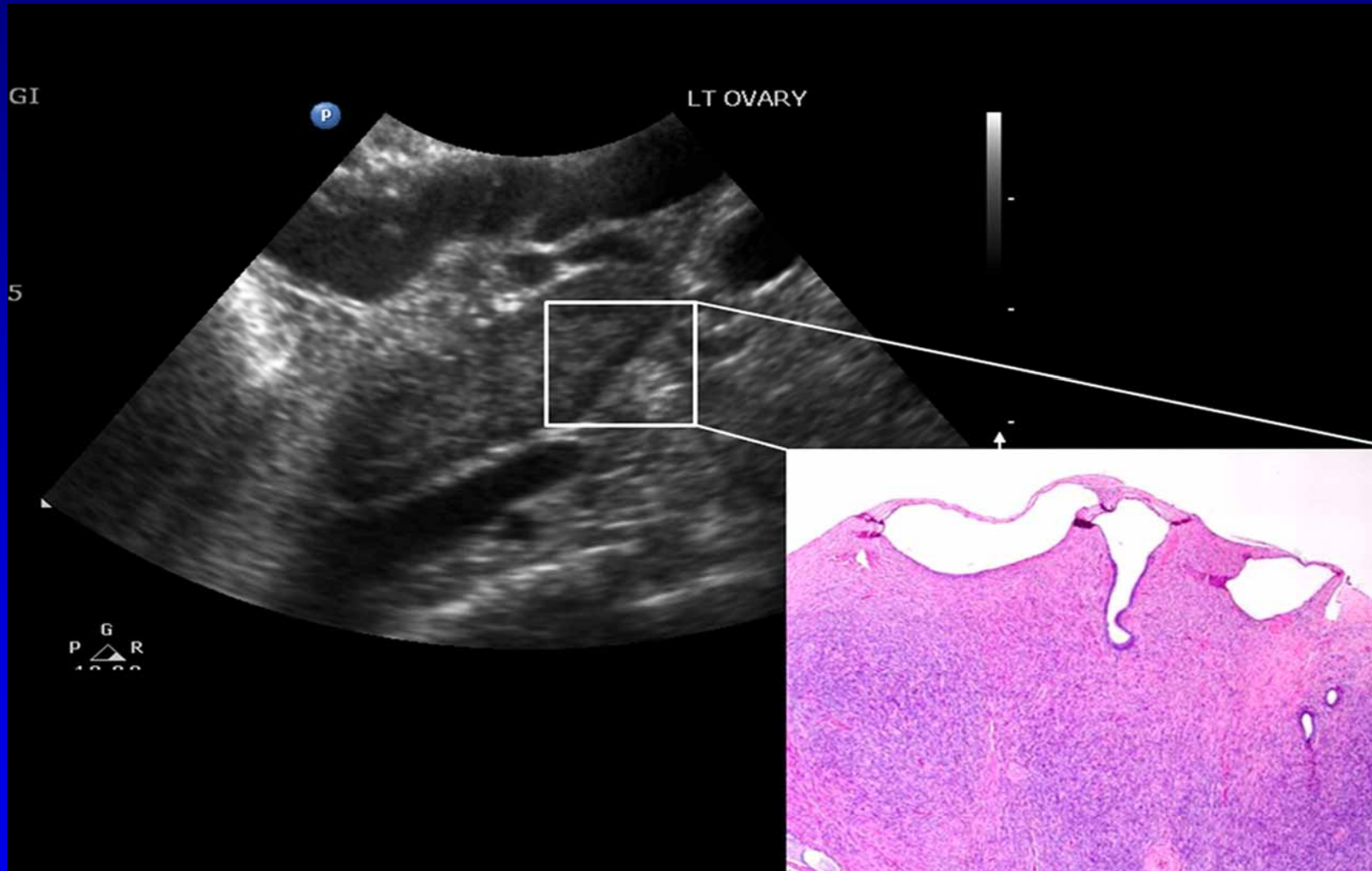
## Criteria for Polycystic Ovarian Morphology in Polycystic Ovary Syndrome as a Function of Age

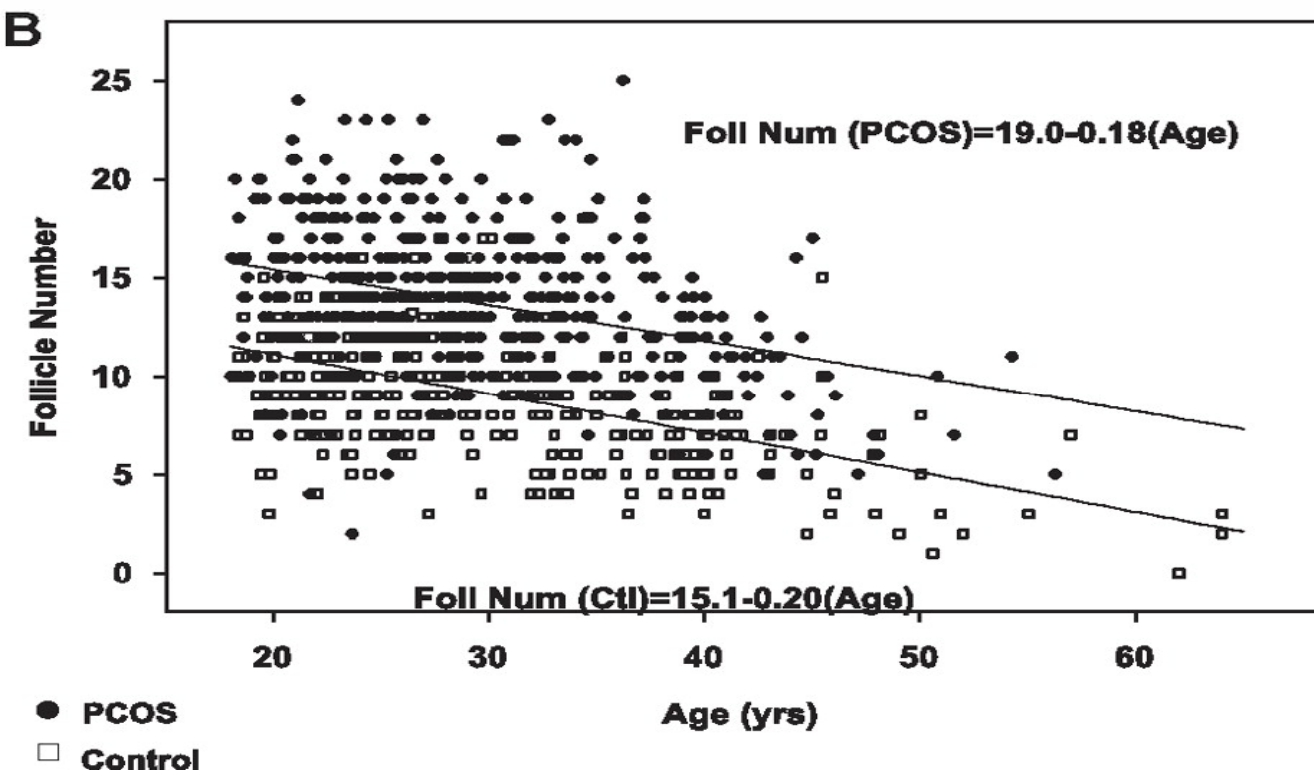
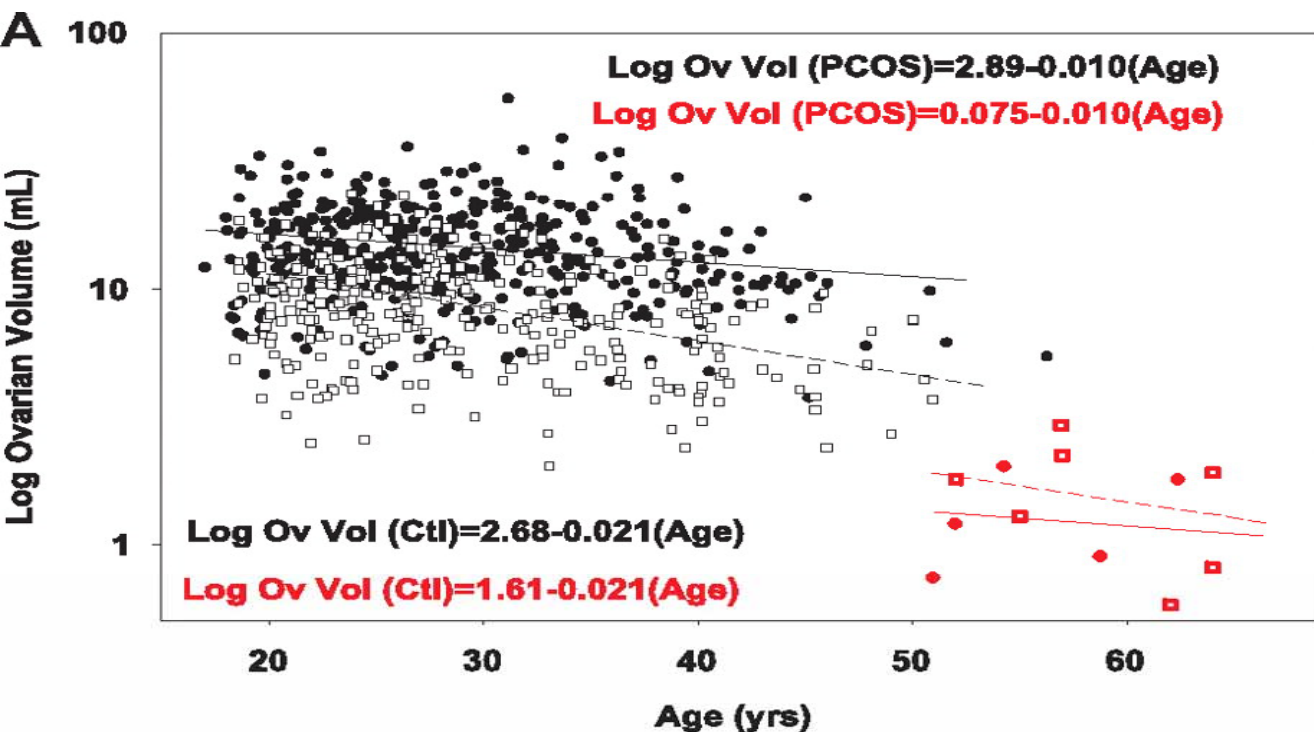
S. Alsamarai, J. M. Adams, M. K. Murphy, M. D. Post, D. L. Hayden, J. E. Hall, and C. K. Welt

Reproductive Endocrine Unit (S.A., J.M.A., M.K.M., J.E.H., C.K.W.), Department of Medicine (M.K.M.), and Department of Biostatistics (D.L.H.), Massachusetts General Hospital, Boston Massachusetts 02114; and Department of Pathology (M.D.P.), University of Colorado Denver, Aurora, Colorado 80045

**Conclusions:** Ovarian volume and follicle number decrease with age in women with PCOS and controls necessitating age-based criteria to define polycystic ovarian morphology. It is possible to use these criteria to distinguish PCOS in women over age 40 yr.

# Postmenopausal ovary viewed on transvaginal ultrasound and under light microscopy





Log ovarian volume (A) and follicle number (B) as a function of age in PCOS (black circles) and control subjects (open squares) and postmenopausal PCOS (red circles) and control subjects (red squares)

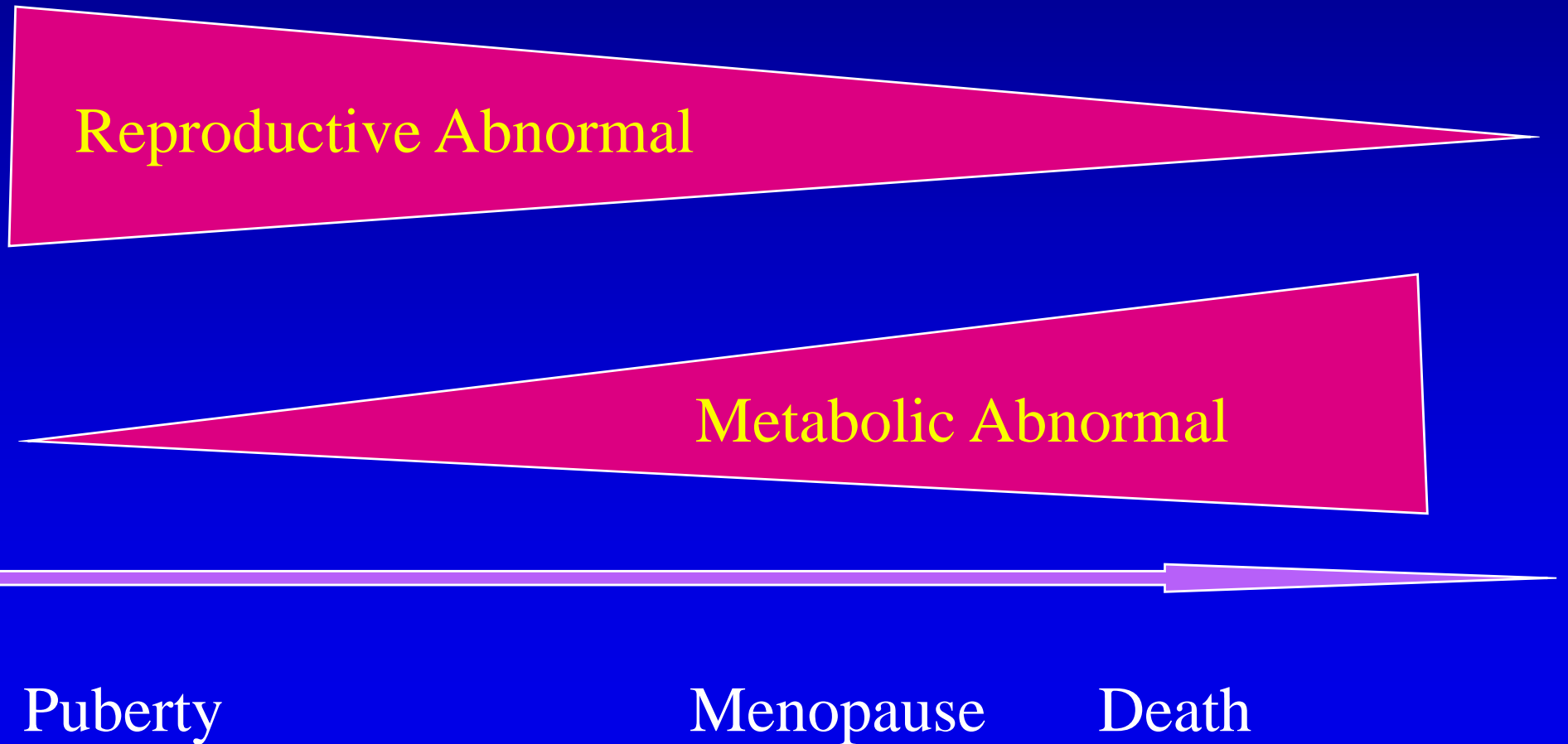
Alsamarai, S. et al. J Clin Endocrinol Metab 2009;94:4961-4970

A) Box and whisker plots of the FSH-sensitive follicle cohorts, as estimated by the E2 (*Open box*) and the inhibin B increment (Hatched box) in 24 hours after 300 IU of FSH = inhibin B increment (B) Box and whisker plot of the follicle counts in women with PCOS

QuickTime™ and a  
decompressor  
are needed to see this picture.



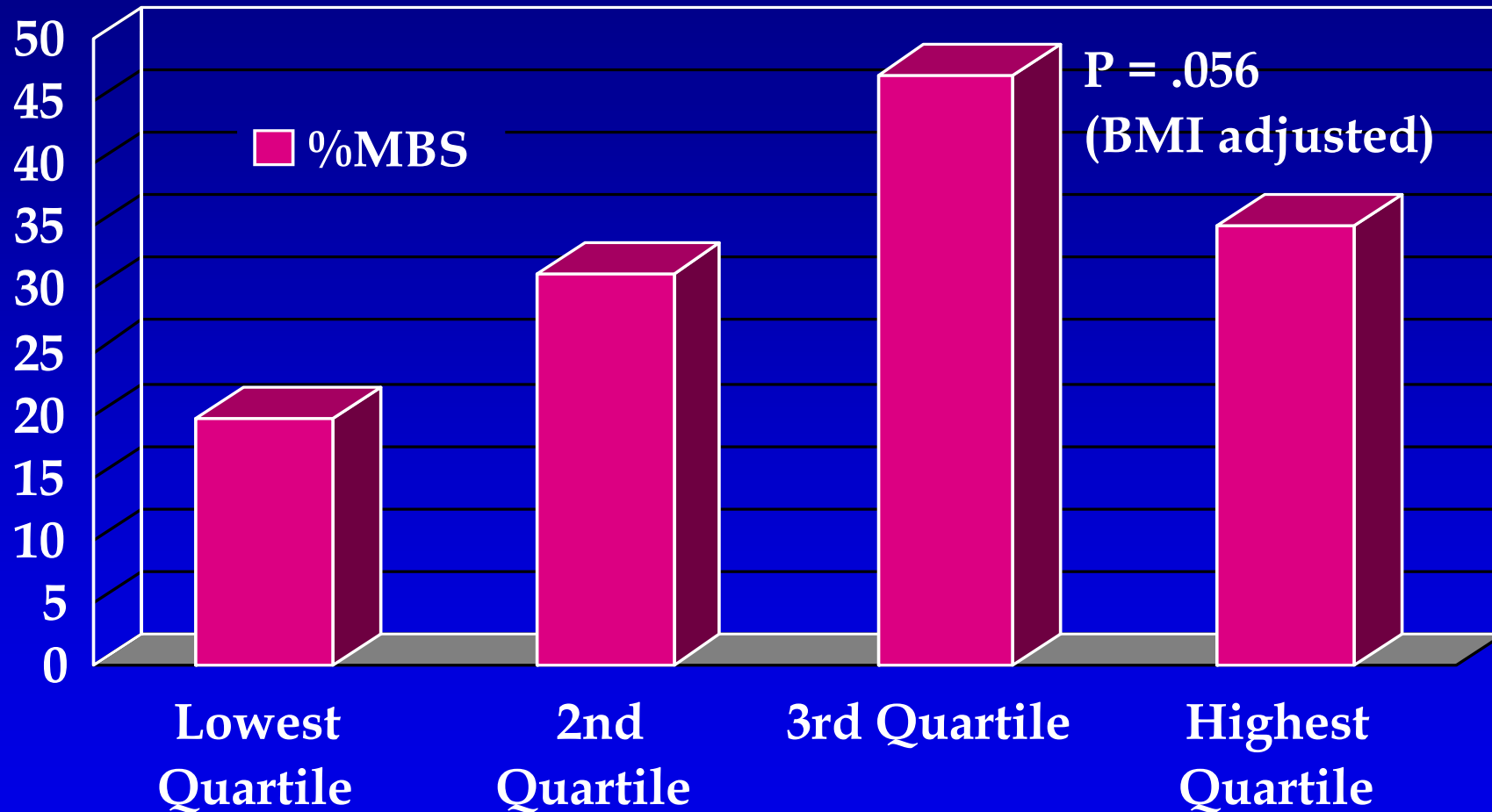
# Age Related Changes in PCOS Phenotype



# The Importance of Diagnosing Hyperandrogenemia in PCOS

- 1) A diagnostic feature that allows for discrimination from other causes of the combination of oligomenorrhea and polycystic ovaries
- 2) The feature that is best associated with metabolic abnormalities
  - ◆ Insulin Resistance/Metabolic Syndrome (MBS)
  - ◆ CVD Risk
- 3) A prognostic factor for treatment success
- 4) An objective criteria that best allows for the conduct of multi-center trials

# Association Between Metabolic Syndrome and Free Testosterone in PCOS

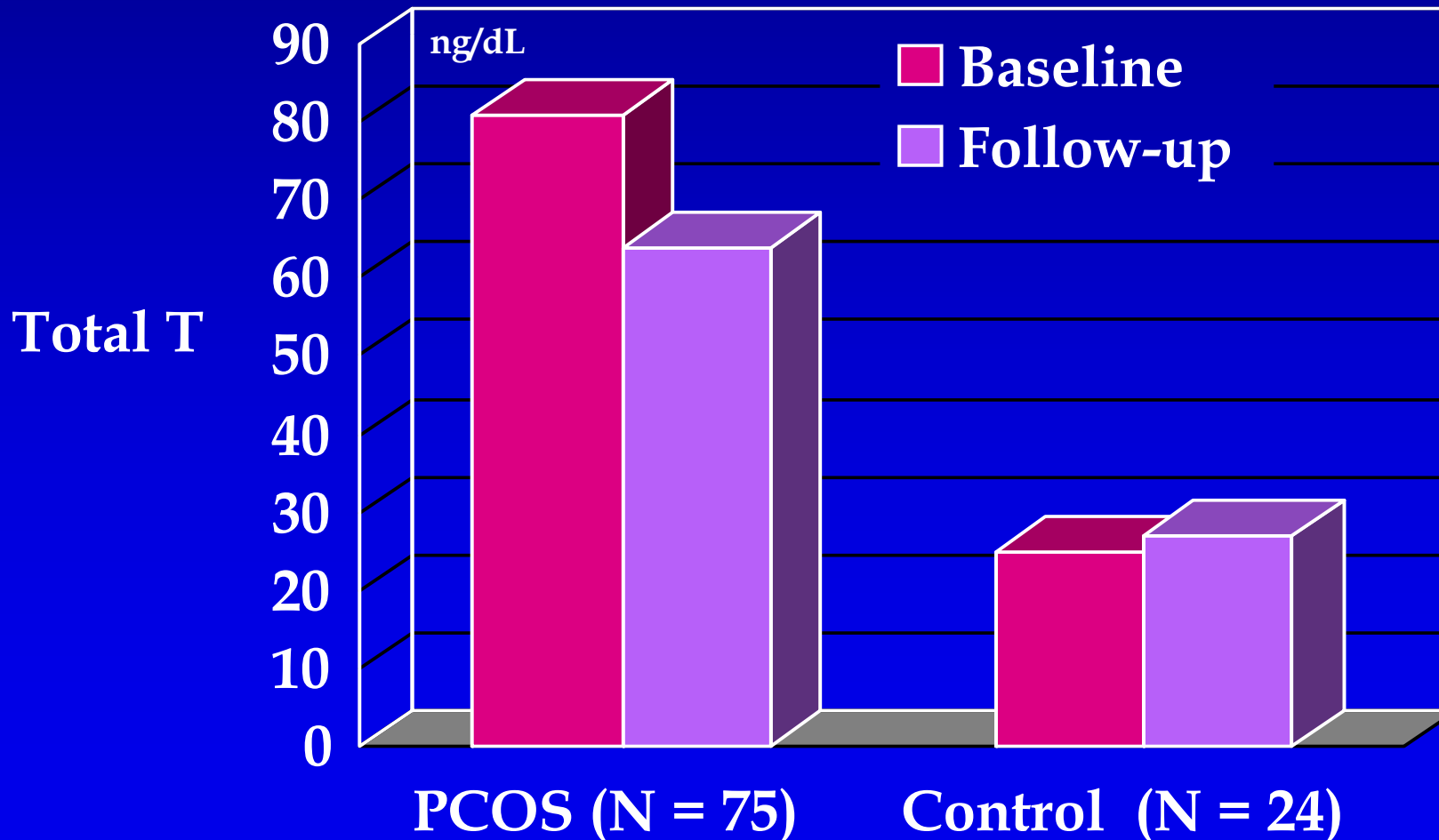


Ehrmann et al. JCEM 2006

# Changes in Glucose Tolerance over Time in Women with Polycystic Ovary Syndrome: A Controlled Study

Richard S. Legro, Carol L. Gnatuk, Allen R. Kunselman, and Andrea Dunaif

Departments of Obstetrics and Gynecology (R.S.L., C.L.G.) and Health Evaluation Sciences (A.R.K.), Penn State College of Medicine, Hershey, Pennsylvania 17033; and Division of Endocrinology, Metabolism, and Molecular Medicine (A.D.), Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611



Mean follow-up  
2-3 yrs later

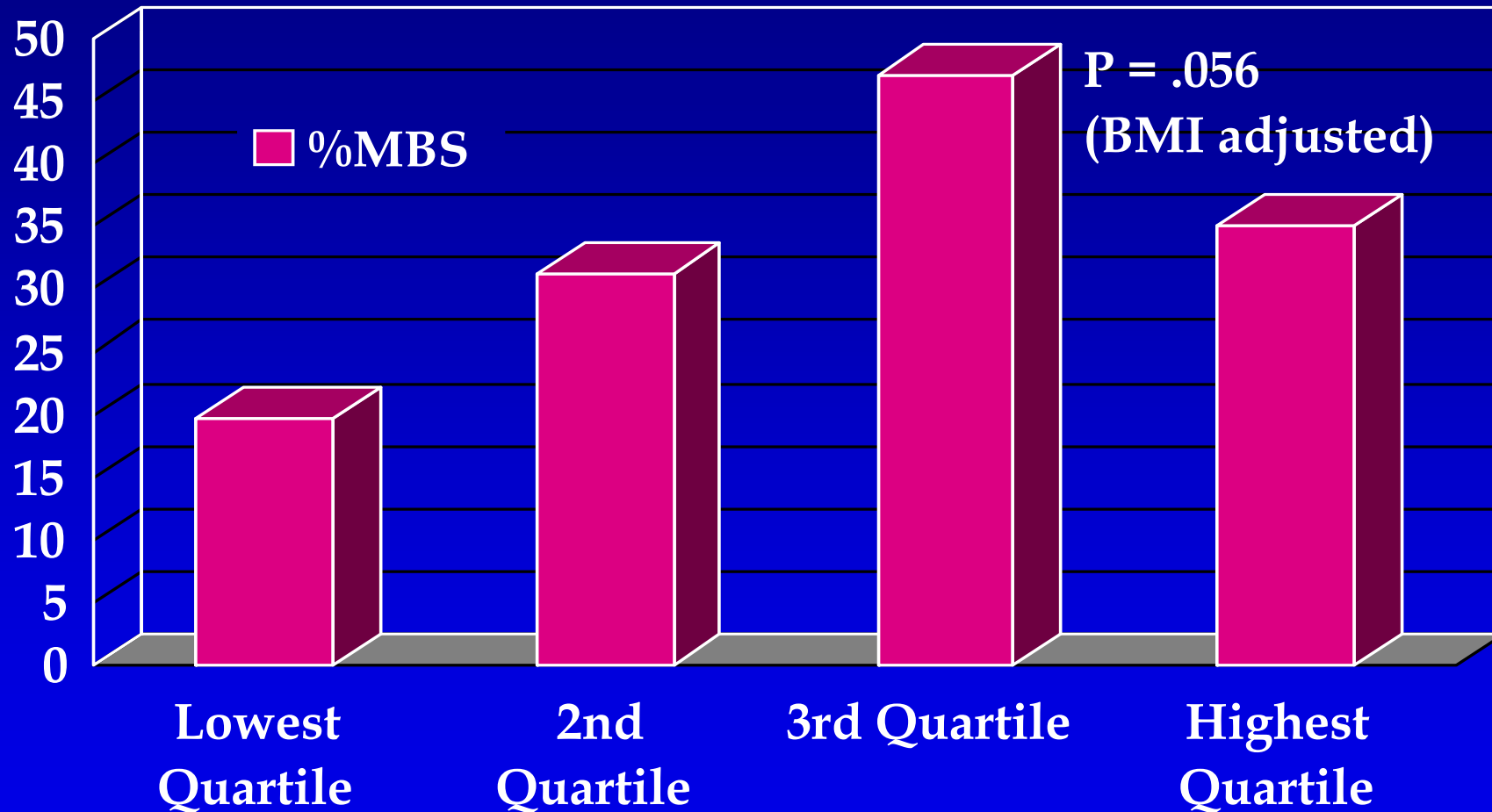
14 women with  
PCOS on  
confounding  
meds: (10 OCP,  
4 Metformin)

# University of Pittsburgh Case Control Study of CVD Risk Factors

- 200+ cases /200+ community based controls identified
- Age-matched ~35 yrs
- Followed for 10+ years
  - ◆ with biometric, serum markers, imaging techniques, etc.

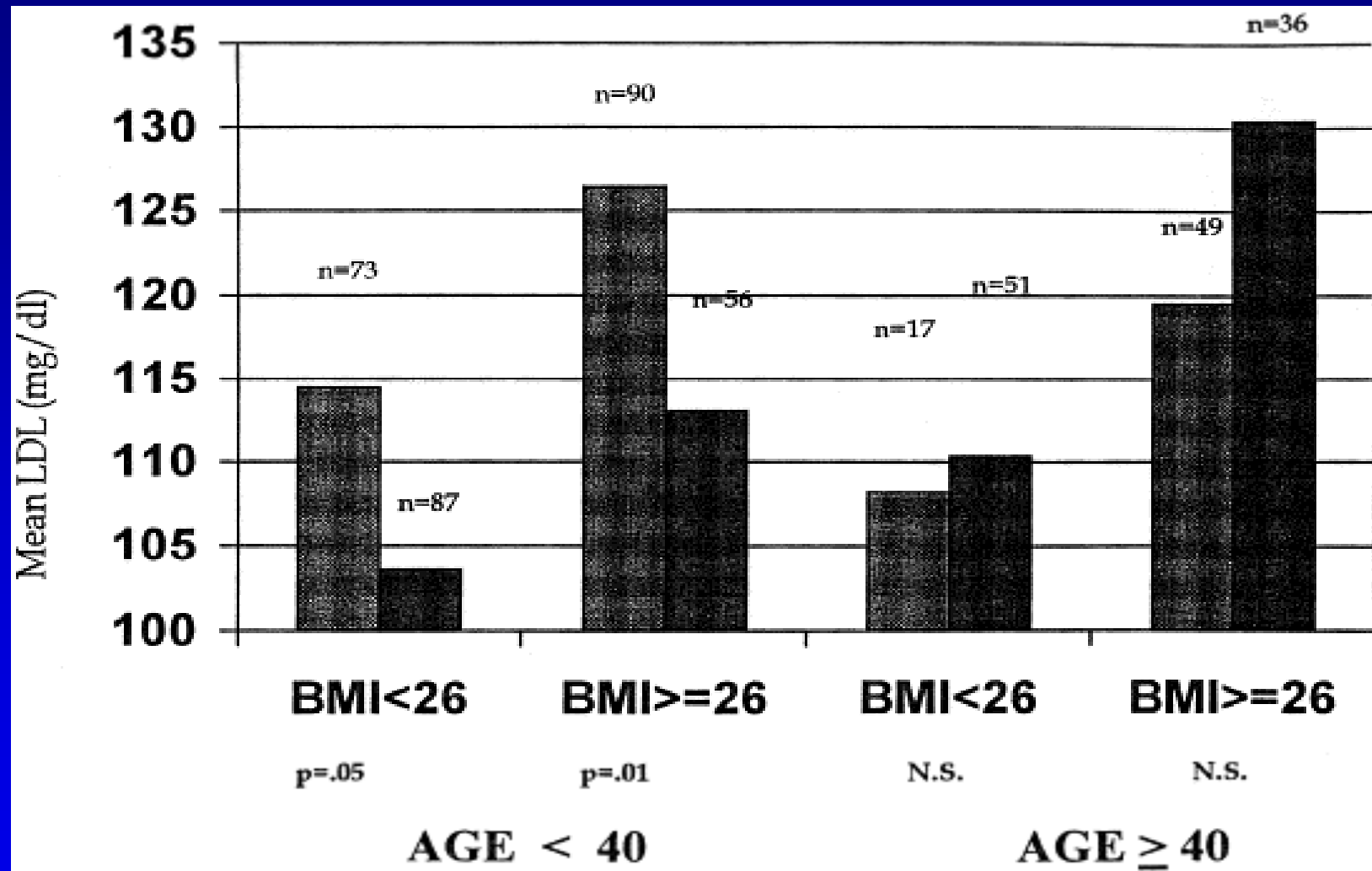


# Association Between Metabolic Syndrome and Free Testosterone in PCOS



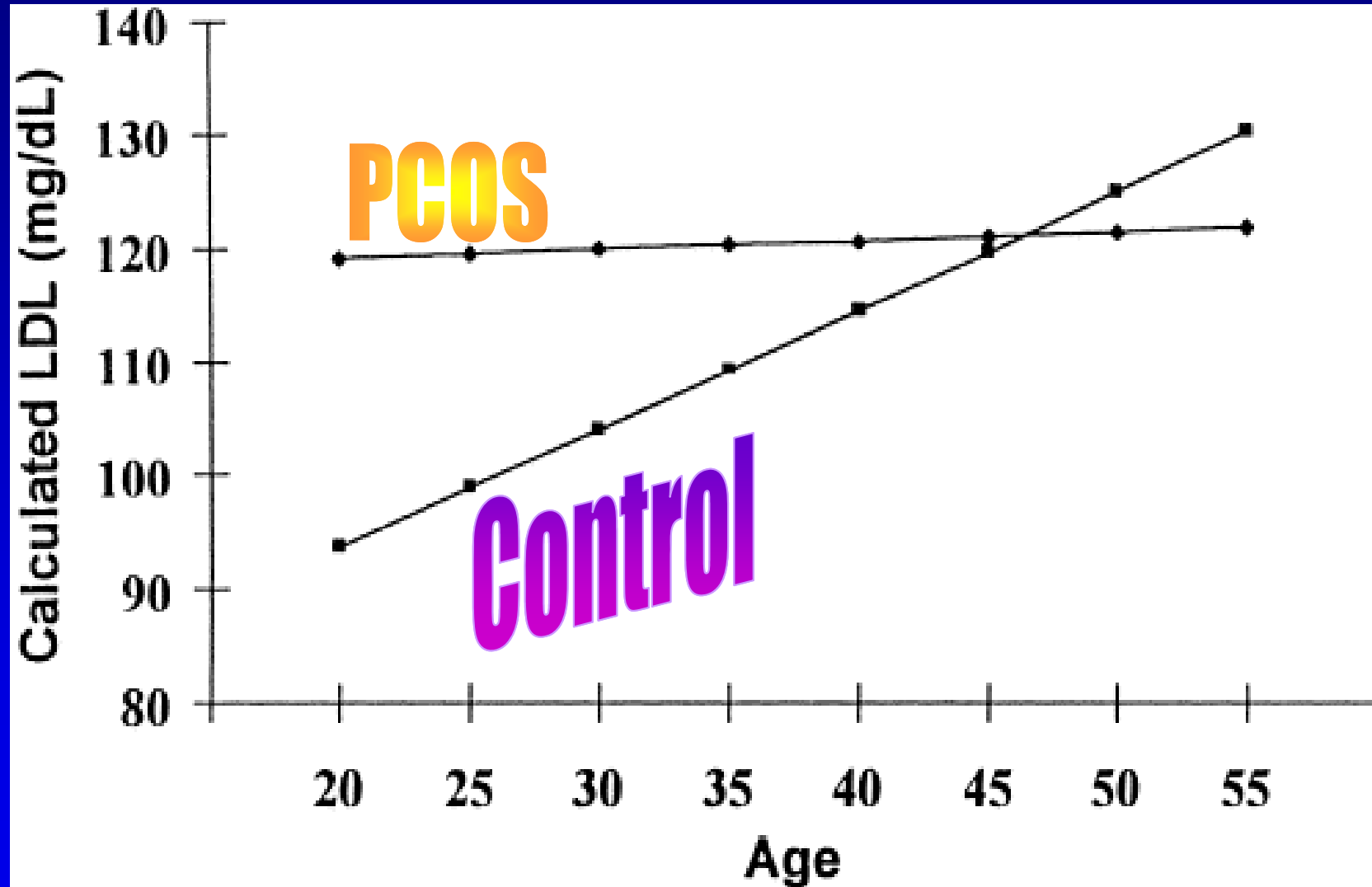
Ehrmann et al. JCEM 2006

# Elevated LDL in Younger Women with PCOS

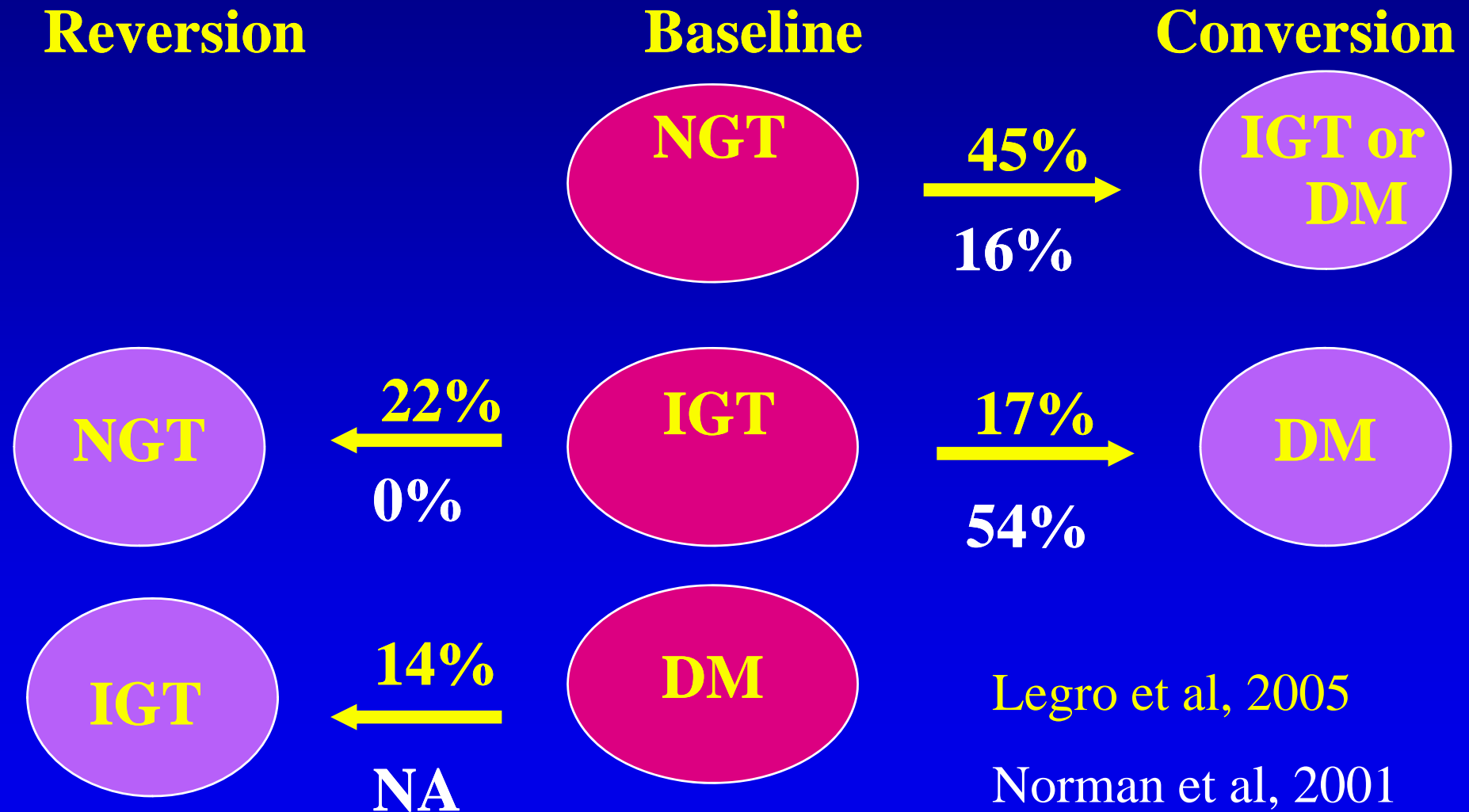


- Talbott EO et al, J Clin Epidemiol, 1998

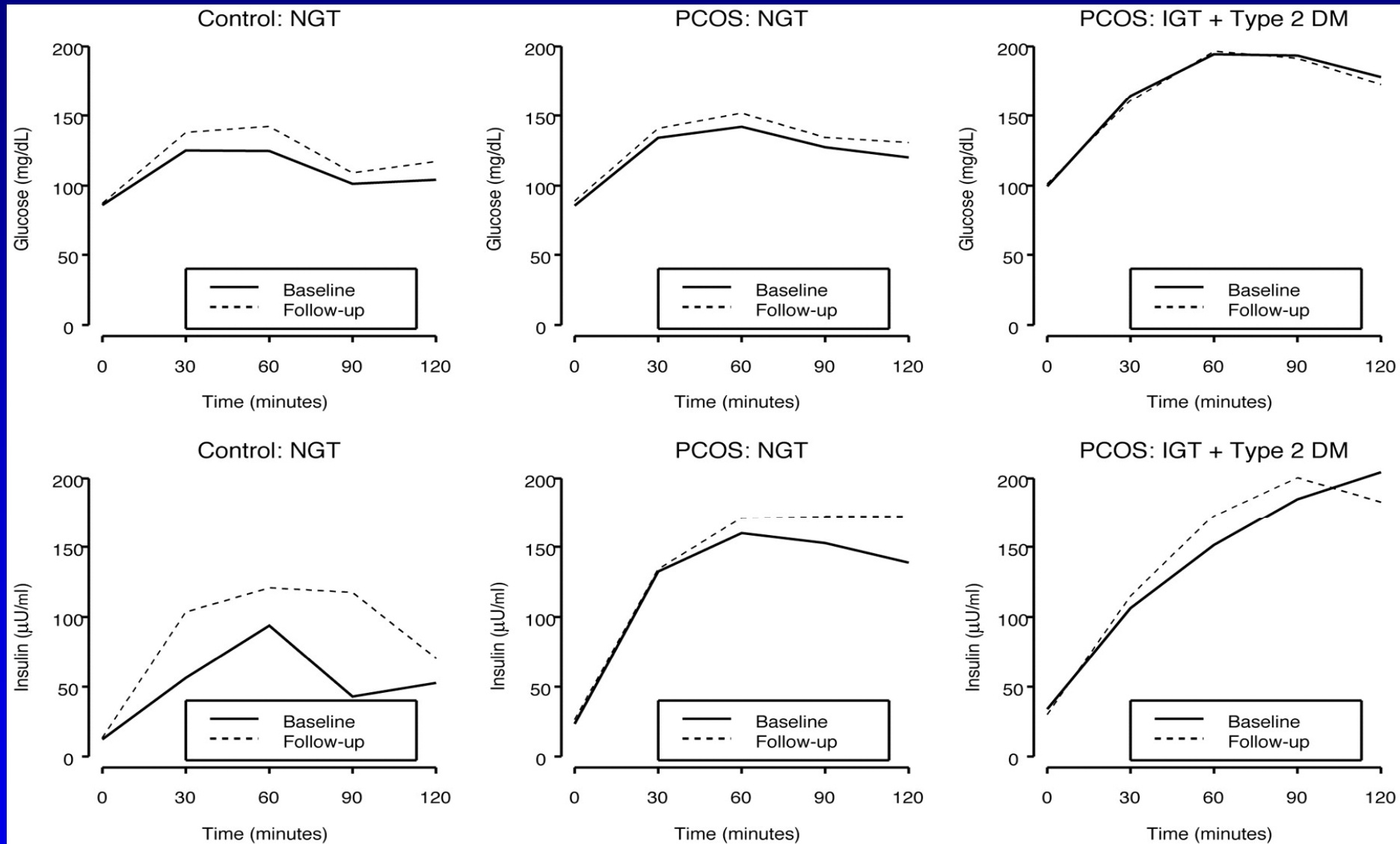
# Effect of Age on LDL-C



# Effect of Time on Glucose Tolerance in PCOS (Combined N =138)



# Glucose and insulin levels during a 2-h OGTT in control women and women with PCOS at baseline and follow-up



Legro, R. S. et al. J Clin Endocrinol Metab 2005;90:3236-3242



# Summary- Age and PCOS Phenotype

- **Reproductive Abnormalities Lessen and may completely normalize**
  - ◆ Hyperandrogenemia
  - ◆ Oligomenorrhea
  - ◆ Polycystic ovary size and morphology
- **Metabolic Abnormalities**
  - ◆ Do they plateau?

# Talk Outline

- 1. What happens to the phenotype of women with PCOS as they age?
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- 4. Where should research go in this area?

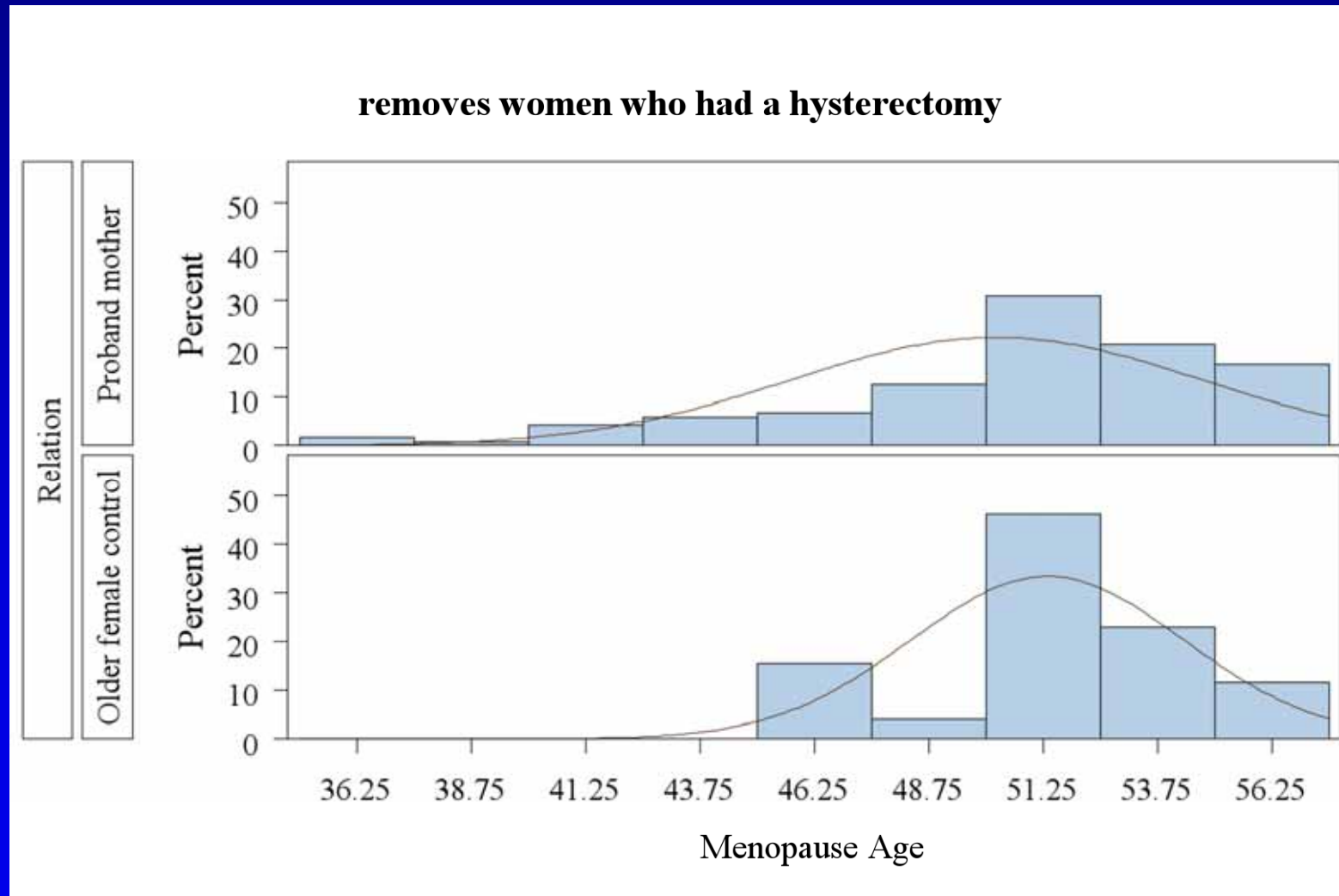
# Age of Menopause: Indicator of Health Risks

- **Early Menopause**
  - ◆ Increased risk of cardiovascular disease
  - ◆ Increased risk osteoporosis
- **Late Menopause**
  - ◆ Increased risk of breast cancer

# Reproductive Milestones in PCOS Families-Hershey

Relation	N	Mean(yr)	Std Dev(yr)
<b>Age of Menarche</b>			
PCOS Proband	601	12.5	2.1
PCOS Mother	374	12.6	1.6
Control Mother (PM)	37	12.9	
<b>Age of Menopause (No Hysterectomy)</b>			
PCOS Mother	120	50.2	4.5
Control Mother (PM)	26	51.3	3.0

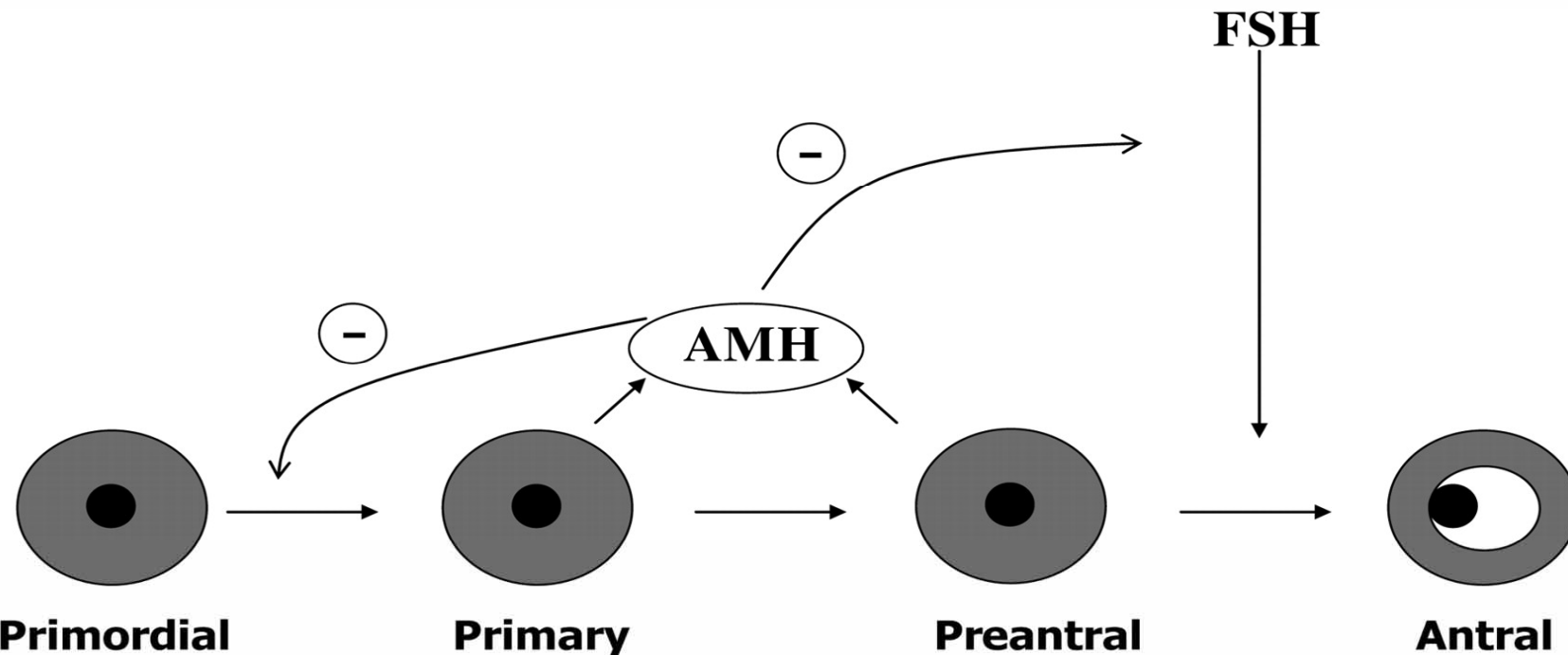
# Distribution of Age of Menopause in PCOS Mothers



# In women, Anti Mullerian Hormone (AMH) expression can first be observed in primary follicles, and is strongest in pre-antral and small antral follicles

## Possible actions of AMH in the ovary

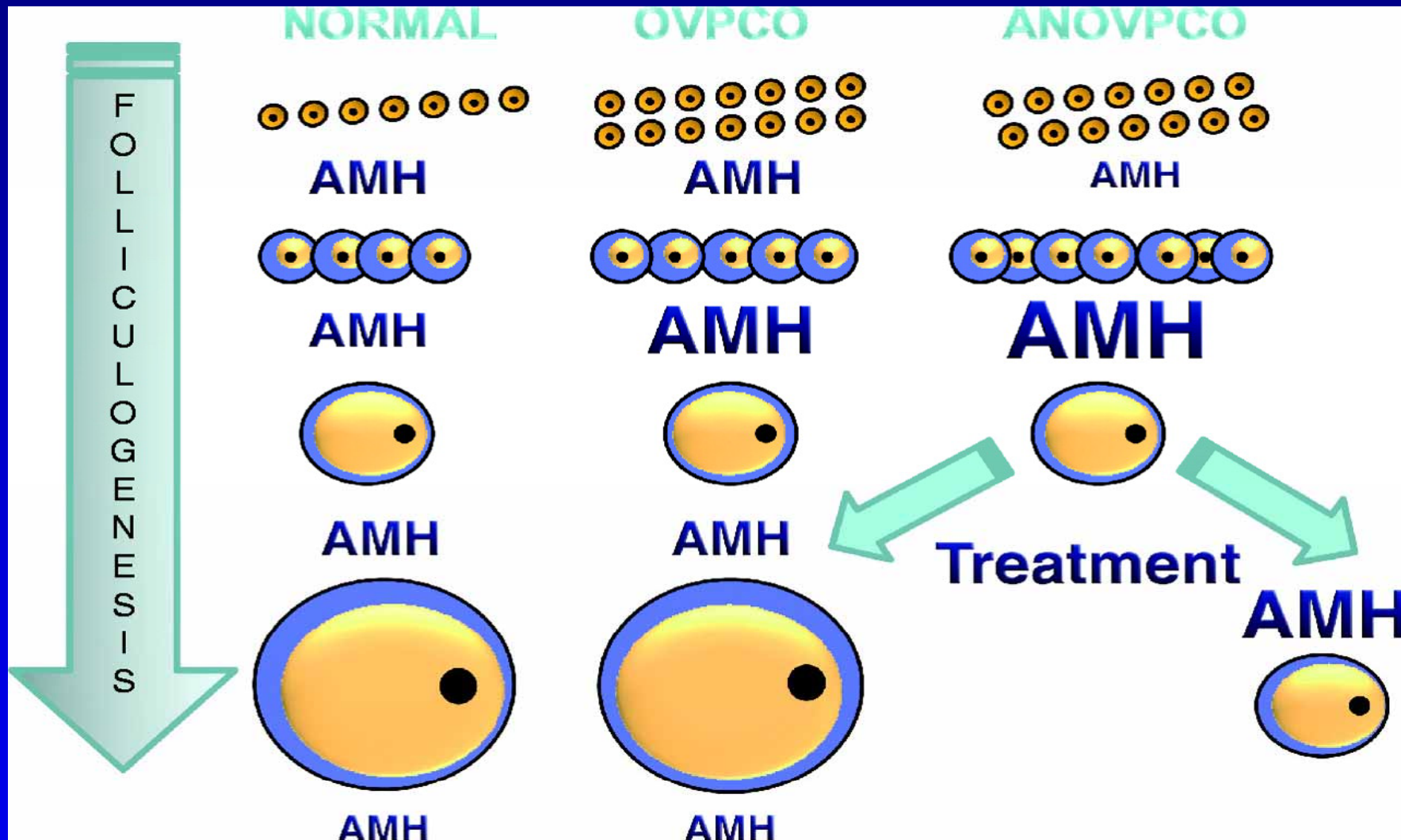
- ✓ Inhibition of follicular activation and growth
- ✓ Inhibition of FSH stimulated growth
- ✓ Inhibition of GC growth
- ✓ Inhibition of aromatase







**Hypothesis of the effects of AMH on follicles in polycystic ovaries: both ovulatory and anovulatory polycystic ovaries increased the numbers of preantral follicles than normal ovaries and more of these ovaries progress to antral stages in both; however, anovulatory ovaries contain the most follicles**



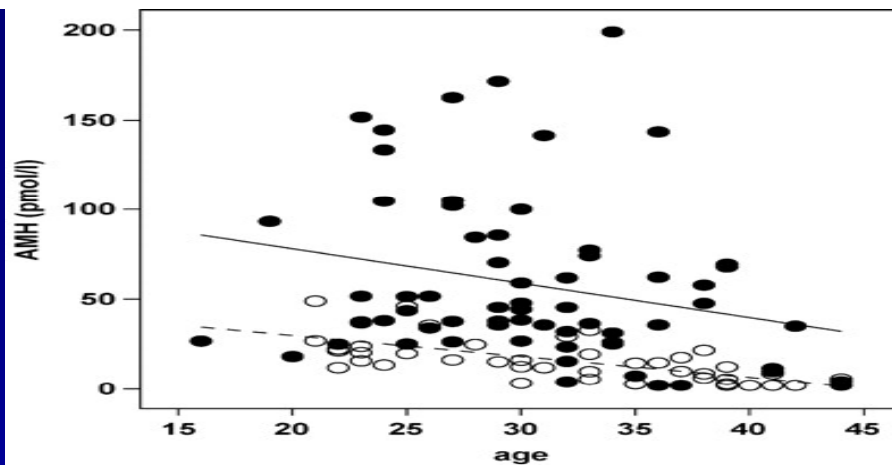
## **Serum anti-Müllerian hormone levels remain high until late reproductive age and decrease during metformin therapy in women with polycystic ovary syndrome**

**Terhi Piltonen<sup>1</sup>, Laure Morin-Papunen<sup>1</sup>, Riitta Koivunen<sup>1</sup>, Antti Perheentupa<sup>2</sup>,  
Aimo Ruokonen<sup>3</sup> and Juha S.Tapanainen<sup>1,4</sup>**

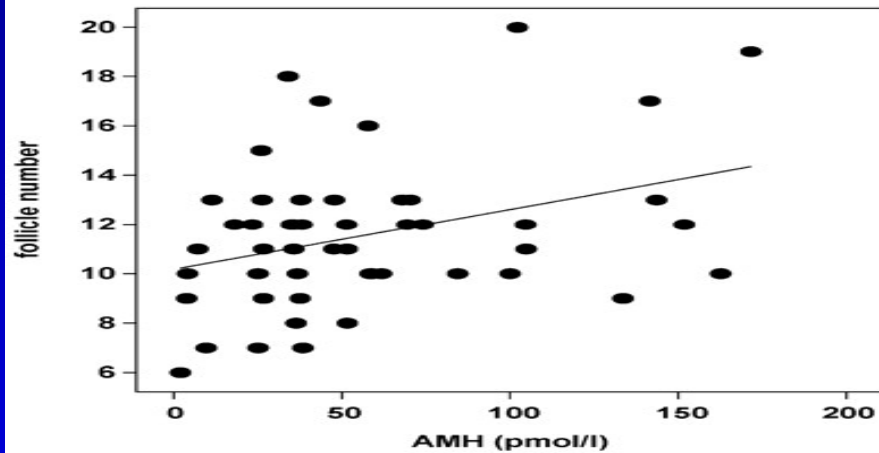
<sup>1</sup>Departments of Obstetrics and Gynecology and <sup>3</sup>Clinical Chemistry, Oulu University Hospital, Oulu and <sup>2</sup>Departments of Obstetrics and Gynecology and Physiology, Turku University Hospital, Turku, Finland

**CONCLUSION:** Serum AMH levels decreased with age both in healthy women and in women with PCOS, although they were always 2- to 3-fold higher and remained elevated until 40 years of age in PCOS subjects.

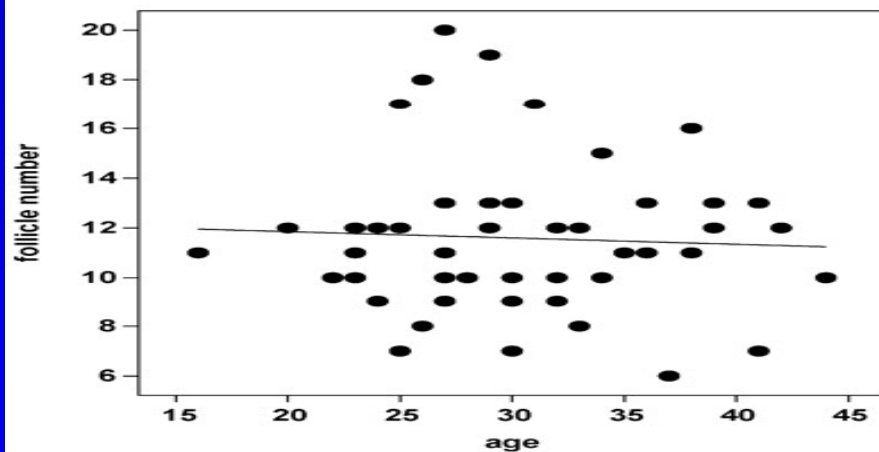
**Correlation between AMH and age in control women 21–44 years (open circles, n=44) and in women with PCOS aged 16–44 years (filled circles, n=65) and correlations between follicle number, AMH and age in women with PCOS.**



CONTR:  $r = -0.691$   $p = <0.001$   
PCOS:  $r = -0.300$   $p = 0.014$



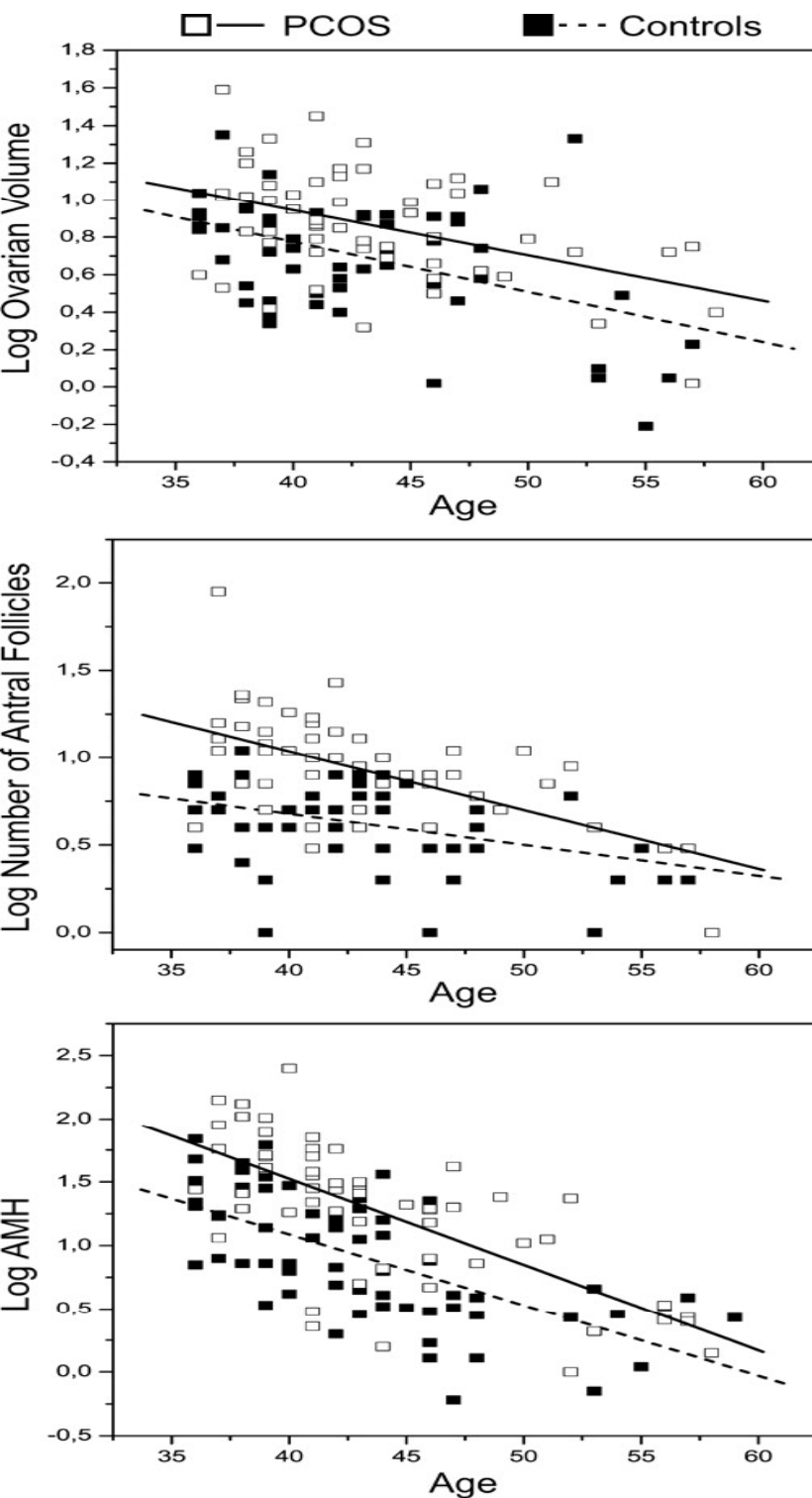
PCOS:  $r = 0.352$   $p = 0.012$



PCOS:  $r = -0.052$   $p = 0.723$

Piltonen T et al. Hum. Reprod. 2005;20:1820-1826

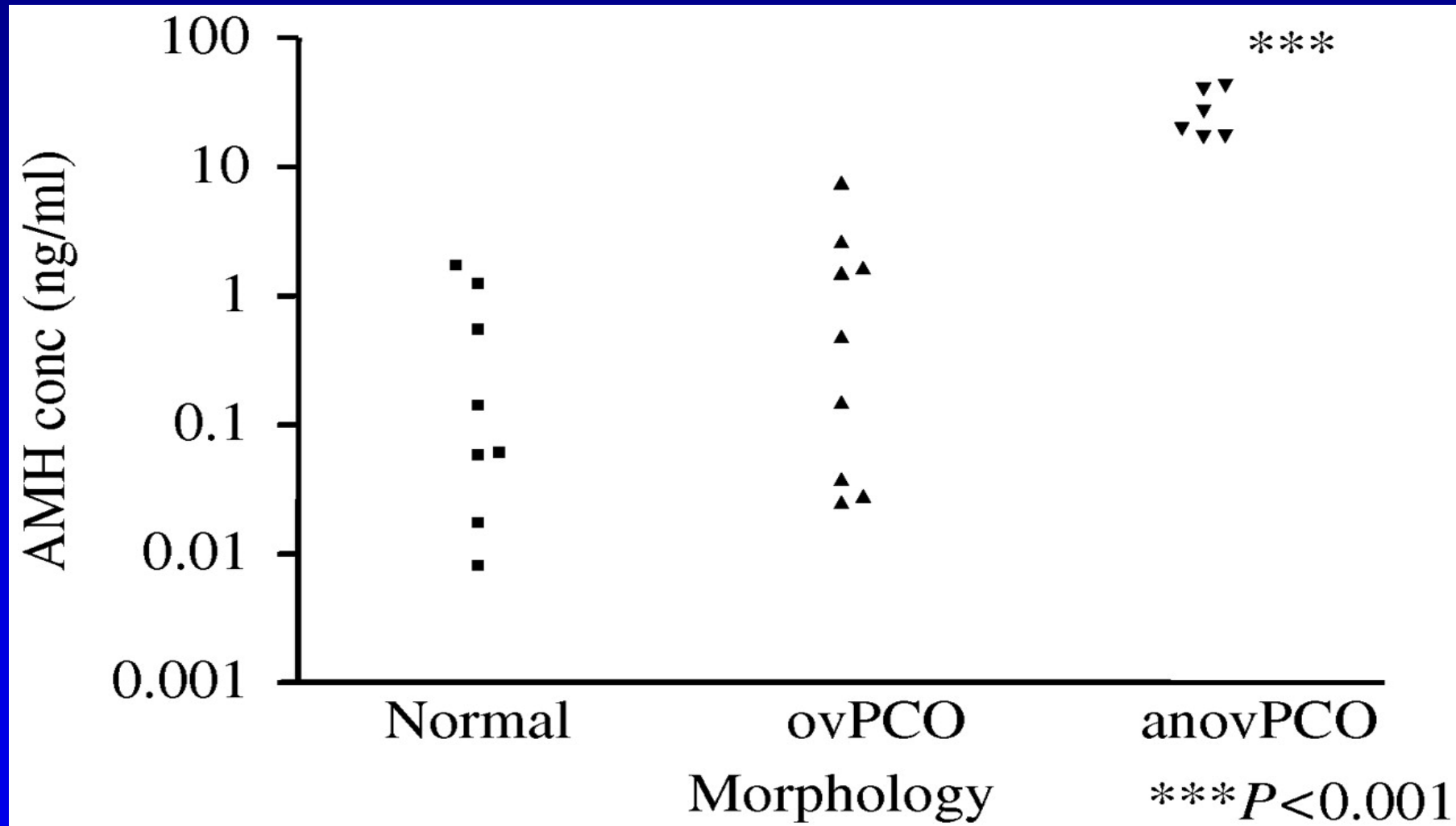
# Increased Ovarian Reserve among Women with PCOS



The relationship between ovarian volume, number of antral follicles, AMH serum concentrations, PCOS status and age in 57 pre- and post-menopausal PCOS patients and 64 pre- and post-menopausal controls without hormonal treatment.

Hudecova M et al. Hum. Reprod. 2009;24:1176-1183

# Comparison of AMH Production from Cultured Granulosa Cells from Follicles





# Is polycystic ovary syndrome an exception for reproductive aging?

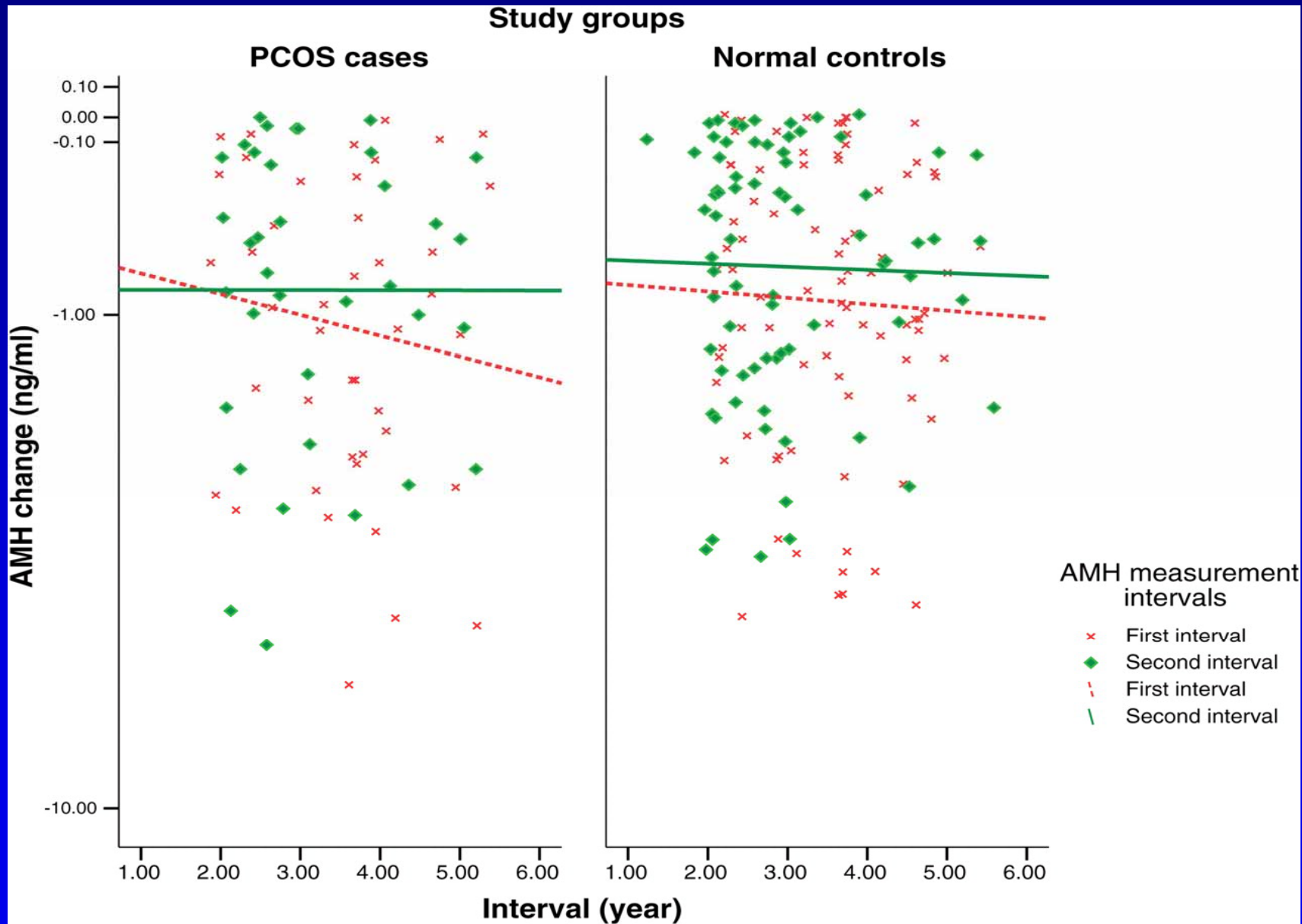
**Fahimeh Ramezani Tehrani<sup>1,\*</sup>, Masoud Solaymani-Dodaran<sup>2,3</sup>,  
Mehdi Hedayati<sup>4</sup>, and Fereidoun Azizi<sup>5</sup>**

<sup>1</sup>Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University (MC), 24 Parvaneh, Yaman Street, Velenjak, PO Box 19395-4763, Tehran 1985717413, Iran <sup>2</sup>Department of Epidemiology, School of Public Health, Iran University of Medical Sciences Tehran, Tehran, Iran <sup>3</sup>Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK <sup>4</sup>Endocrine Research Center, Shaheed Beheshti University (MC), Tehran, Iran <sup>5</sup>Research Institute for Endocrine Sciences, Shahid Beheshti University (MC), Tehran, Iran

\*Correspondence address. Tel: +98 21 22409309; Fax: +98 21 22402463; E-mail: ramezani@endocrine.ac.ir; framezan@post.harvard.edu

**CONCLUSIONS:** The reproductive lifespan of PCOS women extends on average 2 years beyond that of normo-ovulatory women.

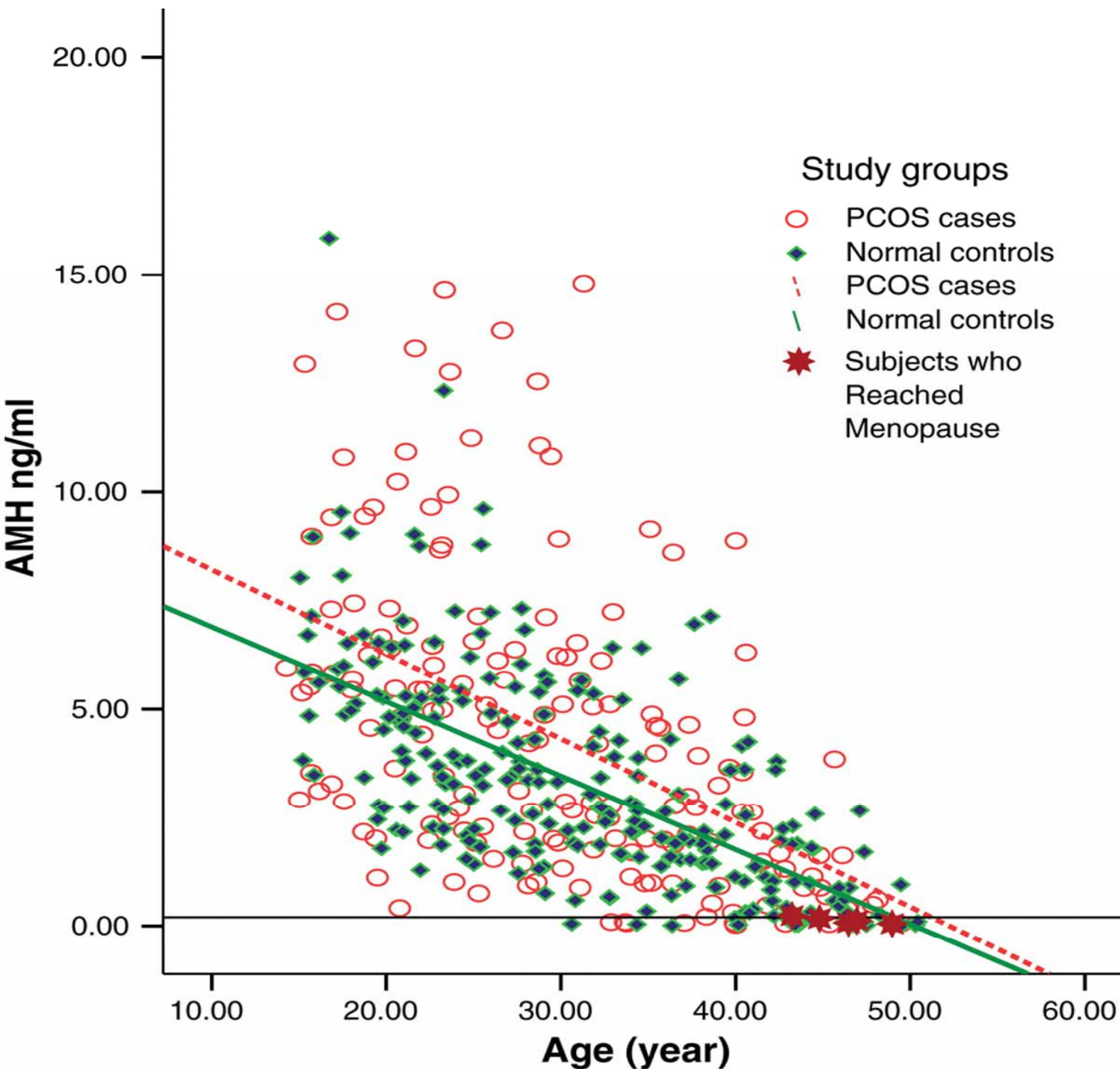
# Change in the AMH levels (value visit 2–value visit 1) in relation to time intervals between visit 1 and visit 2



Ramezani Tehrani F et al.  
Hum. Reprod.  
2010;25:1775-1781

Human  
Reproduction

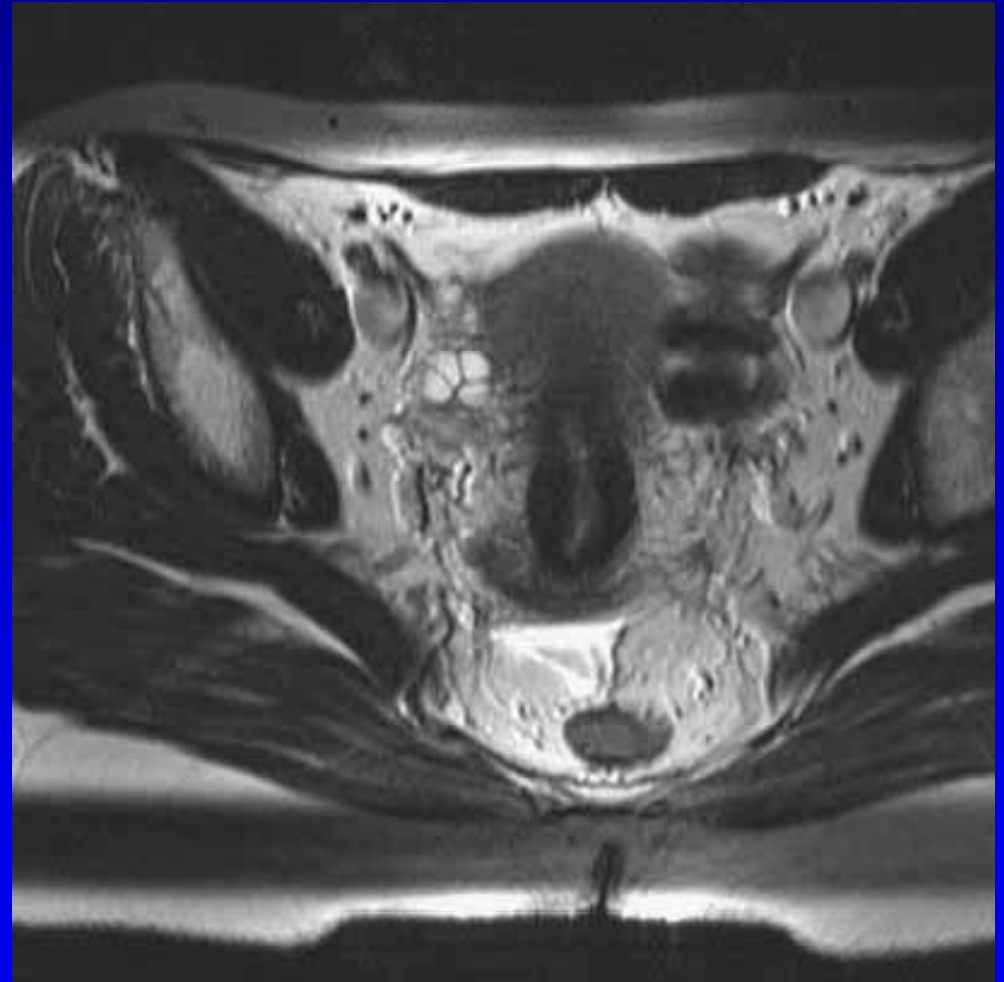
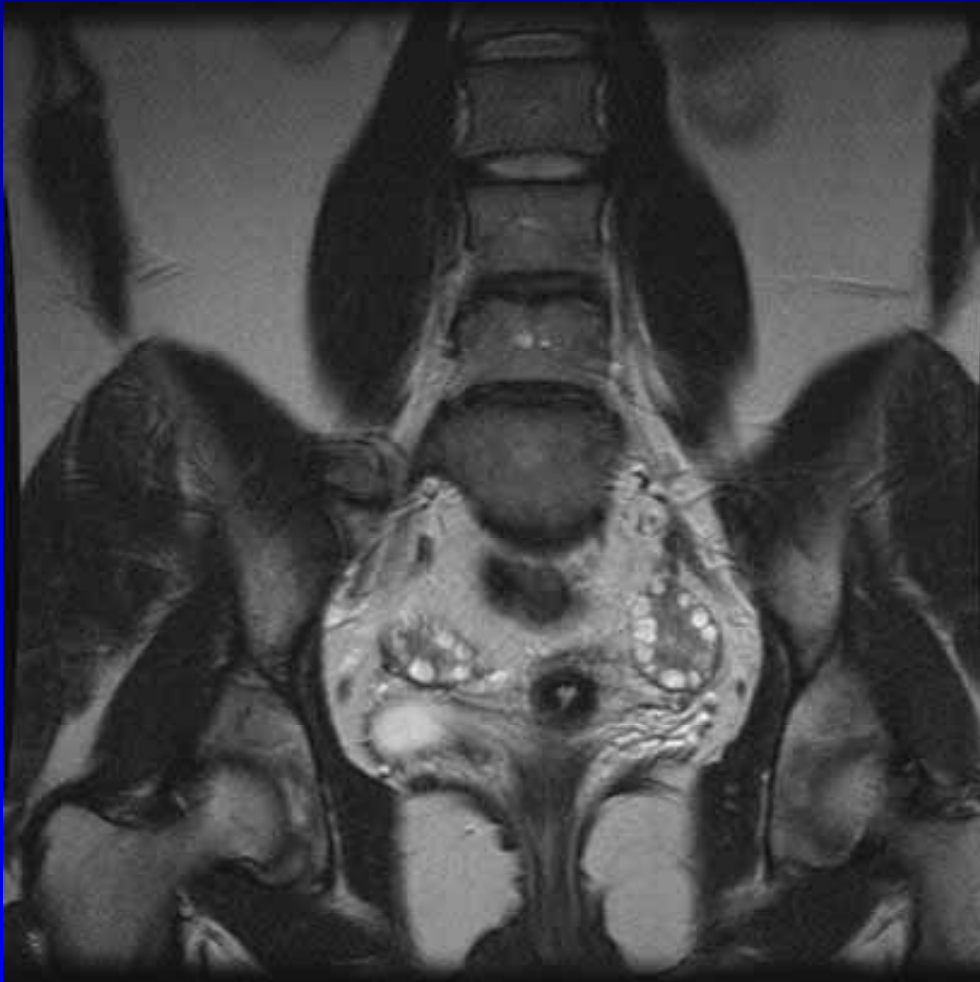




**Serum levels of AMH in relation to age in PCOS cases (dotted line and open circles) and normo-ovulatory controls (solid line and black diamonds).**

Ramezani Tehrani F et al. Hum. Reprod. 2010;25:1775-1781

# MRI: Polycystic vs Normal Ovaries



# Increased Density of Follicles in PCOS

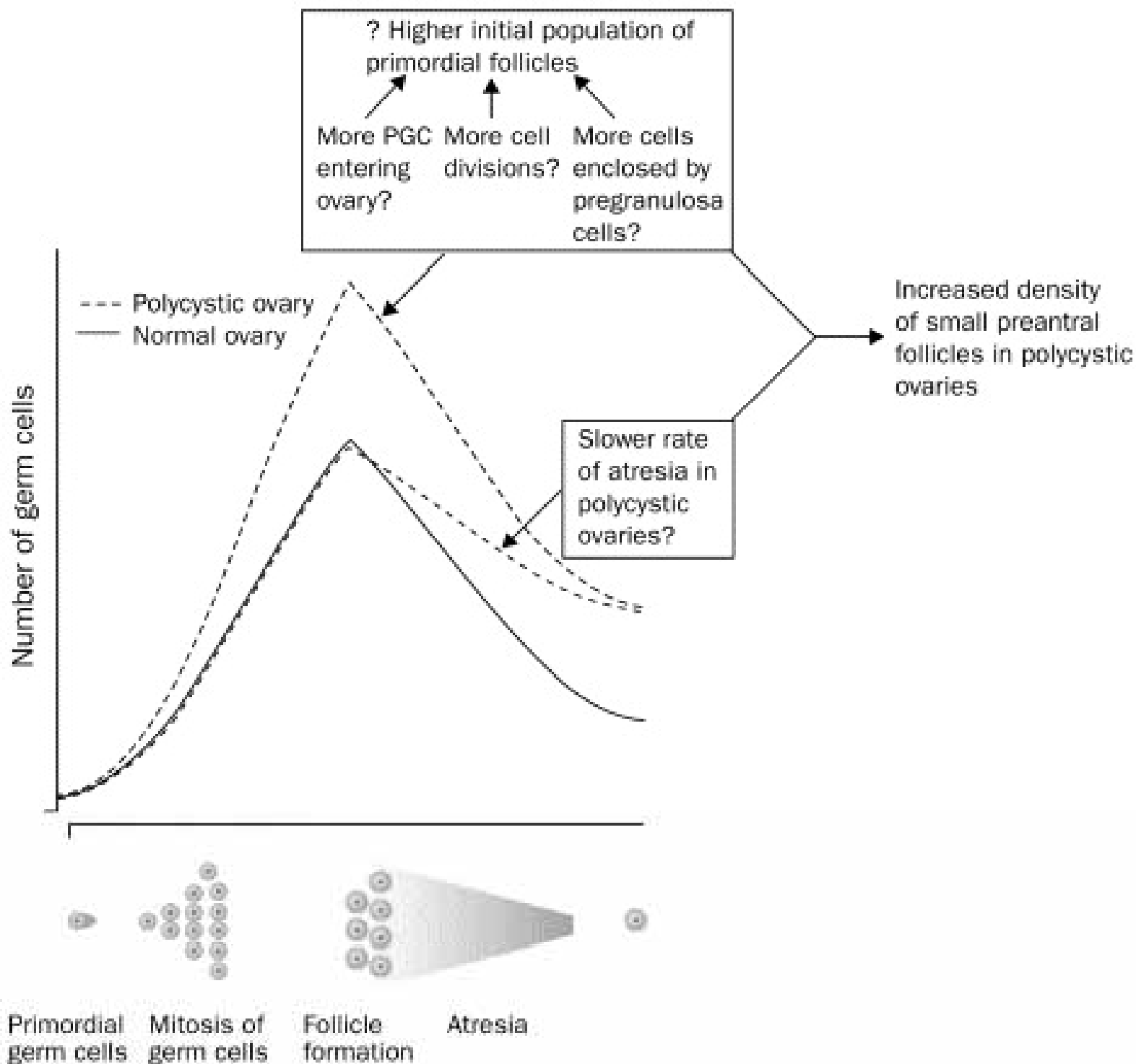
QuickTime™ and a  
decompressor  
are needed to see this picture.

Webber et al,  
Lancet, 2003

**Increase in the percentage of early growing (primary) follicles and  
a reciprocal decrease in the proportion of primordial follicles  
compared with normal ovaries**

QuickTime™ and a  
decompressor  
are needed to see this picture.

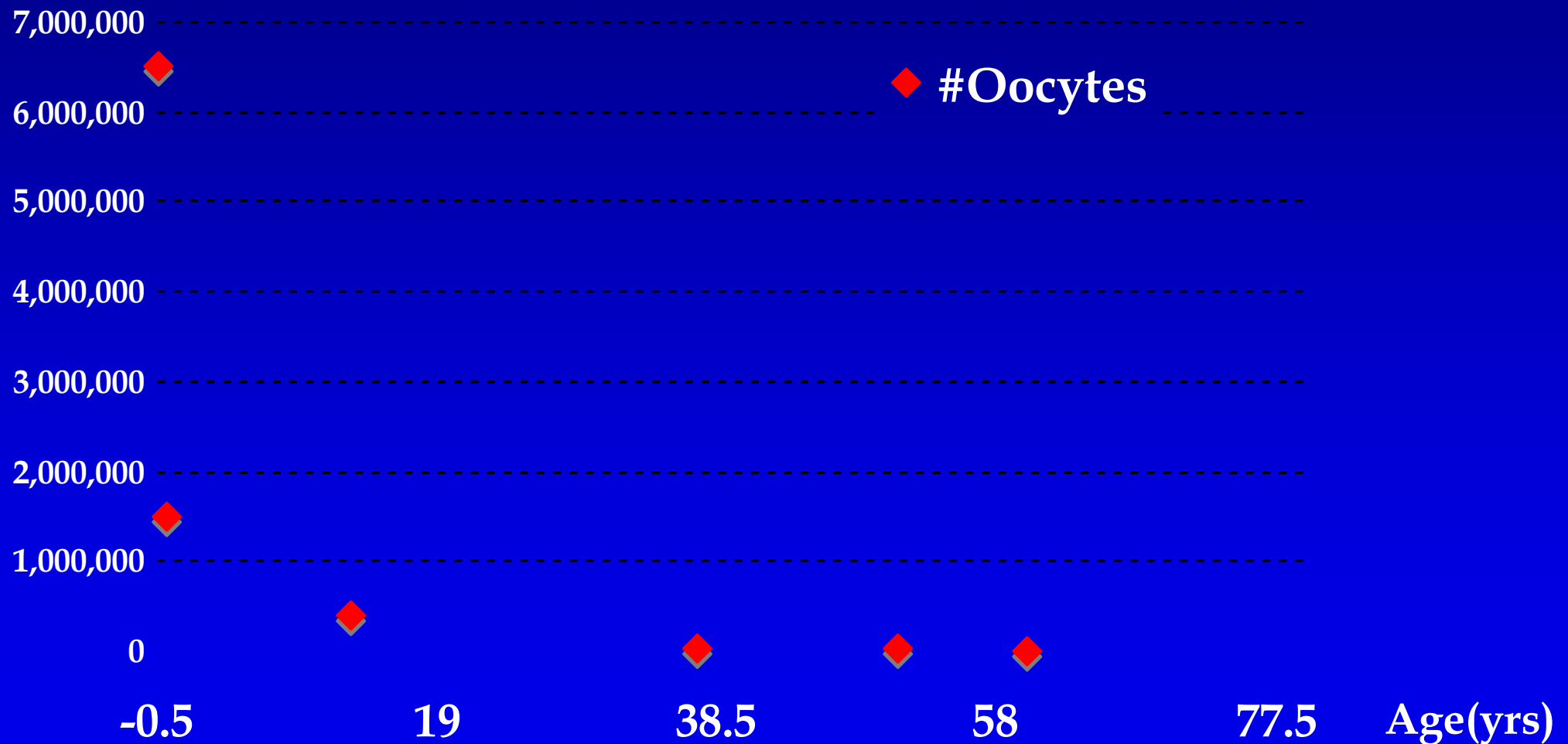
Webber et  
al, Lancet,  
2003



The increased density of small preantral follicles in polycystic ovaries could result from increased population of the fetal ovary by germ cells, or from decreased rate of loss of oocytes during late gestation, childhood, and puberty

Webber et al,  
Lancet, 2003

# Loss of Oocytes with Age



BIOLOGY OF REPRODUCTION 80, 2–12 (2009)

Published online before print 27 August 2008.

DOI 10.1095/biolreprod.108.069088

## Minireview

# The Current Status of Evidence for and Against Postnatal Oogenesis in Mammals: A Case of Ovarian Optimism Versus Pessimism?<sup>1</sup>

Jonathan L. Tilly,<sup>2</sup> Yuichi Niikura, and Bo R. Rueda

*Vincent Center for Reproductive Biology, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital/  
Harvard Medical School, Boston, Massachusetts 02114*



# Summary-Prolonged Ovarian Function

- **There is evidence of increased ovarian reserve in women with PCOS compared to age matched control**
- **There are little data on long term fecundity and age of menopause in women with PCOS**

# Talk Outline

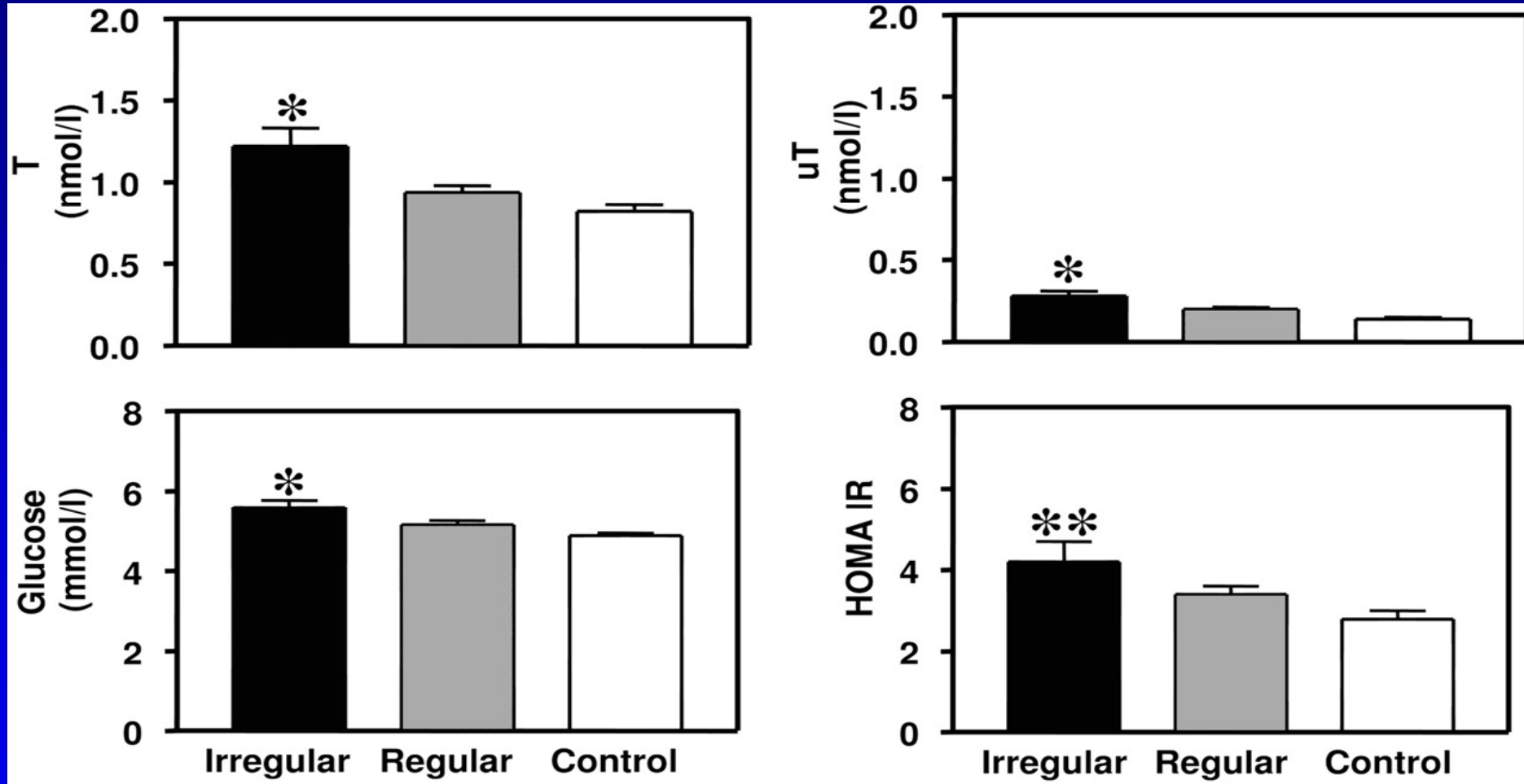
- 1. What happens to the phenotype of women with PCOS as they age?
- 2. Is there prolonged ovarian function in women with PCOS?
- 3. Is there a menopausal PCOS Phenotype?
- 4. Where should research go in this area?

# **Polycystic Ovaries and CVD- United Kingdom**

- **Retrospective Case Control Study**
- **Identified 786 women with polycystic ovaries 1930-79, 30 yrs of Follow-up**
- **Most with some documented clinical ovarian dysfunction**
- **Compared death rates with national mortality rates**

Pierpoint T et al, J Clin Epidemiol, 1998

# Mothers of women with PCOS with history of irregular menses have elevated T and Insulin Resistance



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

*Menopause*. 2007 ; 14(2): 284–292. doi:10.1097/GME.0b013e31802cc7ab.

## **Searching for Polycystic Ovary Syndrome in Postmenopausal Women: Evidence for a Dose-Effects Association with Prevalent Cardiovascular Disease**

**Andrew J. Krentz, M.D. [British Heart Foundation International Research Fellow], Denise von Mühlen, M.D., Ph.D. [Assistant Adjunct Professor], and Elizabeth Barrett-Connor, M.D. [Chief Professor]**

*Division of Epidemiology, Dept of Family & Preventive Medicine, University of California San Diego, La Jolla, California, USA.*

QuickTime™ and a  
decompressor  
are needed to see this picture.

# Rancho Bernardo Postmenopausal PCOS Criteria ( $\geq 3$ )

- (1) a history of irregular menses
- (2) hirsutism, *or* current biochemical evidence of relative hyperandrogenism (i.e., values in the highest quintile for total testosterone or bioavailable testosterone, or the lowest quintile for SHBG)
- (3) a history of personal infertility *or* inability to carry pregnancies to term
- (4) central obesity defined as a waist circumference  $>88$  cm
- (5) insulin resistance, defined either as a HOMA-IR value in the top quintile for the cohort, or, in women for whom insulin levels were not available, a fasting plasma glucose concentration  $\geq 6.1$ .

# Prevalence of PCOS in Rancho Bernardo Cohort

- **N = 713 postmenopausal women**
- **9.3% with  $\geq 3$  of the criteria in whole cohort**
- **5.8% among those women without diabetes**

# Prevalence of individual and composite features of a putative PCOS phenotype among affected

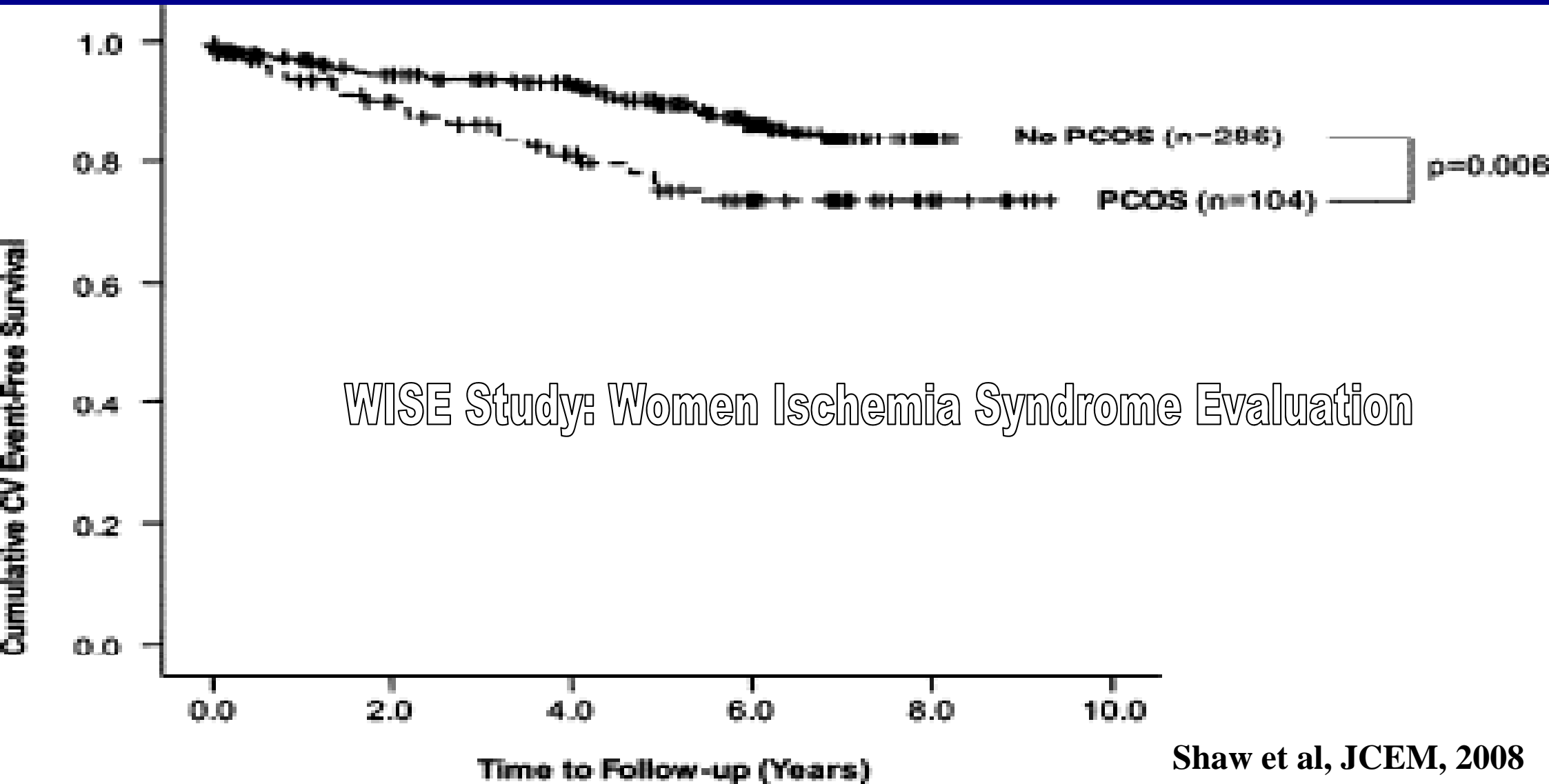
	PCOS	No PCOS	P value
Menstrual irregularity	13.6	3.6	<0.001
Biochemical hyperandrogenism	95.5	34.2	<0.001
Infertility or miscarriage	31.8	3.9	<0.001
Central obesity	68.2	12.8	<0.001
Biochemical insulin resistance	75.6	18.4	<0.001



# Binary logistic regression of CVD and CHD in non-diabetic non-oophorectomized women (N = 610)

	Estimated Odds Ratio	95% Confidence Interval	P
<b>Cardiovascular disease</b>			
Age	1.06	1.021-1.093	<0.01
PCOS	1.36	1.052-1.762	0.02
<b>Coronary heart disease</b>			
Age	1.05	1.012-1.090	<0.01
PCOS	1.36	1.030-1.796	0.03

# Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival



# Determination of Menopausal PCOS-WISE Study

- **History of irregular menses during reproductive life**
  - ◆ Since menses onset, before menopause (excluding the perimenopausal years) did they had periods that occurred on a monthly basis
- **Current hyperandrogenemia in the upper quartile**
  - ◆ Testosterone (>30.9 ng/dL (1.07 nmol/L))
  - ◆ Free Testosterone (>4.5 pg/mL)
  - ◆ Androstenedione (701 pg/mL)

**Of 104 women with “PCOS”  
(from 336 postmenopausal  
women with ovaries)**

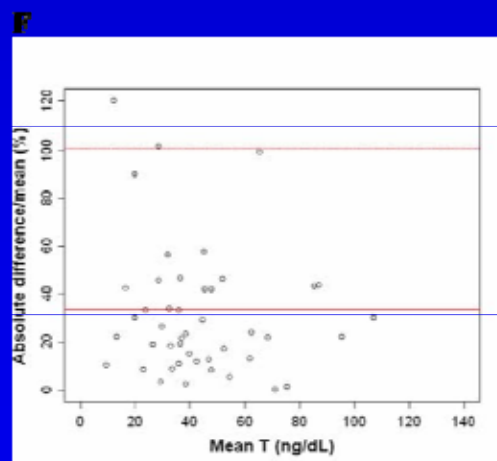
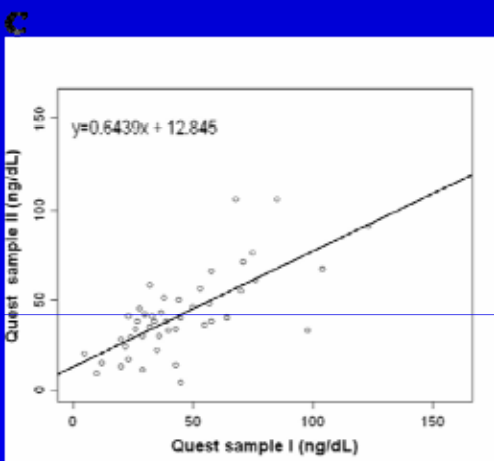
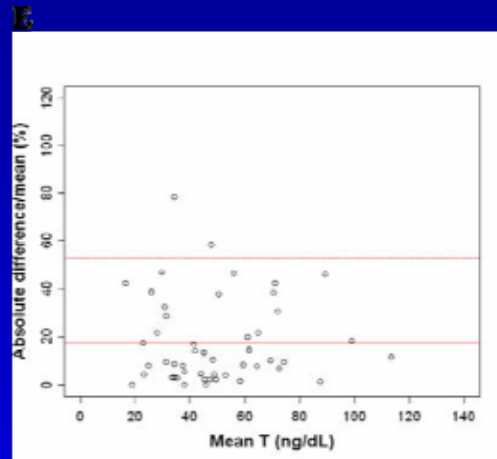
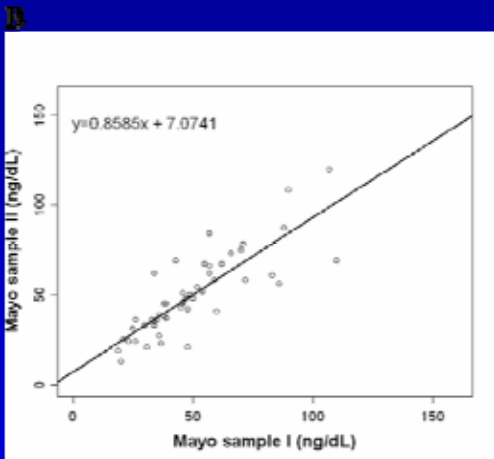
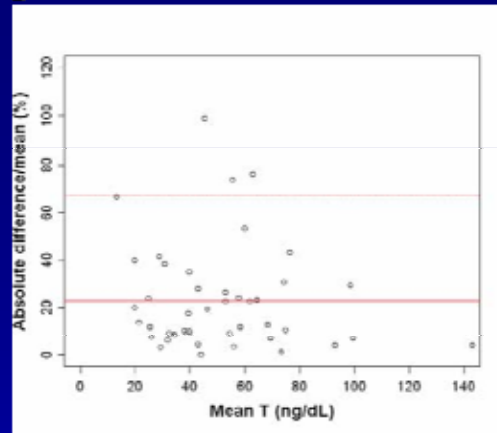
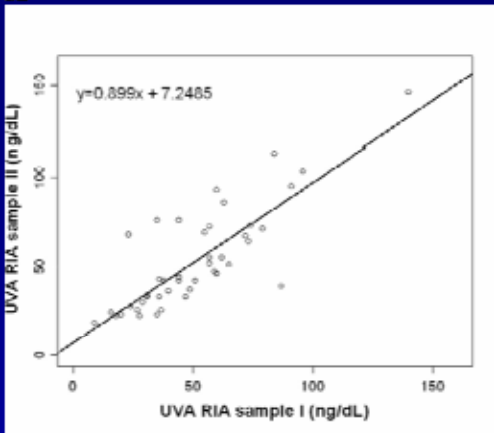
**20 with history of PCOS, 85%  
reported irregular menses, 82% with  
current T and Free T in the upper  
quartile**

# Intra Assay Variability (LC/MS and RIA)

## Bland Altman Plots of absolute percentage differences in serum T levels between the duplicate samples

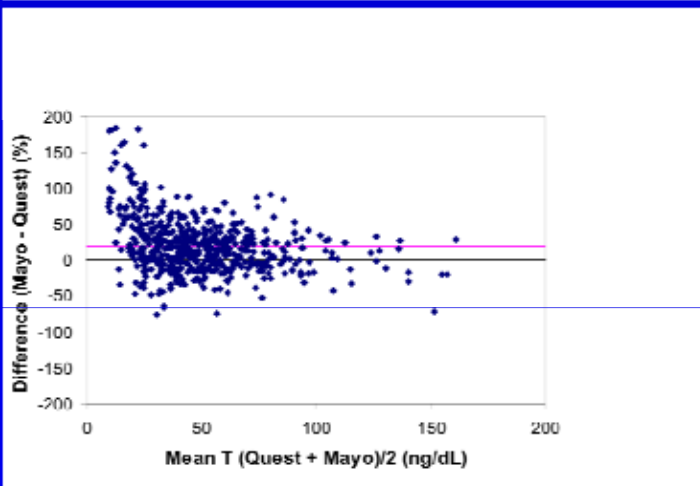
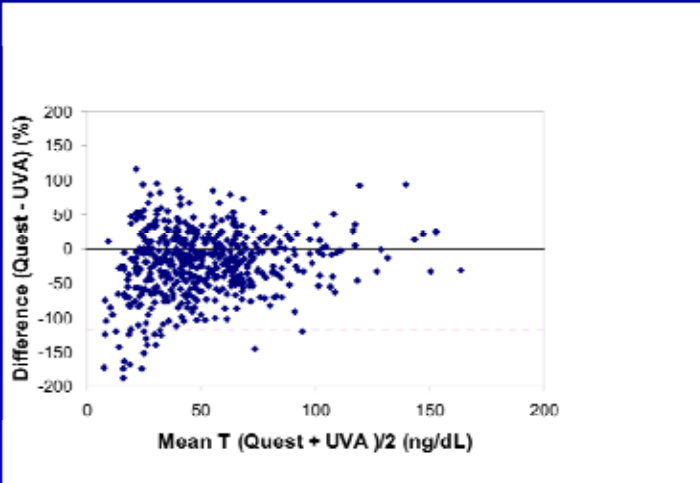
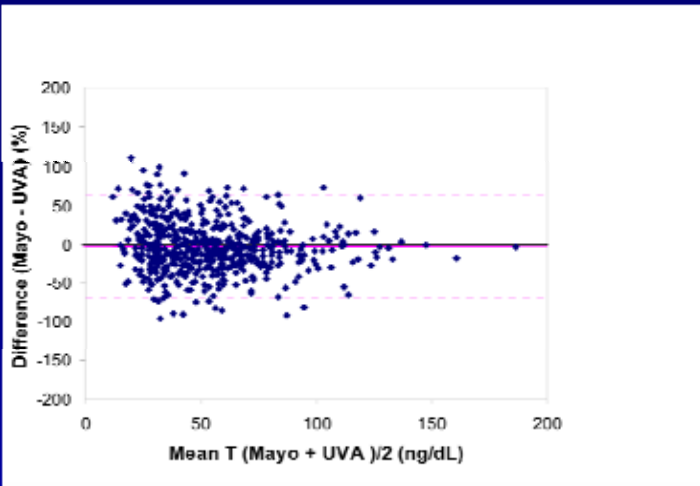
The bold solid line represents 0%, the light solid line the mean percentage difference between the methods, and the dashed line 2 SD of the absolute mean percentage difference.

Legro et al, JCEM,  
In press



# Testosterone Inter Assay Variability (LC/MS and RIA)

Bland Altman plots of percentage differences in serum testosterone levels



The bold solid line represents 0%, the light solid line the mean percentage difference between the methods, and the dashed lines 2 SD of the mean percentage difference.

Legro et al, JCEM, In press

# Coefficient variation of serum testosterone measurement

	All	%	T ≤ 50 ng/d	%	T > 50ng/dL	%
<b>Intra-Assay</b>						
UVA (RIA)	16.3	(11.5 - 21.1)	16.6	(9.3 - 23.9)	16.1	(9.2 - 22.9)
Mayo (LC/MS)	12.2	(8.6 - 15.8)	11.4	(6.3 - 16.6)	13.4	(8.3 - 18.6)
Quest (LC/MS)	23.8	(16.9 - 30.8)	25.3	(16.4 - 34.2)	20.0	(8.8 - 31.2)
<b>Inter-Assay</b>						
Mayo-UVA	18.3	(17.1 - 19.6)	20.6	(18.7 - 22.5)	16.2	(14.5 - 17.8)
Quest-UVA	28.2	(26.1 - 30.3)	32.8	(29.6 - 36.1)	22.4	(20.0 - 24.7)
Quest-Mayo	21.9	(20.2 - 23.6)	26.2	(23.5 - 28.8)	15.9	(14.3 - 17.5)

# Summary- Menopausal PCOS Phenotypes

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- **There is a plethora of PCOS menopausal phenotypes**
- **None of these have been validated in prospective studies**
- **There are no assays that are precise in menopausal testosterone levels**



# Talk Outline

- 1. What happens to the phenotype of women with PCOS as they age?
- 2. Is there prolonged ovarian function in women with PCOS?
- 3. Is there a menopausal PCOS Phenotype?
- 4. **Where should research go in this area?**

**AVOID: Post Hoc Determination  
of PCOS Phenotype in Existing  
Cohorts or Studies**

**Subject to selection and publication  
bias**

# Research Agenda I

- **Long Term Multi-Center Cohort Studies**
  - ◆ Nurse's Health Study
  - ◆ SWAN (Study of Women's Health Across the Nation)
- **Establish**
  - ◆ The menopausal phenotype
  - ◆ Cardiovascular event determination
  - ◆ Cancer
  - ◆ Other morbidity/mortality

# Research Agenda II

- **Utilize Genome Wide Association Studies to identify new genes/pathways involved in ovarian function**
  - ◆ **GWAS of genes related to age of menopause**
  - ◆ **GWAS of PCOS Genes**

# Age at Menopause

- **Complex genetic trait**
- **Heritability – Wide range 31-87%**
  - ◆ **Twin, Sib/sib, mother/daughter studies**
- **Environment**
  - ◆ **Smoking**
  - ◆ **Chemotherapy/Radiation, etc.**

# **A large-scale candidate gene association study of age at menarche and age at natural menopause**

**Chunyan He · Peter Kraft · Daniel I. Chasman · Julie E. Buring · Constance Chen · Susan E. Hankinson · Guillaume Paré · Stephen Chanock · Paul M. Ridker · David J. Hunter**

A total of 18,862 genotyped and imputed single nucleotide polymorphisms (SNPs) in 278 genes were assessed for their associations with these two traits among a total of 24,341 women from the Nurses' Health Study (NHS, N = 2,287) and the Women's Genome Health Study (WGHS, N = 22,054).

# Genes Associated with Age at Natural Menopause

<b>Biologic Pathway or phenotype</b>	<b>Unadjusted P value of most significant SNP</b>	<b>Associated Gene</b>	<b>Observed Number of Significant Genes</b>
Steroid-hormone metabolism and biosynthesis	0.000062	(LHCGR)	5
IGF pathway	0.00018	(IGF1)	2
TGF- $\beta$ superfamily and signaling pathway	0.0010	(SMAD7)	2
Obesity and obesity-related phenotypes	0.00041	(EIF2B4)	3
Polycystic ovary syndrome	0.000010	(NBN)	1

# **Nibrin (NBN)**

- **Nibrin is a protein associated with the repair of double strand breaks(DSBs) which pose serious damage to a genome.**
- **a 754 amino acid protein**
- **Located on Chr. 8**



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