

PCOS: Does it exist and how should it be diagnosed?

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Polycystic ovaries do exist

- Included in the initial description by Stein and Leventhal in 1935
- But are also present in the ultrasound scans of as many as 23 % of healthy women!!!
 - ◆ Polson et al. 1988

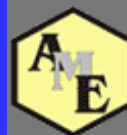


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Polycystic ovary syndrome **S** do
also exist...

■ The problem is that
there are too
many!!!!



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What is PCOS?

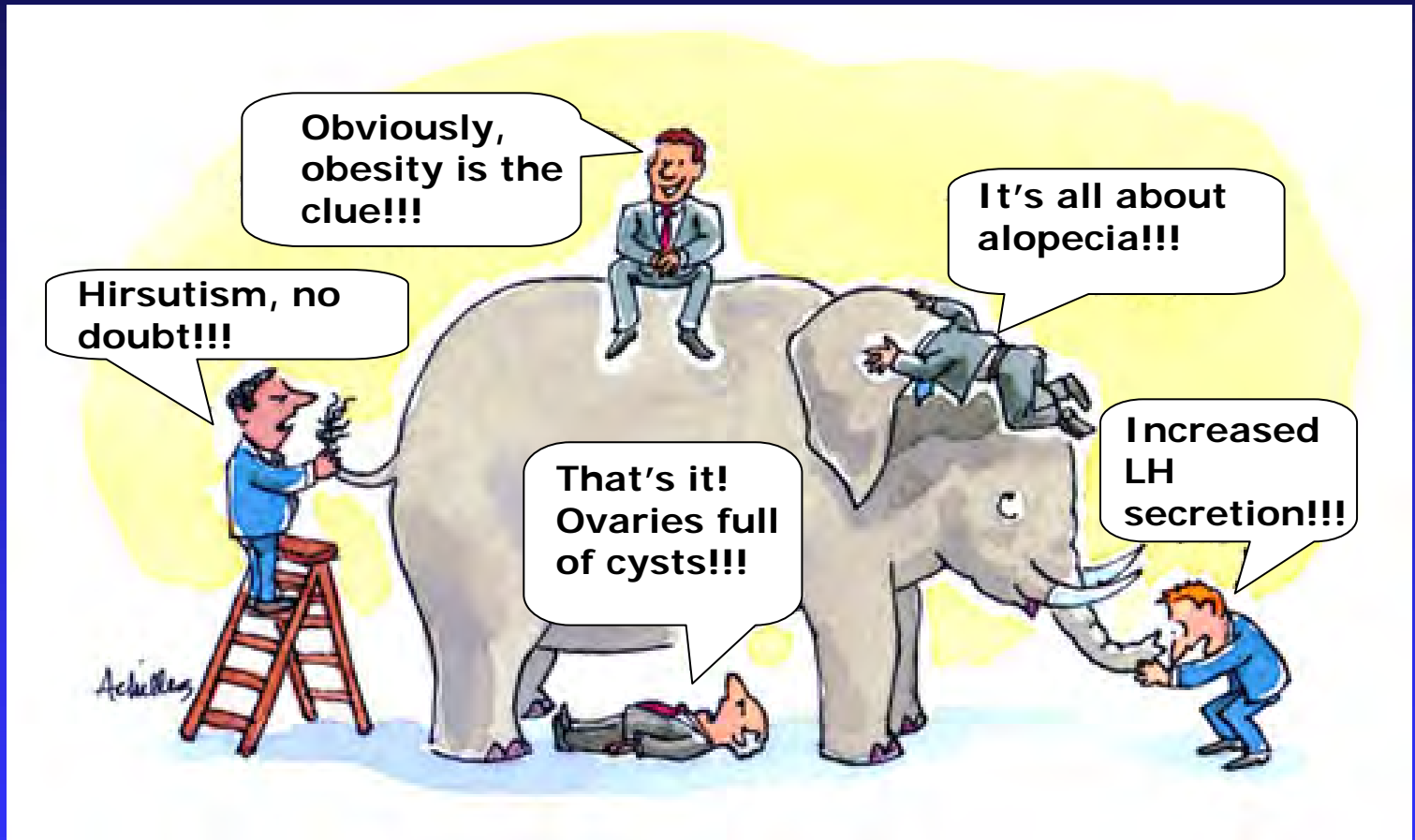
- Definition of syndrome (Oxford's dictionary): **a group of symptoms which consistently occur together**
- Which are the symptoms that predominate in your PCOS patients?
 - ◆ Hirsutism (if you are an Endocrinologist)
 - ◆ Acne or alopecia (if you are a Dermatologist)
 - ◆ Menstrual disturbances, infertility and/or PCO (if you are an ObGyn)
 - ◆ Premature pubarche (if you are a Pediatrician)
 - ◆ Obesity and perhaps abnormal glucose tolerance (if you are a General Practitioner or a Diabetologist)
 - ◆ Increased serum androgen and insulin levels (if you work in a Lab)



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So we usually end like the five blind men describing an elephant!!!



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...and that explains why there are almost as many definitions of PCOS as researchers interested in the disorder



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Definitions of PCOS

NICHD 1990 criteria

Chapter 32 _____
Diagnostic Criteria for
Polycystic Ovary Syndrome:
Towards a Rational Approach

JOANNA K. ZAWADZKI & ANDREA DUNAIF

Table 32.2 Polycystic ovary syndrome (PCO) research diagnostic criteria (NIH April 1990, n = 58). Numbers in parentheses indicate number of participants who listed this criterion in this category.

Definite or probable	Possible
Hyperandrogenemia (37) 64%	Insulin resistance (40) 69%
Exclusion of other etiologies (35) 60%	Perimenarchal onset (36) 62%
Exclusion of CAH (34) 59%	Elevated LH/FSH (32) 55%
Menstrual dysfunction (30) 52%	PCO by ultrasound (30) 52%
Clinical hyperandrogenism (28) 48%	Clinical hyperandrogenism (30) 52%
	Menstrual dysfunction (26) 45%



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Definitions of PCOS

NICHD 1990 criteria

- Even when there was no consensus at all, the NICHD definition was a complete success:
 - ◆ Provided a “common language” to PCOS researchers across the world
 - ◆ Resulted in major advances in our understanding of this prevalent disorder
- ...yet it was not free of caveats



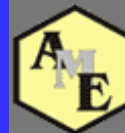
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Definitions of PCOS

NICHD 1990 definition

■ Pros

- ◆ Recognizes the major role of hyperandrogenism and of ovarian dysfunction in PCOS
- ◆ Requires exclusion of “PCOS-like” disorders of known etiology
- ◆ Convenient: no techniques are actually needed for a clinical diagnosis



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Definitions of PCOS

NICHD 1990 criteria

■ Cons:

- ◆ Do not provide a single clue on how to define and apply each individual criterion
- ◆ Do not include ultrasound in the definition, a must for many people (especially for those who are skillful in obtaining the scans)



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Definitions of PCOS

Rotterdam 2003 definition

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)

The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group

Table I. Revised diagnostic criteria of PCOS

1999 criteria (both 1 and 2)

1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism, and exclusion of other aetiologies

Revised 2003 criteria (2 out of 3)

1. Oligo- and/or anovulation
 2. Clinical and/or biochemical signs of hyperandrogenism
 3. Polycystic ovaries
- and exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing's syndrome)

Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation.



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Definitions of PCOS

Rotterdam 2003 definition

- Includes the women diagnosed of PCOS according to NICHD criteria
- Adds two new phenotypes:
 - ◆ Hyperandrogenism and PCO in US
 - ◆ Oligoovulation and PCO in US
- The exclusion of other etiologies is maintained



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Definitions of PCOS

Rotterdam 2003 definition

■ Pros:

- ◆ ObGyn and Commonwealth researchers love them
- ◆ A clear definition of ultrasonographic PCO is provided (at least one ovary > 10 mL or > 12 follicles of 2 – 9 mm in diameter)



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Definitions of PCOS

Rotterdam 2003 definition

■ Cons:

- ◆ Again, no single clue is provided on how to define hyperandrogenism and oligo-ovulation
- ◆ The PCOS phenotype is even more heterogeneous than before
- ◆ Doubts that oligoovulation plus US PCO is actually PCOS



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Definitions of PCOS

Androgen Excess Society 2006 definition

J Clin Endocrinol Metab. First published ahead of print August 29, 2006 as doi:10.1210/jc.2006-0178

AES PCOS Phenotype Task Force Report 8/23/2006

POSITION STATEMENT:

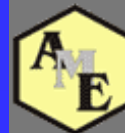
CRITERIA FOR DEFINING POLYCYSTIC OVARY SYNDROME AS A PREDOMINANTLY HYPERANDROGENIC SYNDROME: AN ANDROGEN EXCESS SOCIETY GUIDELINE

Task Force on the Phenotype of the Polycystic Ovary Syndrome
of The Androgen Excess Society

Figure 1
ANDROGEN EXCESS SOCIETY: SUGGESTED CRITERIA FOR
THE DIAGNOSIS OF THE POLYCYSTIC OVARY SYNDROME

- 1- Hirsutism and/or hyperandrogenemia
and
- 2 - Oligo-anovulation and/or polycystic ovaries
and
- 3 - Exclusion of other androgen excess or related disorders*

*Possibly including 21-hydroxylase deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia.



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Definitions of PCOS

Androgen Excess Society 2006 definition

■ Pros:

- ◆ Recognizes PCOS as a predominantly hyperandrogenic syndrome
- ◆ Reduces heterogeneity in the PCOS phenotype by excluding the oligo-ovulation plus US PCO phenotype
- ◆ Still gives some satisfaction to those researchers who perform ultrasonography



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Definitions of PCOS

Androgen Excess Society 2006 definition

■ Cons

- ◆ Once again, no clear definition is provided for hyperandrogenism and oligo-ovulation
- ◆ Does not convince some researchers who prefer Rotterdam criteria



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Definitions of PCOS

Table 5. All possible phenotypes based on the presence or absence of oligo-anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome.

FEATURES	POTENTIAL PHENOTYPES															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligo-anovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	√	√	√	√	√	√										
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√						
AES 2006 criteria	√	√	√	√	√	√	√	√	√							
Escobar 2006	√	√	√	√	√	√	√	√	√		√			√	√	

2014

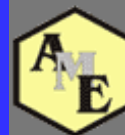
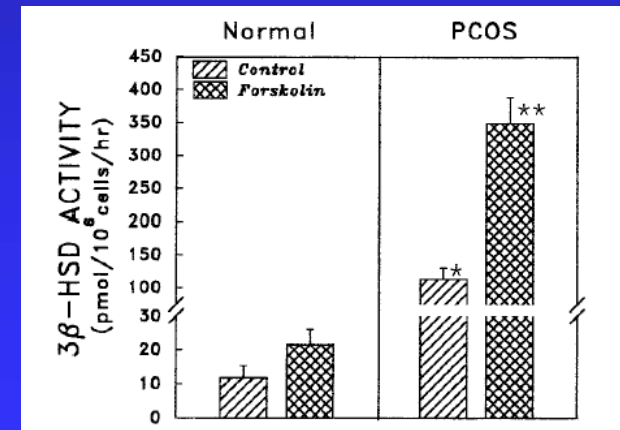
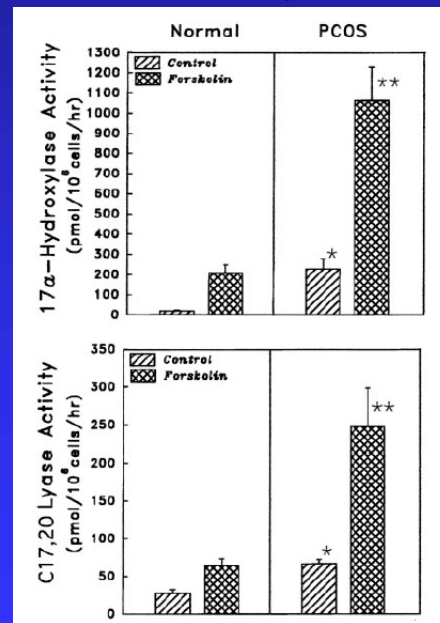
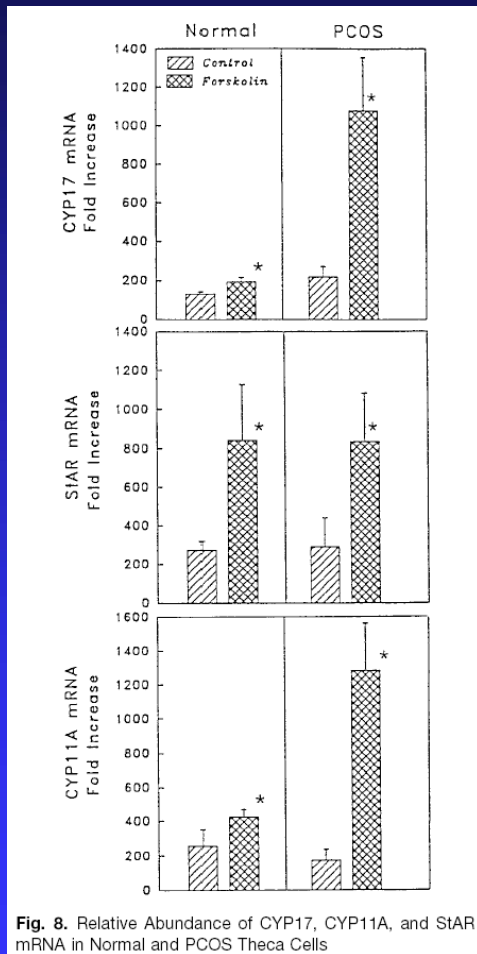
◆ Adapted from Azziz et al. JCEM in press



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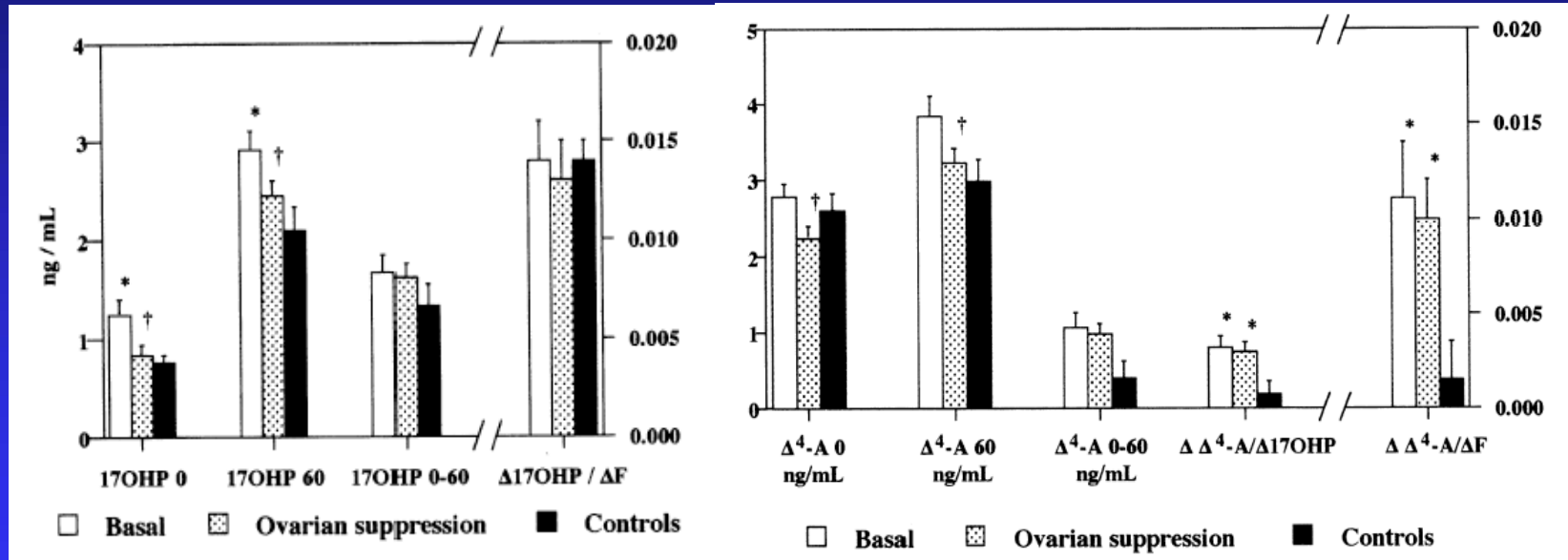
Androgen excess is central in PCOS

- Theca cells from PCOS patients overexpress steroidogenic enzymes and secrete more androgens compared with controls, even after culture (Nelson et al. *Mol Endocrinol* 1999;13:946 & *JCEM* 2001;86:5925)
- **Conclusion: ovarian androgen excess is a primary abnormality in PCOS**

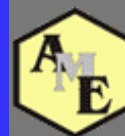


Androgen excess is central in PCOS

- Even idiopathic hirsutism might not be 'idiopathic' at all



◆ Escobar-Morreale et al. *Metabolism* 1997



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Androgen excess is central in PCOS

- In some PCOS patients the disorder in androgen secretion is so severe that obesity, insulin resistance and other triggering factors do not contribute at all.
- In others, obesity and / or insulin resistance trigger a very mild defect in androgen secretion resulting in PCOS.
- There is a continuum in the relative contributions of dysfunctional androgen synthesis and triggering factors between both extremes.

Disorder of androgen synthesis

Obesity, insulin resistance,
others

- But all patients have a dysfunctional androgen secretion!!!



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Definitions of PCOS

Table 5. All possible phenotypes based on the presence or absence of oligo-anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome.

FEATURES	POTENTIAL PHENOTYPES															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligo-anovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	√	√	√	√	√	√										
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√						
AES 2006 criteria	√	√	√	√	√	√	√	√	√							
Escobar 2006	√	√	√	√	√	√	√	√	√		√			√	√	

2013

Your name here	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
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2013

... as long as you know what you are talking about!!!



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Definitions of PCOS

■ Because....

- ◆ **What is hyperandrogenism?**
 - ◆ Clinical:
 - Hirsutism alone?
 - Acne and alopecia?
 - ◆ Hyperandrogenemia:
 - Increased testosterone only?
 - Which (total or free) testosterone?
 - What about androstenedione and DHEAS?
 - And SHBG?
- ◆ **What is oligo-ovulation?**
 - ◆ Menstrual dysfunction?
 - Oligomenorrhea?
 - Amenorrhea?
 - ◆ Basal body temperature?
 - ◆ Luteal phase serum progesterone?



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How should you diagnose PCOS?

My recommendation

- Use the definition that better suits the diagnostic tools you have available
- Know the diagnostic tools you are using with precision
- Take your time to reach a diagnosis
- Describe the diagnosis with precision



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How should you diagnose PCOS?

My recommendation

- Hyperandrogenism (in order of importance):
 - ◆ Clinical history
 - ◆ Physical examination: use the modified Ferriman-Gallwey hirsutism score
 - ◆ Rely on serum androgens for the diagnosis **ONLY** if you are convinced of the accuracy and diagnostic performance of your assays!!!
 - ◆ Always measure serum androgens during the follicular phase of the menstrual cycle



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How should you diagnose PCOS?

My recommendation

- Ovulatory dysfunction:
 - ◆ Obtain a detailed menstrual history **from menarche**
 - ◆ In case of doubt, or in regularly menstruating women, take your time and monitor basal body temperature or luteal phase progesterone for at least 3 cycles



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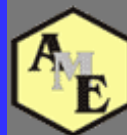
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How should you diagnose PCOS?

My recommendation

■ Ultrasound:

- ◆ Use a transvaginal probe if possible
- ◆ Do it yourself (if you know how...)
- ◆ If not, convince the ObGyn or Radiologist of your choice to measure ovarian volume and to count the number of follicles with precision, and **NEVER RELY** on the “polycystic appearance of the ovaries”



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How should you diagnose PCOS?

My recommendation

- Other useful tools:
 - ◆ Measure waist circumference
 - ◆ Obtain an OGTT for insulin and glucose
 - ◆ Obtain a lipid profile and an ABPM recording

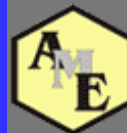


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And finally...

- Describe your diagnosis with precision (i.e. PCOS: hirsutism and PCO without insulin resistance, or PCOS: increased testosterone and anovulation, obesity and insulin resistance)....
- *...because the long-term consequences of a PCOS diagnosis ARE NOT THE SAME for every patient*



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The PCOS group at HRC



José Luis San Millán



Héctor F. Escobar-Morreale

PostDocs



Belén Roldán-Martín



José I. Botella-Carretero

PreDocs



Francisco Álvarez-Blasco



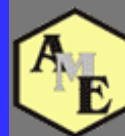
Manuel Luque-Ramírez



Raúl Sanchón



Elena Martínez



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AME-AACE Joint Meeting

*Diagnostic and Therapeutic Dilemmas in
Polycystic Ovary Syndrome*

Reasons for a Symptomatic Approach to PCOS

Roberto Castello

Division of Endocrinology and Metabolism

Azienda Ospedaliera, Verona, Italy



Main determinants of impaired quality of life in PCOS

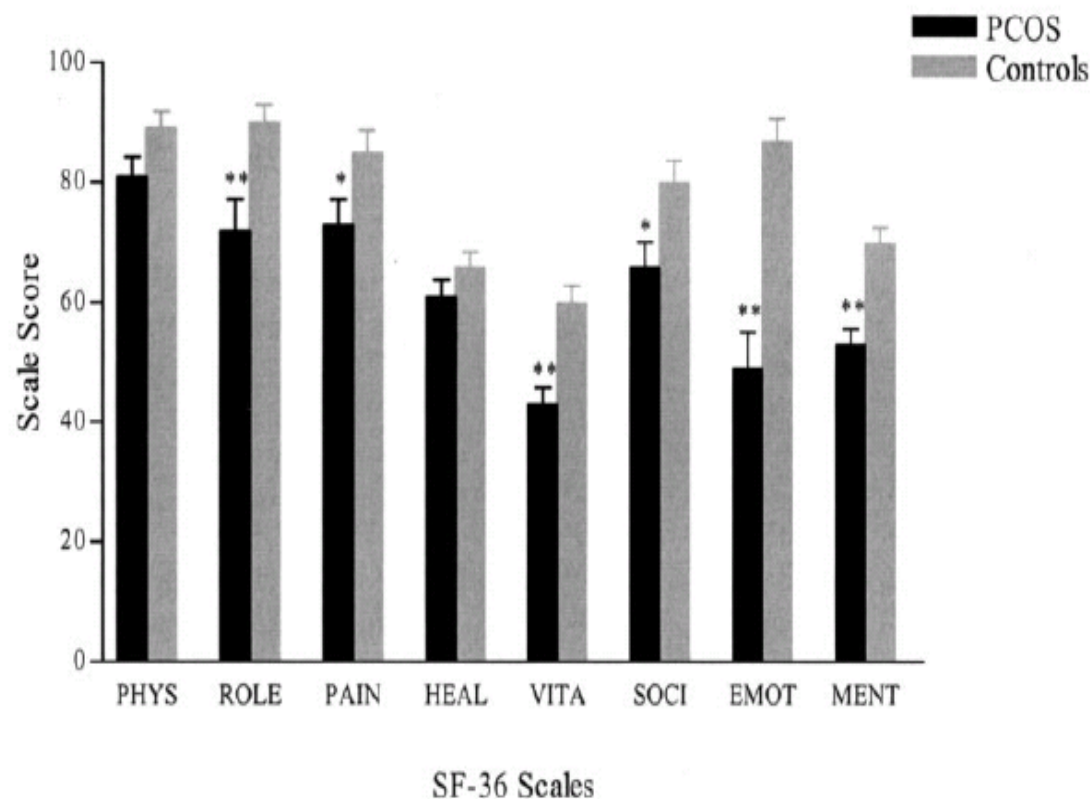
- Cutaneous manifestations of androgen excess
- Reproductive disturbances (menstrual irregularity, infertility)
- Obesity



Quality of Life, Psychosocial Well-Being, and Sexual Satisfaction in Women with Polycystic Ovary Syndrome

SIGRID ELSENBRUCH, SUSANNE HAHN, DANIELA KOWALSKY, ALEXANDRA H. ÖFFNER, MANFRED SCHEDLOWSKI, KLAUS MANN, AND ONNO E. JANSSEN

Department of Medical Psychology (S.E., M.S.) and Division of Endocrinology, Department of Medicine (S.H., D.K., K.M., O.E.J.), University of Essen, 45122 Essen, Germany; and Division of Angiology, Department of Medicine (A.H.Ö.), Hospital Schwabing, 80804 Munich, Germany



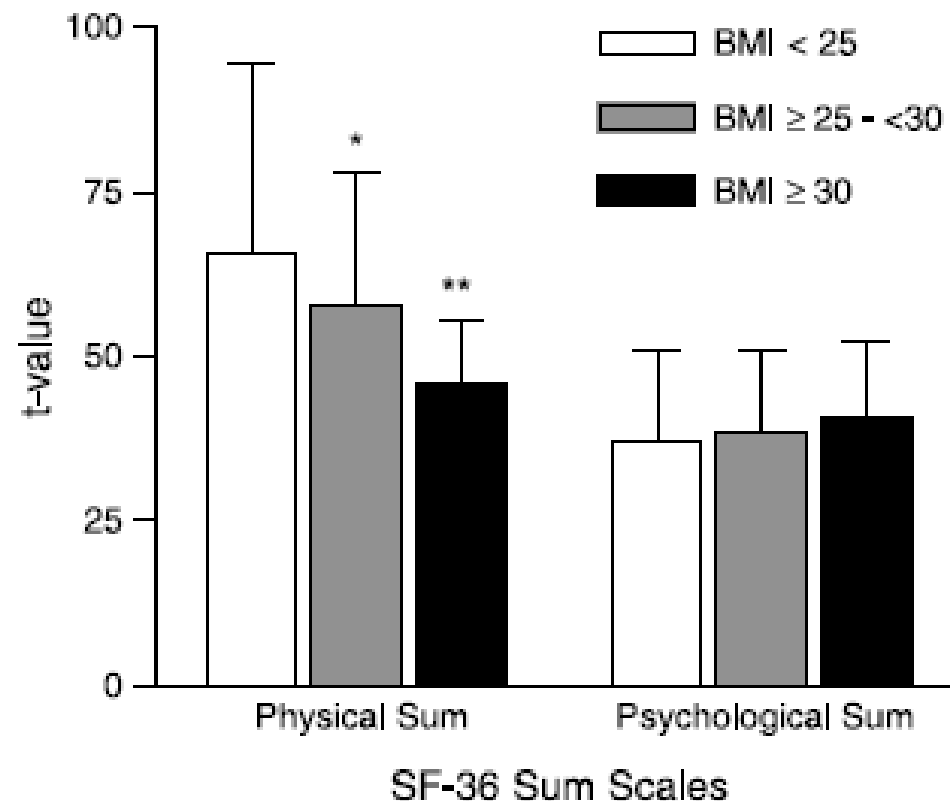


CLINICAL STUDY

Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome

Susanne Hahn, Onno E Janssen, Susanne Tan, Katja Pleger¹, Klaus Mann, Manfred Schedlowski², Rainer Kimmig³, Sven Benson¹, Efthimia Balamitsa¹ and Sigrid Elsenbruch¹

Division of Endocrinology, Department of Medicine, University of Duisburg-Essen, Germany, Hufelandstr. 55, 45 122 Essen, Germany, ¹Institute of Medical Psychology, University of Duisburg-Essen, Germany, ²Division of Psychology and Behavioral Immunobiology, Swiss Federal Institute of Technology, ETH-Zurich, Switzerland and ³Department of Obstetrics and Gynecology, University of Duisburg-Essen, Germany





Clinical features of hyperandrogenism

Skin abnormalities

- hirsutism
- acne
- androgenetic alopecia

Reproductive abnormalities

- anovulation
- menstrual dysfunction

Metabolic abnormalities (?)



Strategies in hirsutism therapy

- 1) Hair removal
- 2) Androgen drive attenuation

Main cosmetic procedures for symptomatic management of hirsutism

- shaving, depilatory creams
- plucking
- waxing
- bleaching

- electrolysis
- laser photothermolysis





Laser Photothermolysis

Both laser- and light-assisted hair removal are based on the principle of selective photothermolysis.

There is selective absorption of hair chromophores from lasers and broadband light sources which determines destruction of hair follicles without damage to the surrounding skin.

Laser therapy is more effective:

- darker hair
- lighter skin



A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome

W.J. Clayton, M. Lipton,* J. Elford,† M. Rustin and L. Sherr*

Department of Dermatology, The Royal Free Hampstead NHS Trust, London, U.K.

*Primary Care and Population Sciences, Royal Free and University College Medical School, London, U.K.

†Institute of Health Sciences, City University, London, U.K.

Conclusions Laser treatment appeared to reduce the severity of facial hair and time spent on hair removal as well as alleviating depression and anxiety in women with PCOS. These findings suggest that ways of making this method of hair removal more widely available to women with facial hirsutism should be considered.

Licensed drugs for the symptomatic management of PCOS



Menstrual abnormalities

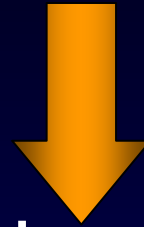
- oral contraceptives
- progestogens

Hirsutism

- oral contraceptives
- oral contraceptives containing cyproterone (*Diane*)
- eflornithine (topical)

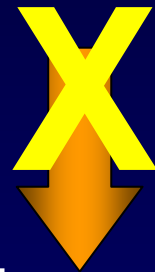
Mechanism of eflornithine action in hirsutism

Testosterone

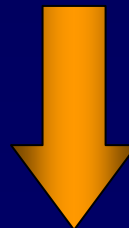


ornithine decarboxylase synthesis

Eflornithine



poliamine synthesis



hair growth





Efficacy of eflornitine

	Eflornitine	Placebo
Disappearance	6%	0%
Market improvement	29%	9%
Improvement	35%	33%
Any improvement / worsening	30%	58%



Oral contraceptives in the treatment of PCOS

PROs

- Lowered serum free androgens (↑ SHBG)
- Regular menstruation
- Reduced risk of endometrial cancer
- Contraception

CONs

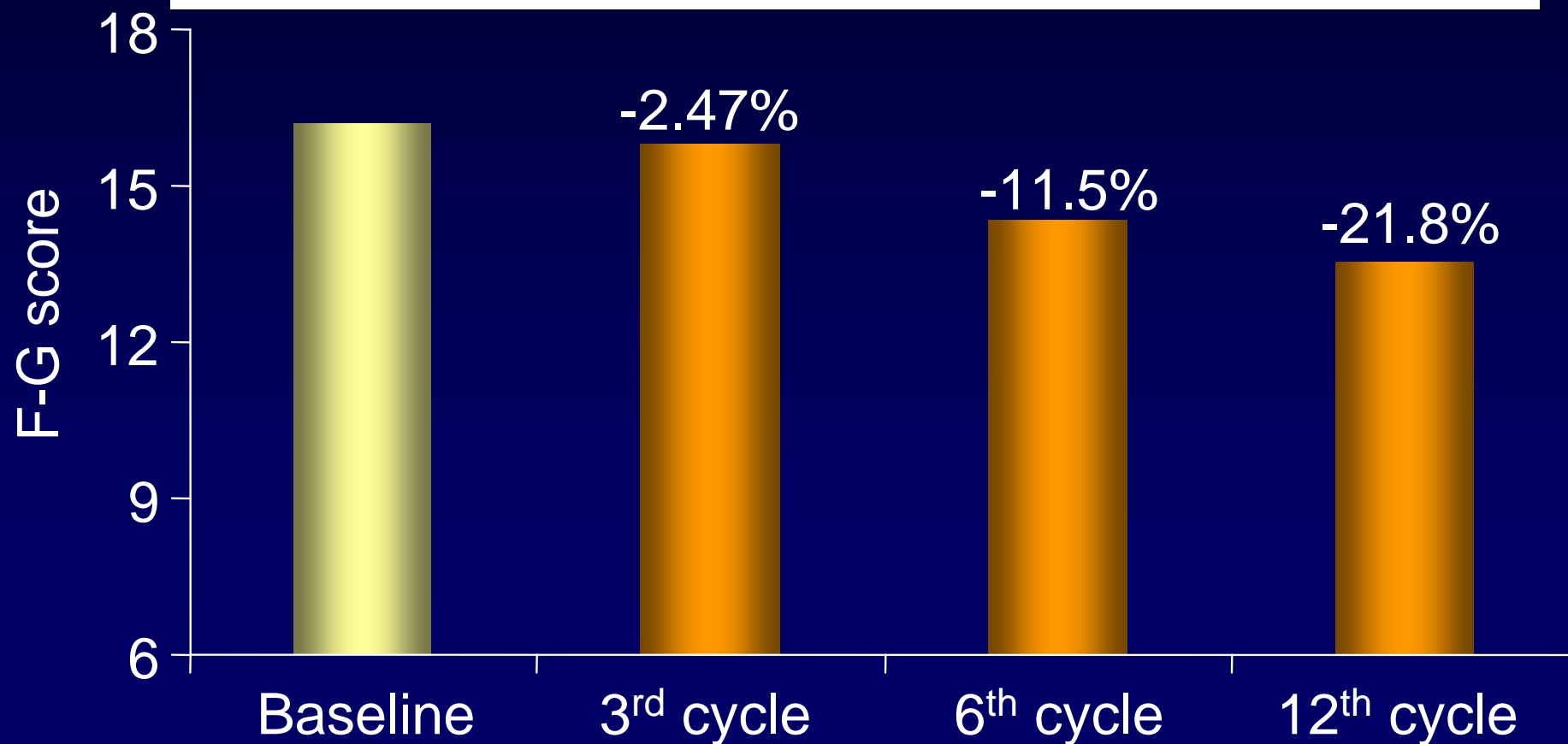
- Limited efficacy on established hirsutism
- Increased thromboembolic risk
- Metabolic impairment
 - abnormal lipid profile
 - insulin resistance



Drospirenone for the Treatment of Hirsute Women with Polycystic Ovary Syndrome: A Clinical, Endocrinological, Metabolic Pilot Study

M. GUIDO, D. ROMUALDI, M. GIULIANI, R. SURIANO, L. SELVAGGI, R. APA, AND A. LANZONE

Department of Obstetrics and Gynecology, Università Cattolica del Sacro Cuore (M.G., D.R., M.Gi., R.S., L.S., R.A., A.L.), 00168 Rome, Italy; and OASI Institute for Researches (A.L.), 94018 Troina, Italy



ORIGINAL ARTICLE

An observational study of Yasmin[®] in the management of women with polycystic ovary syndrome

Manisha Palep-Singh, MRCOG, DNBE, *Research Fellow in Reproductive Medicine, Department of Reproductive Medicine*; **Karen Mook**, *Research Nurse in Reproductive Medicine, Department of Reproductive Medicine*; **Julian Barth**, MD, FRCPath, *Consultant Chemical Pathologist, Department of Clinical Biochemistry*; **Adam Balen**, MD, FRCOG, *Consultant Gynaecologist and Subspecialist in Reproductive Medicine, Department of Reproductive Medicine, Leeds General Infirmary, Leeds, UK*

Key message points

- Yasmin provides control of the menstrual cycle in women with polycystic ovary syndrome (PCOS).
- Acne improves, and hirsutism and BMI do not change, in women prescribed Yasmin for PCOS.









androgen synthesis

activation

hormone-receptor interaction

DHEA

Andro-
stenedione

Testosterone

DHT

DHEA-S

5 α -reductase

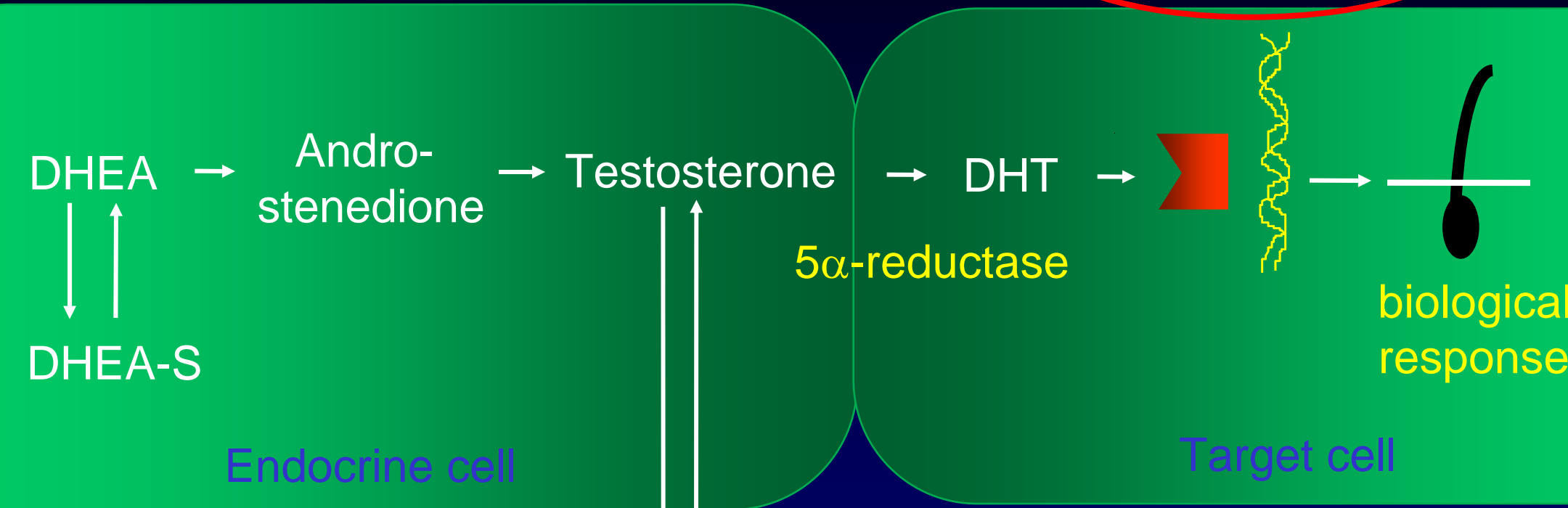
biological
response

Endocrine cell

Target cell

binding
to SHBG

Blood



Antiandrogen drugs for hirsutism



Drug (schedule)	PROs	CONs
Cyproterone acetate (2-100 mg/day; high doses usually on cycle days 5-14)	<ul style="list-style-type: none">- large experience- licensed for this use (only combination 2 mg + EE)	<ul style="list-style-type: none">- combination with estrogens needed- frequent side effects, usually mild (metabolic alterations, mood changes, rare liver toxicity)
Spiroglactone (50-200 mg)	<ul style="list-style-type: none">- large experience- low cost- may improve menstruation	<ul style="list-style-type: none">- necessary to avoid pregnancies- frequent side effects, usually mild (polymenorrhea, diuresis, mastodynia, gastrointestinal alterations, rare hyperkalemia)
Flutamide (62.5-500 mg/day)	<ul style="list-style-type: none">- pure antiandrogen- no adverse effect on ovulation	<ul style="list-style-type: none">- necessary to avoid pregnancies- rare but occasionally severe liver toxicity



Cyproterone acetate for hirsutism

Cochrane Syst. Review
(Van der Spuy and le Roux, 2003)

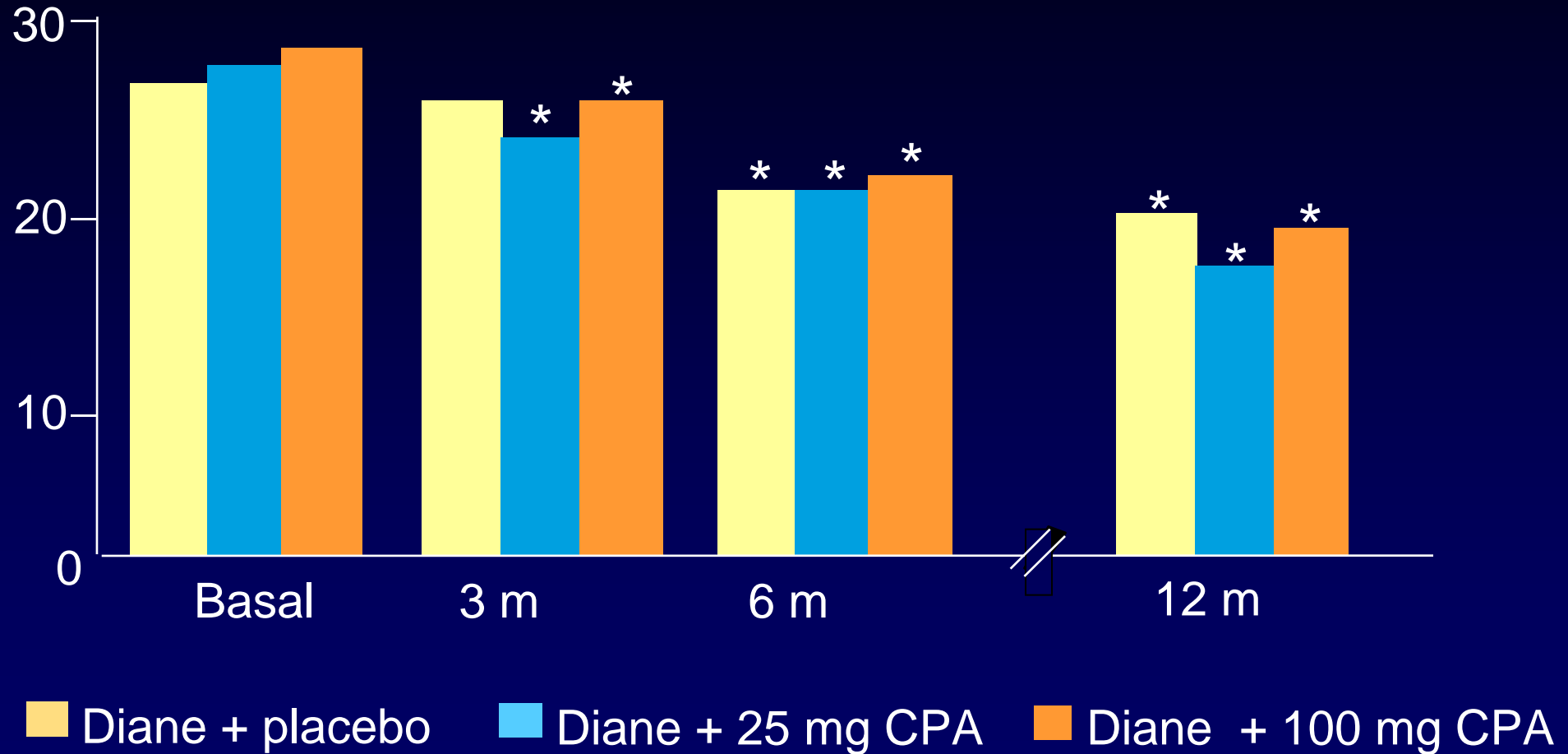
Number of studies suitable for inclusion in efficacy analysis: 9

Conclusions:

- efficacy vs placebo: subjective reduction of hair growth
- efficacy vs other drugs: no differences (but small studies, heterogeneous assessments, lack of objective measures)
- differences in side effects: insufficient data



FERRIMAN-GALLWEY SCORE IN HIRSUTE WOMEN GIVEN DIFFERENT DOSES OF CYPROTERONE ACETATE



*p<0.01 vs basal

Spironolactone vs placebo or in combination with steroids for hirsutism and/or acne

Farquhar et al, Cochrane Review, 2003

Studies suitable for inclusion in efficacy analysis: 2

Treatment duration 6-9 months

Sample size 58 subjects

Hirsutism measurements: Mean Δ (95% C.I.)

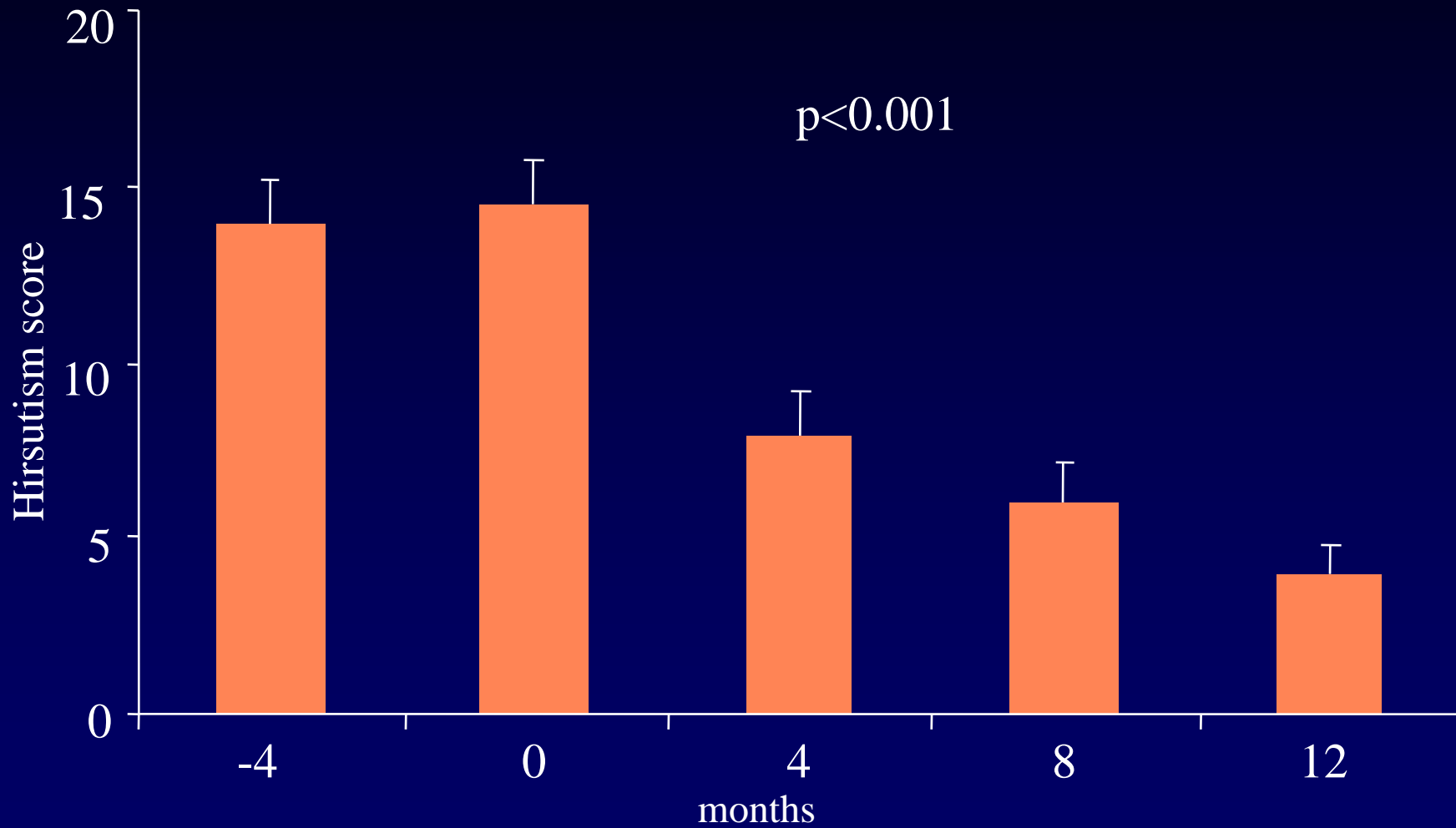
Ferriman-Gallwey score	-7.2 (-11, -3.4)	p<0.001
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Hair diameter	-9.9 (-22.5, +2.6)	p=0.12
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Subjective perception	7.2 (2, 26.3)	p<0.001
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MEAN MODIFIED FERRIMAN-GALLWEY SCORE IN PATIENTS TREATED WITH FLUTAMIDE



Moggetti et al, Fertil Steril 1995



Finasteride in the treatment of hyperandrogenism

- **Mechanisms**

- inhibition of 5- α reductase (type 2)

- **Schedule**

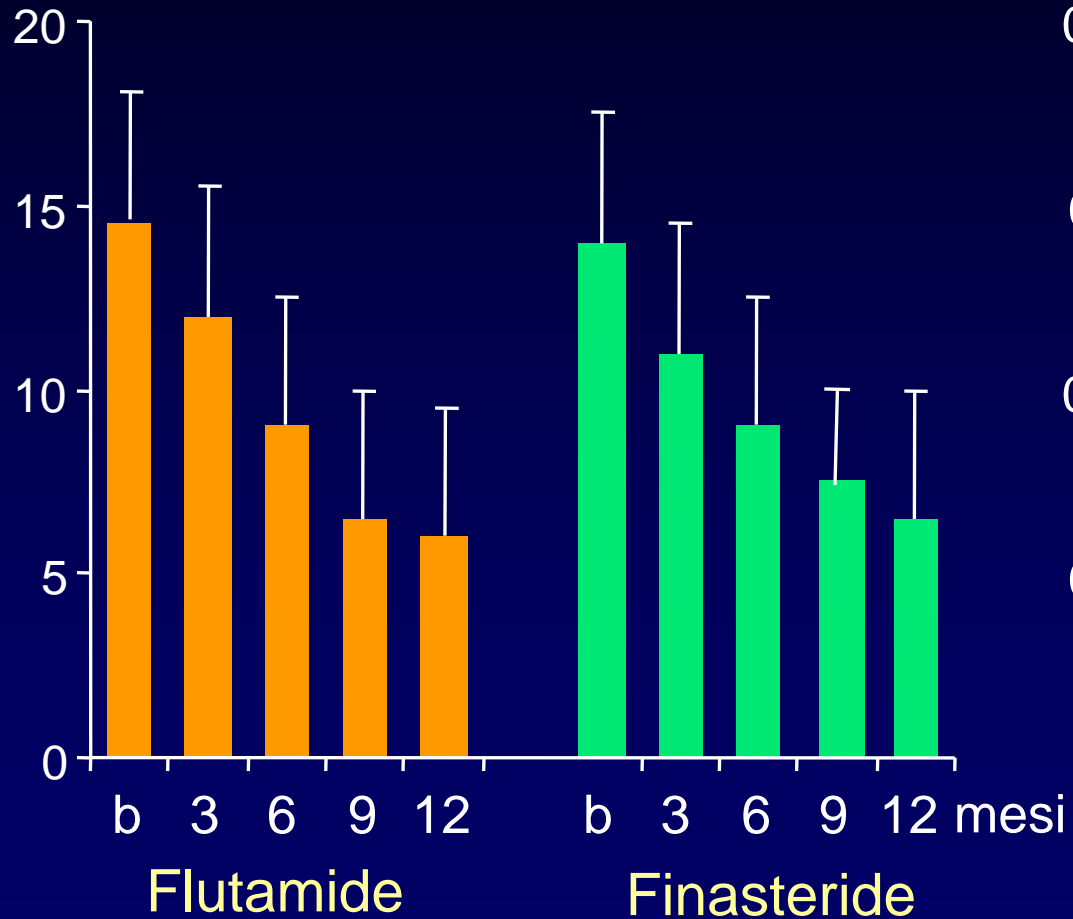
- 1-5 mg/day

- **PROs and CONs**

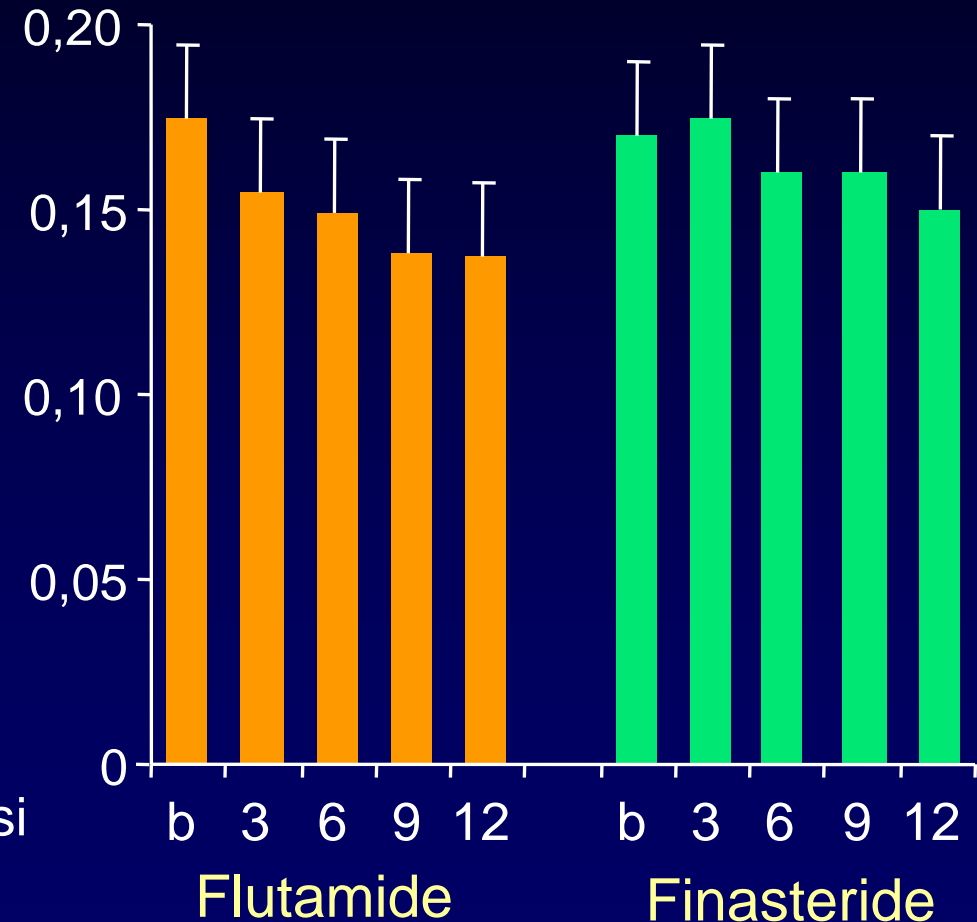
- effective treatment for hirsutism and androgenetic alopecia
- devoid of appreciable side effects
- necessary to avoid pregnancies during treatment

Changes in Ferriman-Gallwey scores and hair diameters after flutamide or finasteride in hirsute women

Hirsutism Score

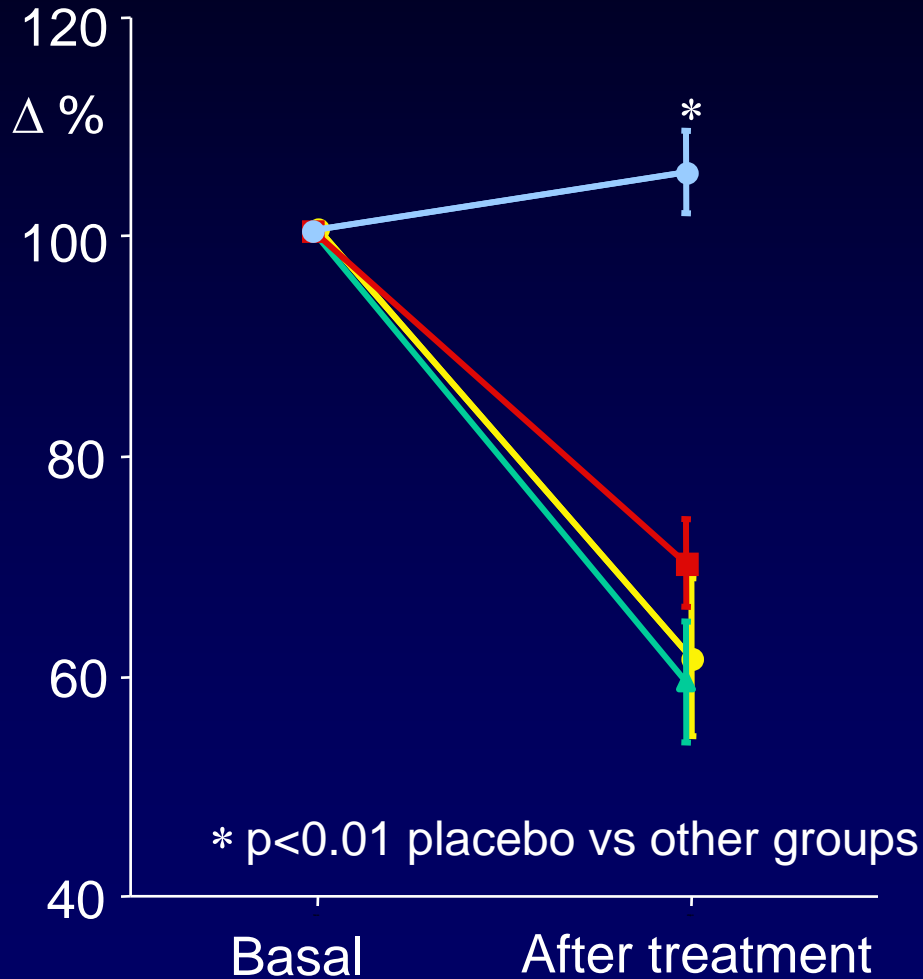


Diameter (mm)

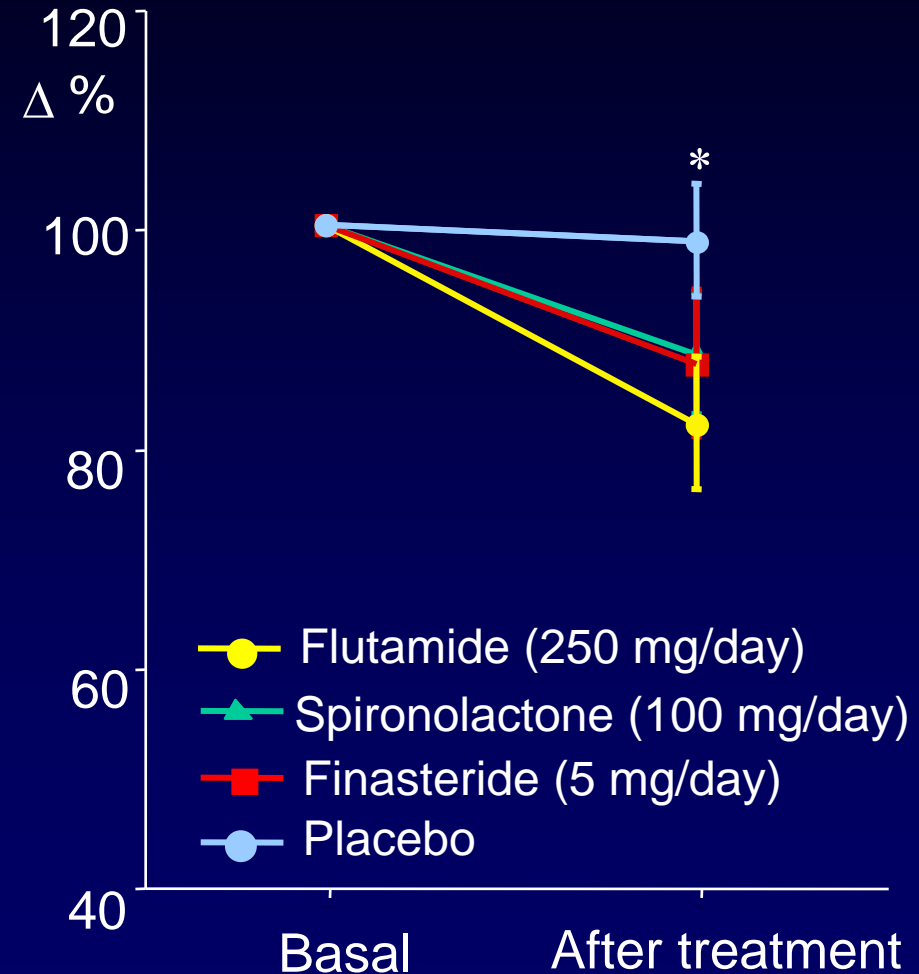


CHANGES IN HAIR GROWTH AFTER SIX MONTHS OF ANTIANDROGEN DRUGS IN HIRSUTE WOMEN

Ferriman-Gallwey score



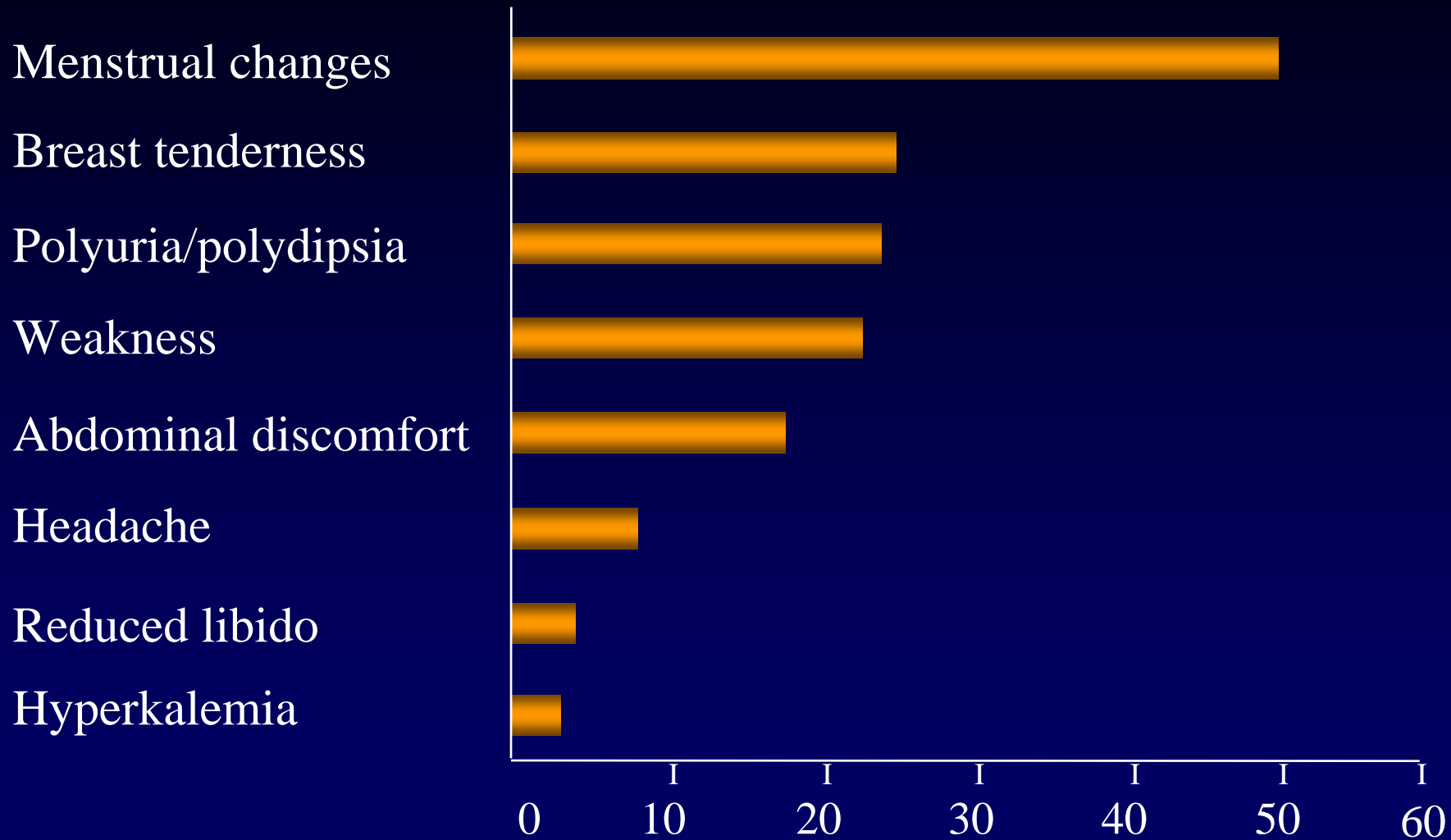
Mean hair diameter



(Moghetti et al, JCEM 85:89, 2000)



SIDE EFFECTS (%) OF SPIRONOLACTONE





Human Reproduction Vol.20, No.7 pp.1833–1836, 2005

Advance Access publication March 31, 2005

doi:10.1093/humrep/dei004

SHORT COMMUNICATION

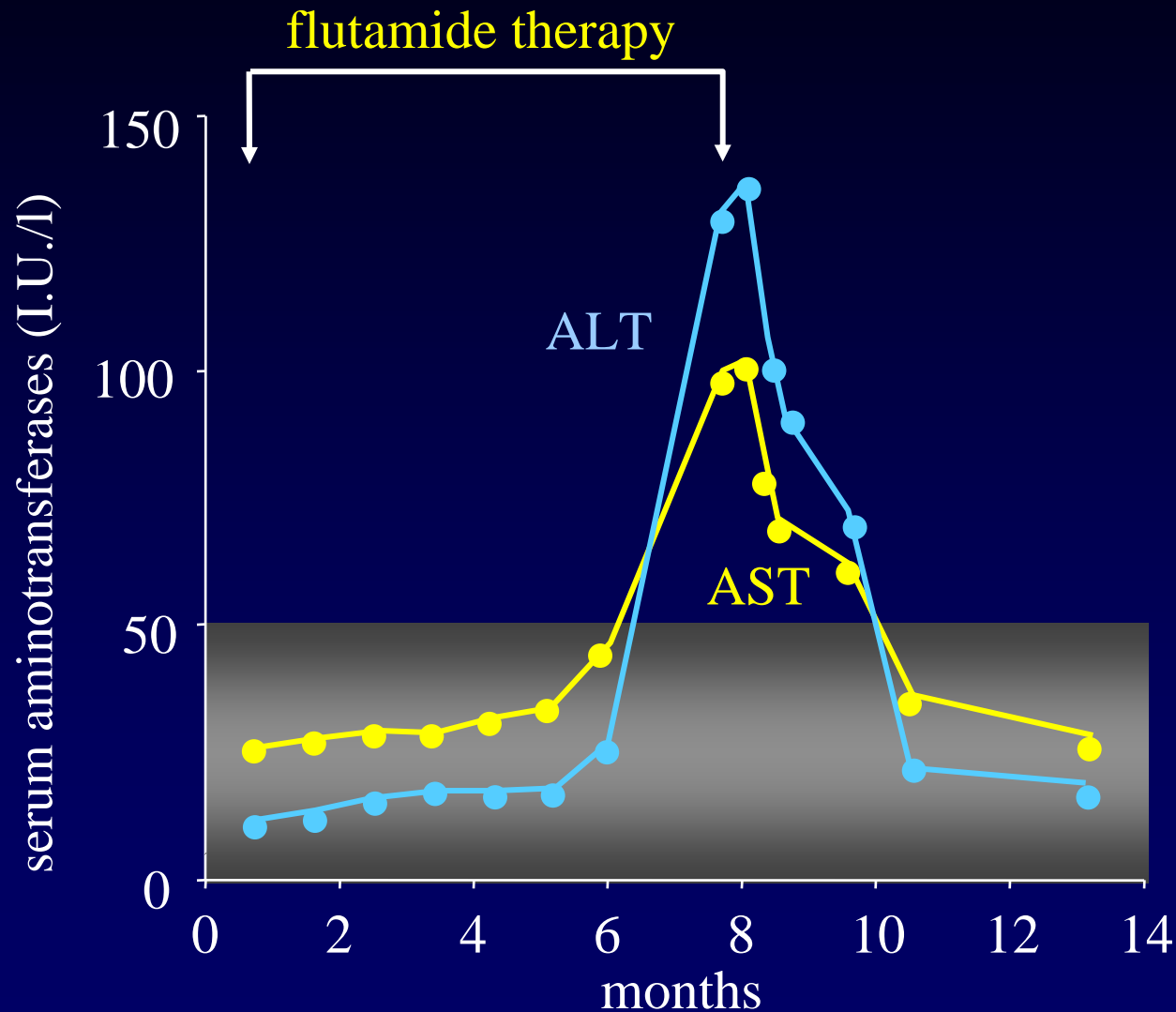
Absence of hepatotoxicity after long-term, low-dose flutamide in hyperandrogenic girls and young women

Lourdes Ibáñez^{1,3}, Adriana Jaramillo¹, Angela Ferrer¹ and Francis de Zegher²

¹Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Passeig de sant Joan de Déu, 2 08950 Esplugues, Barcelona, Spain and ²Department of Pediatrics, University of Leuven, Leuven, Belgium

³To whom correspondence should be addressed. E-mail: libanez@hsjdbcn.org

COURSE OF SERUM TRANSAMINASE LEVELS IN ONE PATIENT WHO PRESENTED LIVER INJURY DURING FLUTAMIDE THERAPY





androgen synthesis

activation

hormone-receptor interaction

DHEA
↓
DHEA-S
↑

Andro-
stenedione

Testosterone

DHT

5 α -reductase

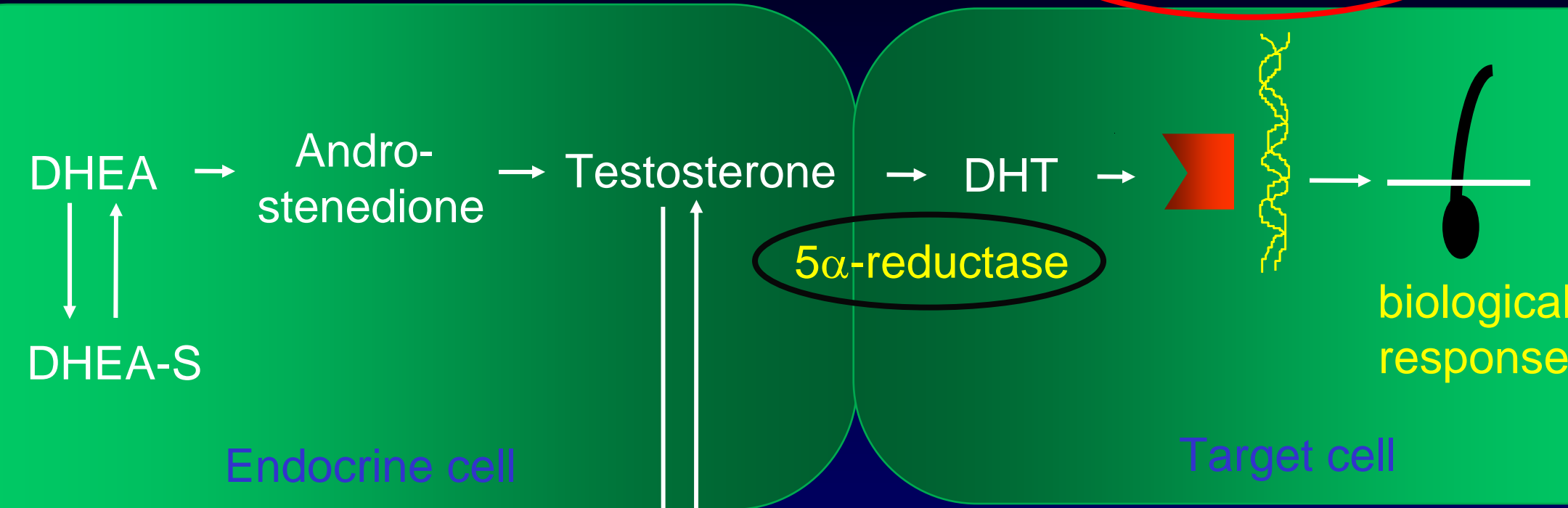
biological
response

Endocrine cell

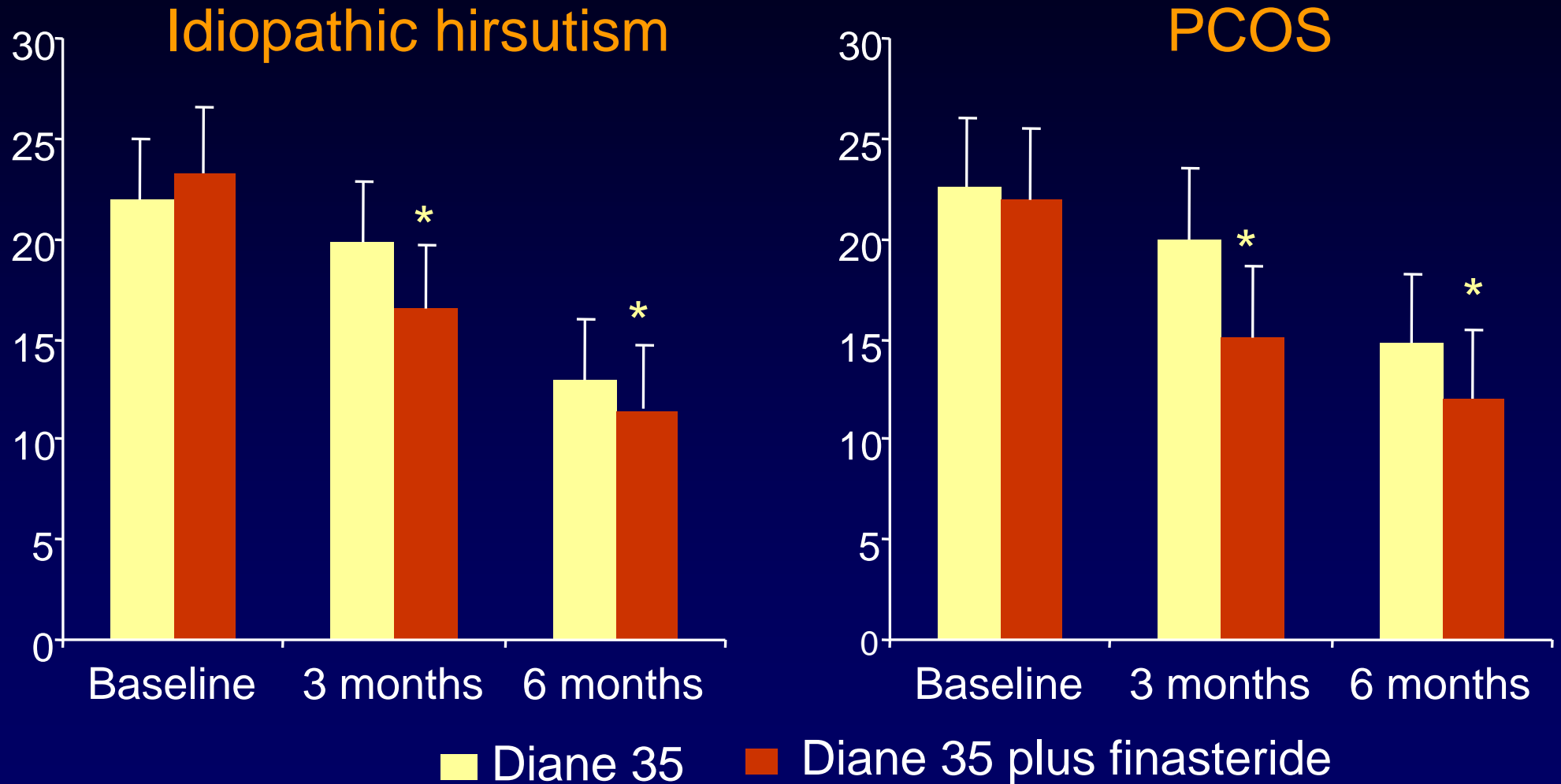
Target cell

binding
to SHBG

Blood



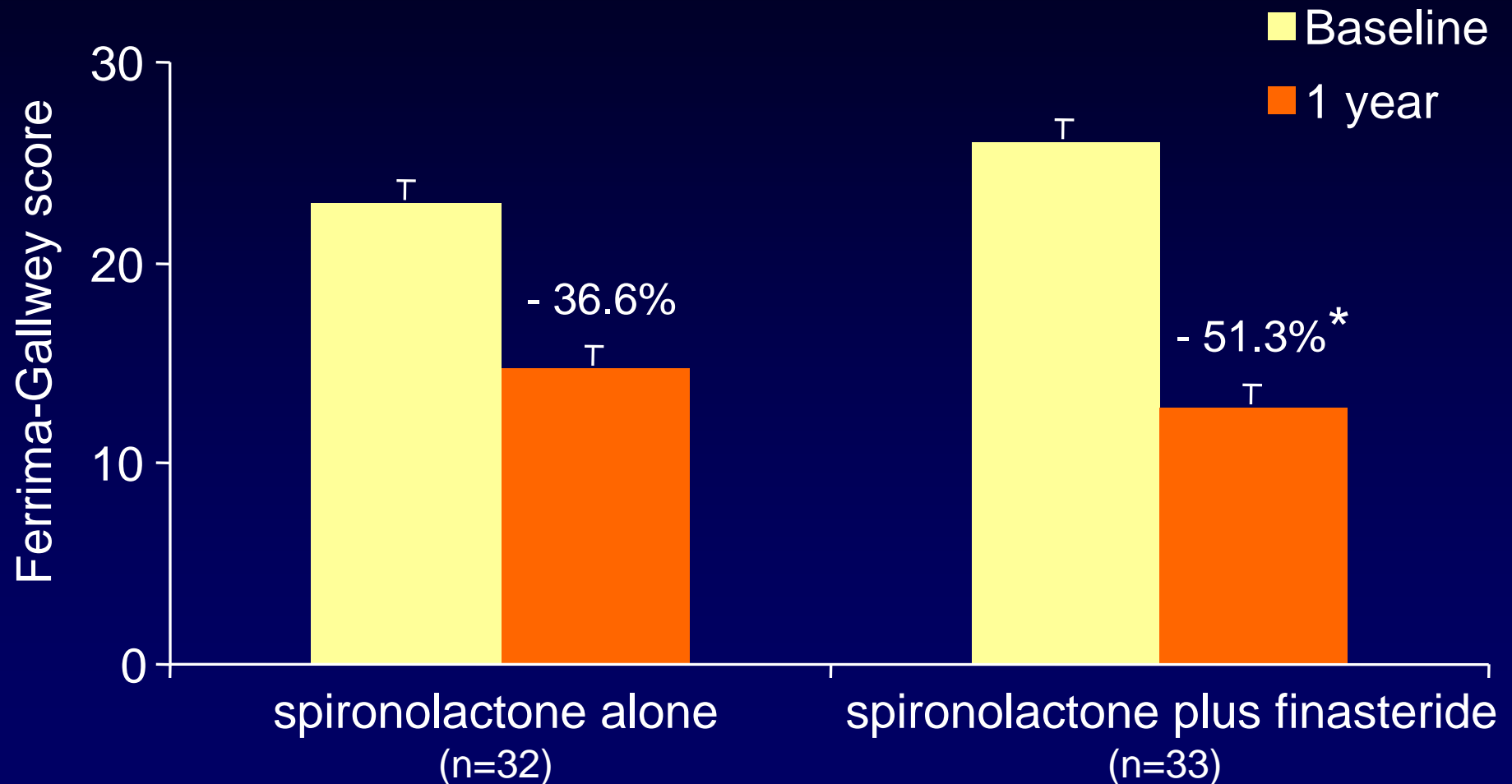
Hirsutism scores before and after treatment with Diane 35 or Diane 35 plus finasteride in women with idiopathic hirsutism or PCOS



*p<0.05 vs Diane alone

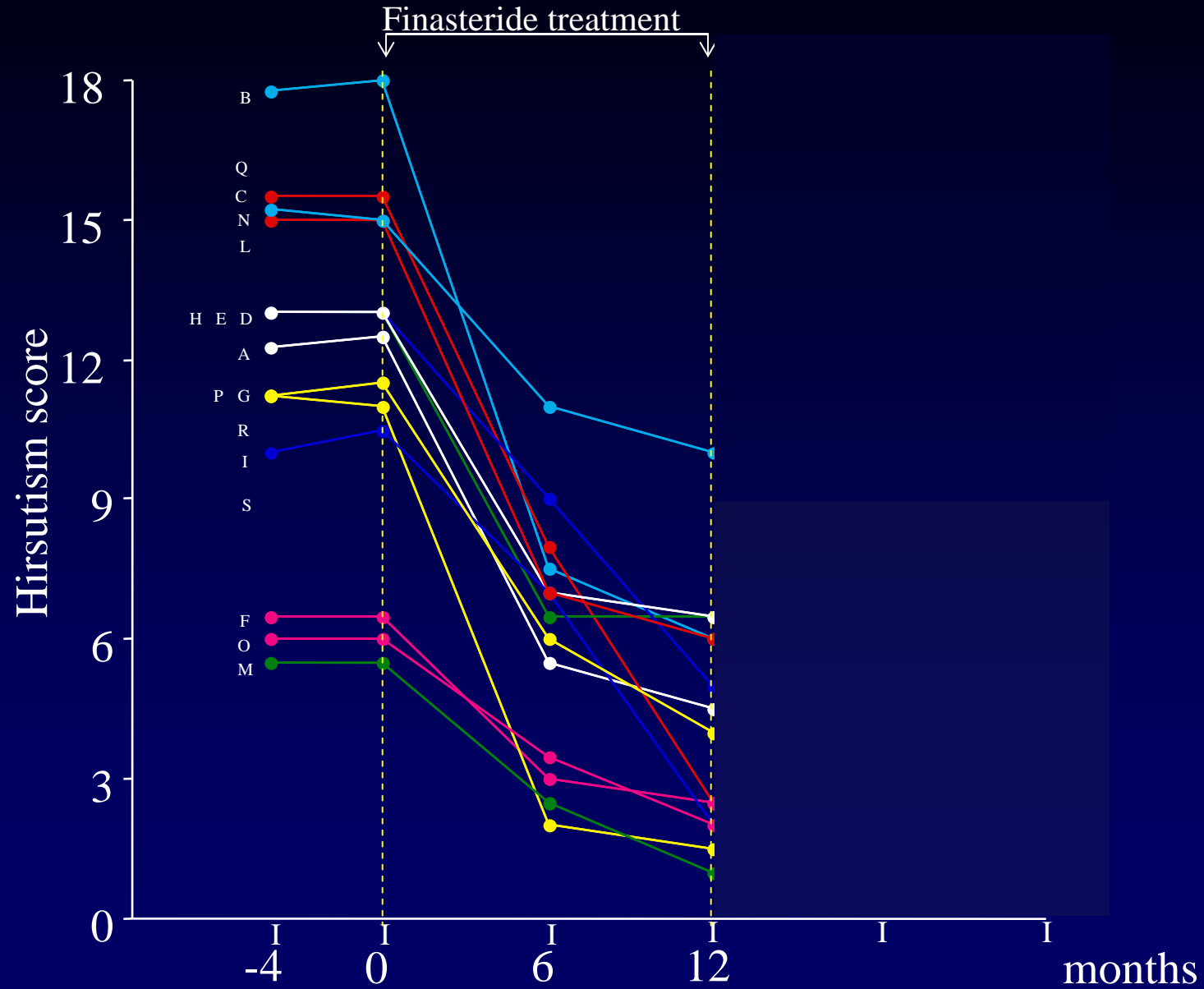
Tartagni et al, Fertil Steril 2000

Hirsutism scores before and after spironolactone alone and spironolactone plus finasteride

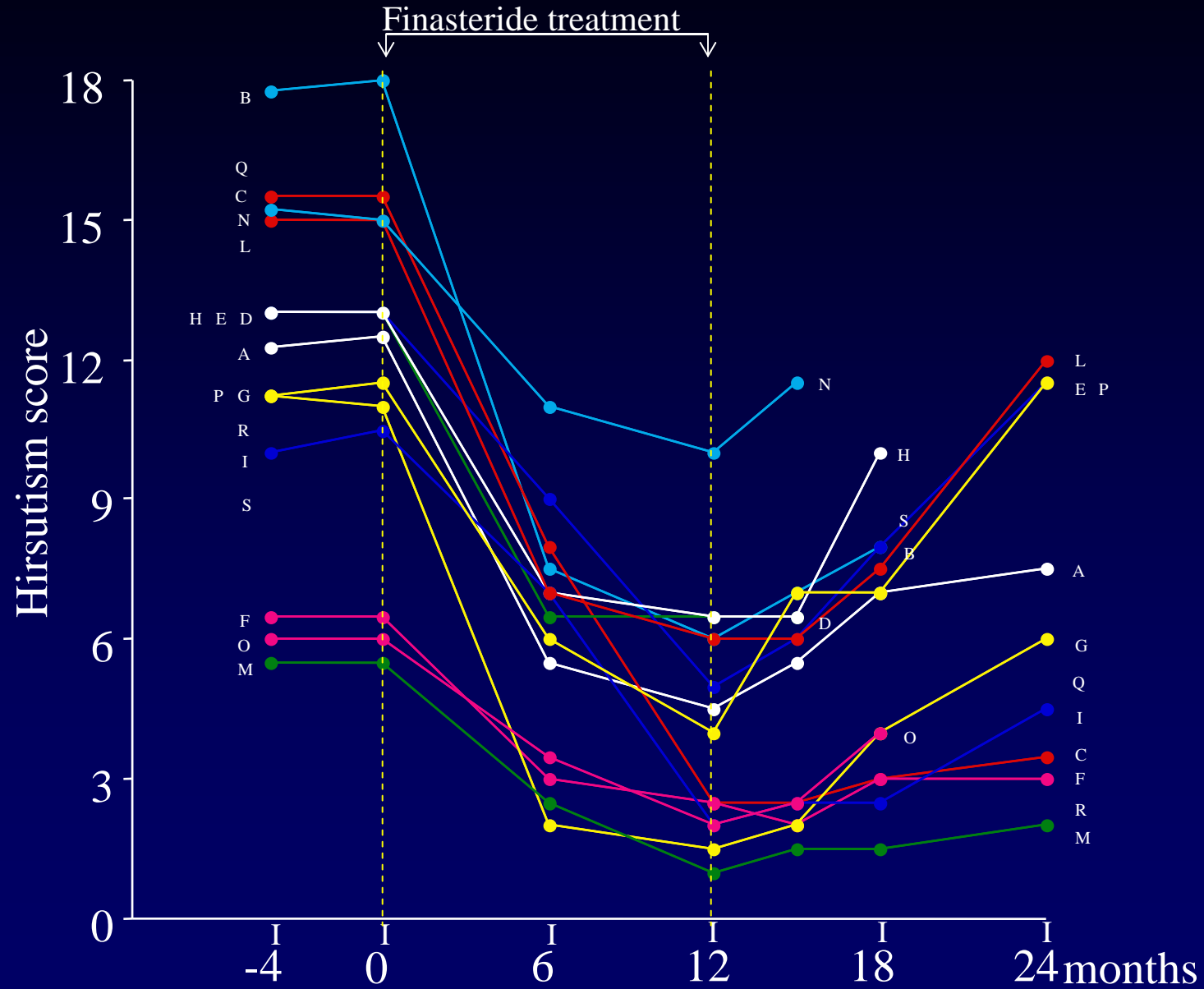


* $p < 0.005$ vs spironolactone alone

CHANGES IN INDIVIDUAL FERRIMAN-GALLWEY SCORES IN 14 WOMEN WITH IDIOPATHIC HIRsutISM TREATED WITH FINASTERIDE ALONE



CHANGES IN INDIVIDUAL FERRIMAN-GALLWEY SCORES IN 14 WOMEN WITH IDIOPATHIC HIRSUTISM TREATED WITH FINASTERIDE ALONE





Conclusions

- Symptoms cause major psychological distress in PCOS women, impairing quality of life.
- Cosmetic measures, in particular laser photothermolysis and electrolysis, may be effective in the treatment of hirsutism. However, in many patients attenuation of androgen drive is also required.
- Antiandrogens seems to be the most effective tool for hirsutism therapy. However, it is necessary to be aware of their potential risks.
- Oral contraceptives may be used for the treatment of menstrual irregularity.

3rd AME-AACE Joint Meeting

*Diagnostic and Therapeutic Dilemmas in
Polycystic Ovary Syndrome*

Verona, 28 October 2006

**Reasons for a Pathogenetic
Approach to PCOS**

Paolo Moghetti

Department of Biomedical and Surgical Sciences

- Section of Endocrinology and Metabolism -

University of Verona, Verona, Italy

Polycystic Ovary Syndrome

- Very common condition in young women
- Major medical implications
 - reproductive
 - psychological
 - metabolic
 - cardiovascular, later in life (?)
 - neoplastic, later in life
- Etiology unknown (possibly heterogeneous)
- Conventional therapy is symptomatic

Can PCOS medical problems be corrected by a symptomatic approach?

Medical problems

- reproductive
- psychological
- metabolic
- cardiovascular (?)
- neoplastic

Efficacy of therapy

+++−

++−−

+−−−

+−−−

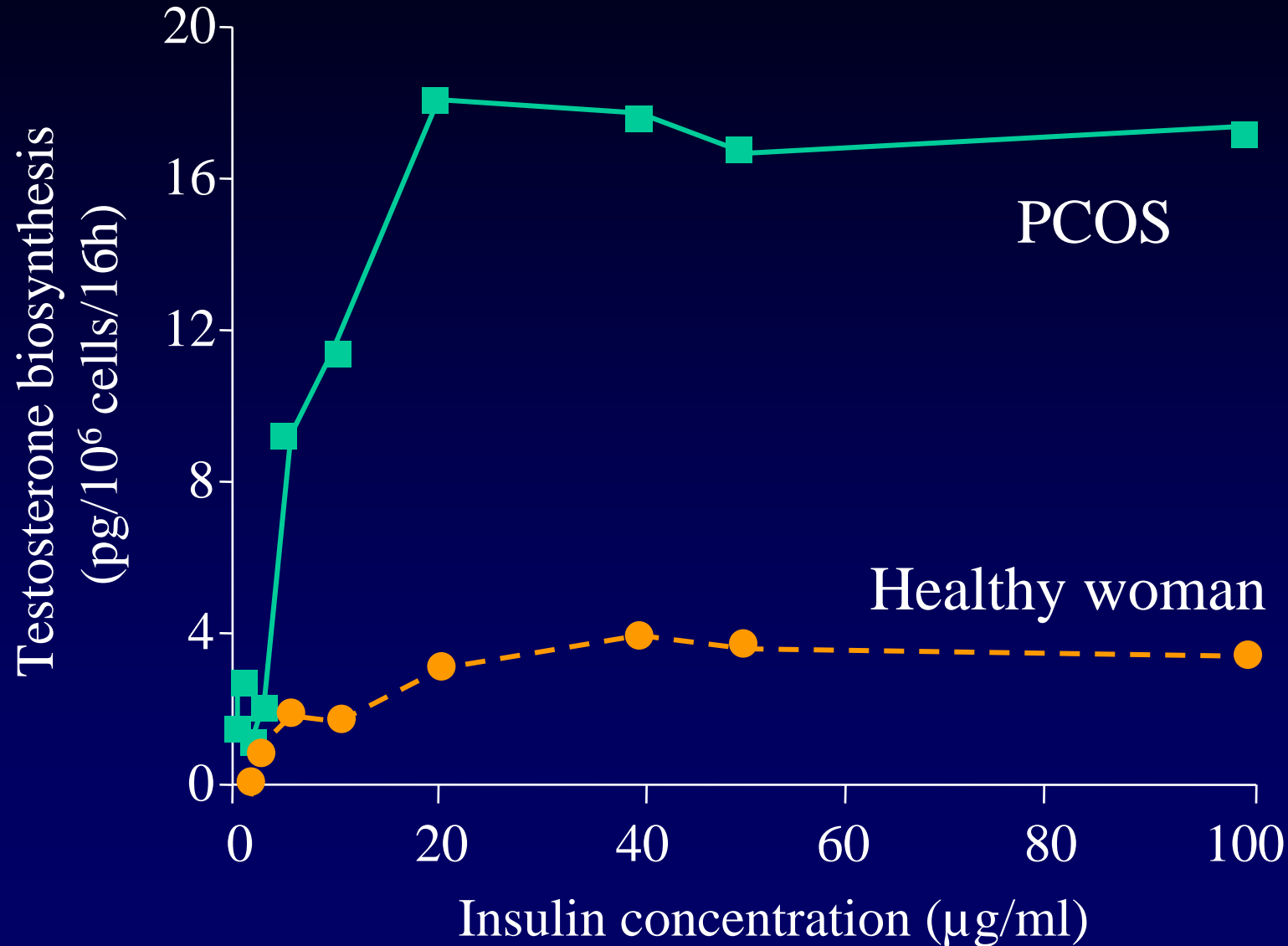
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Is a “pathogenetic” therapy of PCOS
conceivable?

MECHANISMS OF INSULIN-INDUCED HYPERANDROGENISM

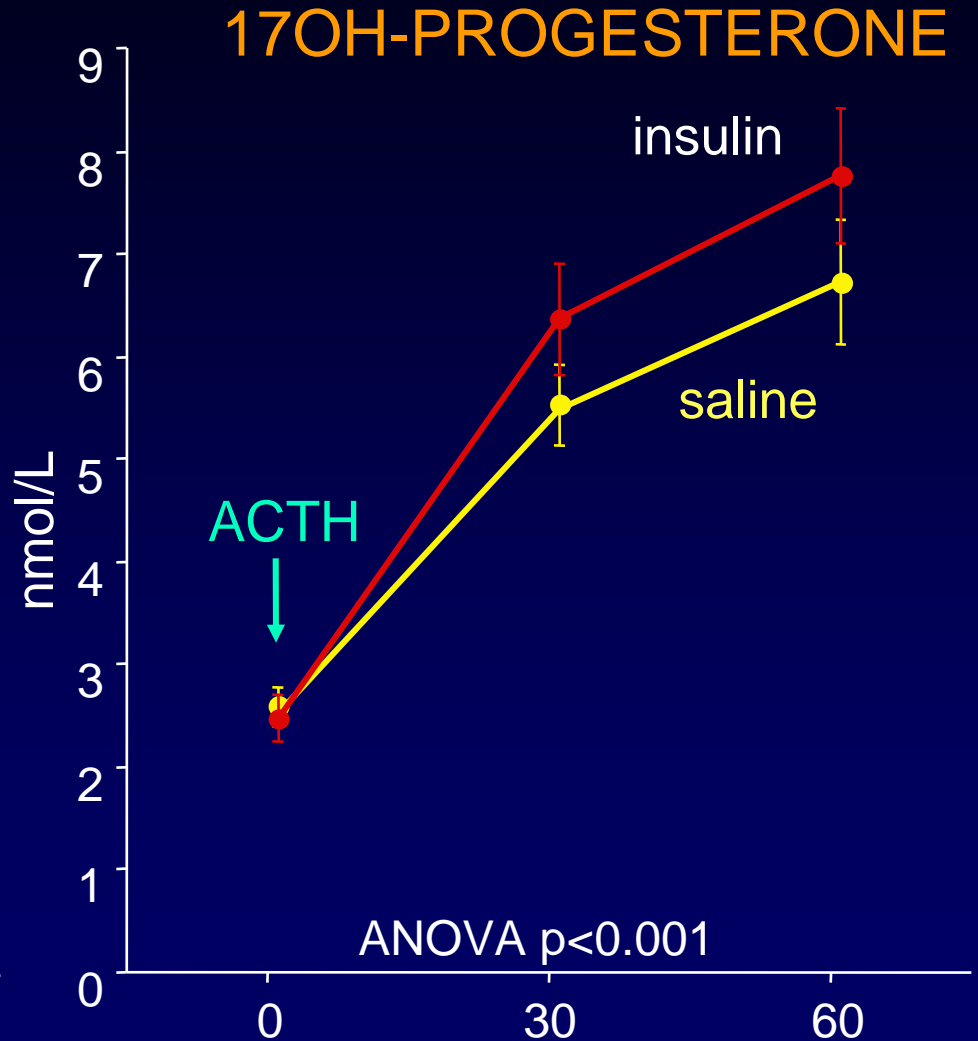
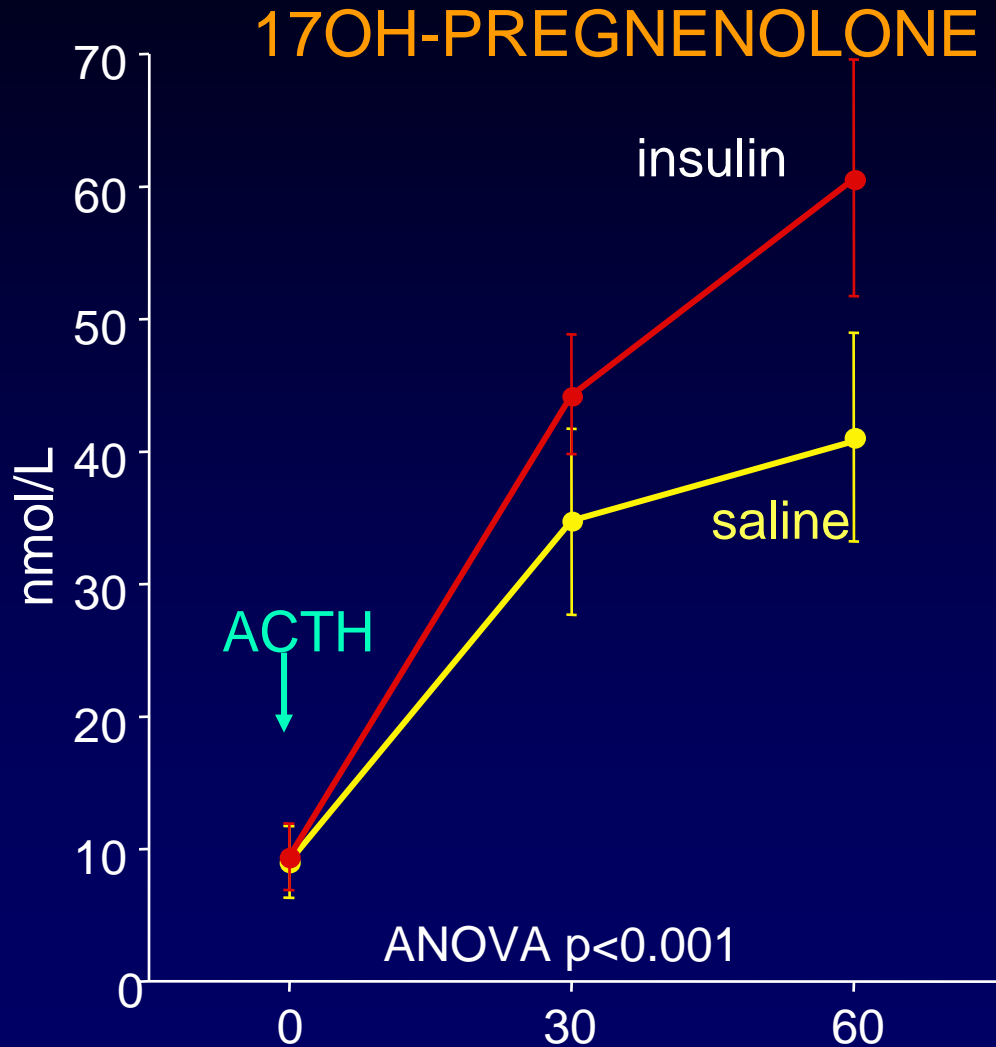
- Direct stimulation of androgen secretion in the ovary (*in vitro*)
- Increased LH secretion (*in vitro*)
- Reduced SHBG synthesis in the liver (increased bioavailable testosterone)
- Reduced IGFBP-1 synthesis in the liver (increased bioavailable IGFs)
- Increased adrenal response to ACTH

Dose-response curves of insulin stimulation of testosterone biosynthesis in PCOS and non-PCOS cultured theca cells



(Nestler et al, JCEM 2003)

EFFECTS OF ACUTE HYPERINSULINEMIA ON ADRENAL RESPONSE TO ACTH



In PCOS women attenuation of hyperinsulinemia is associated with lowered serum androgen, independent of the way by which insulin level was reduced

-weight loss

- low calorie diet
- sibutramine, orlistat
- bariatric surgery

- insulin secretion inhibitors

- diazoxide
- somatostatin

- insulin catabolism enhancers (?)

- opioid antagonists

- insulin sensitizers

- metformin
- glitazons
- D-chiro-inositol

- α -glucosidase inhibitors

- acarbose

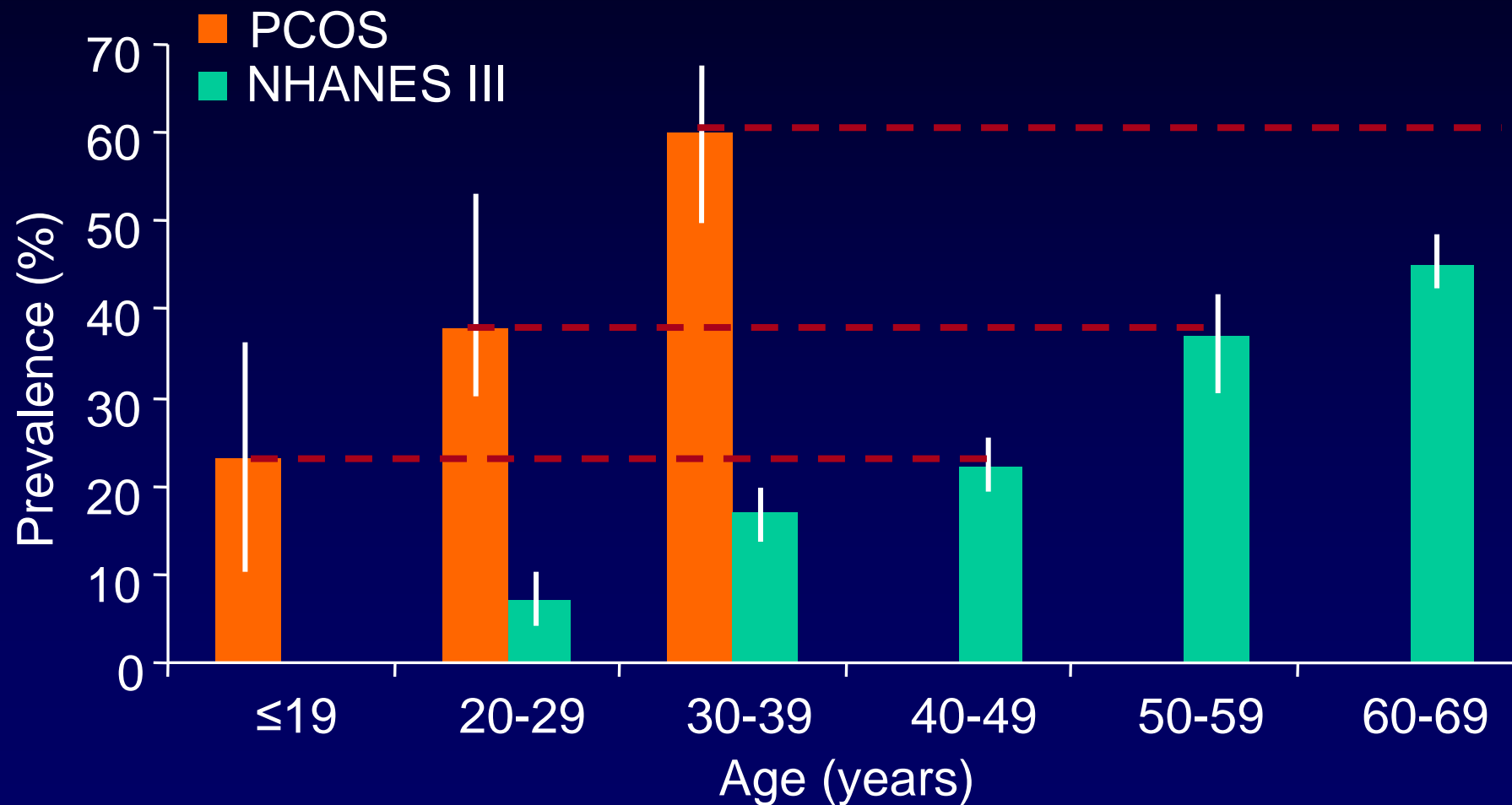
POTENTIAL IMPLICATIONS OF INSULIN RESISTANCE IN PCOS WOMEN

- Pathogenetic role in hyperandrogenism (and reproductive abnormalities?)
- Pathogenetic role in metabolic abnormalities (with increased cardiovascular risk ?)

Metabolic features in PCOS women and controls (means \pm SEM)

	Controls n = 43	PCOS n = 94	p
BMI (Kg/m ²)	23.7 \pm 0.9	24.4 \pm 0.5	0.138
Fasting plasma glucose (mg/dl)	85 \pm 9	85 \pm 1	0.827
Glucose after OGTT (mg/dl)	128 \pm 5	142 \pm 4	0.007
Fasting plasma insulin (μ IU/ml)	10.1 \pm 1.3	12.4 \pm 0.7	0.089
Insulin after OGTT (μ IU/ml)	77.4 \pm 7.4	145.6 \pm 9.6	0.001
Total Cholesterol (mg/dl)	174 \pm 4	188 \pm 3	0.003
LDL Cholesterol (mg/dl)	100 \pm 6	116 \pm 3	0.024
HDL Cholesterol (mg/dl)	64 \pm 3	54 \pm 2	0.002
Triglycerides (mg/dl)	73 \pm 4	102 \pm 7	0.001
Uric acid (mg/dl)	0.22 \pm 0.01	0.24 \pm 0.01	0.028
Systolic BP (mmHg)	120 \pm 2	129 \pm 2	0.001
Diastolic BP (mmHg)	72 \pm 1	78 \pm 1	0.001

Age-specified prevalence of the metabolic syndrome among 106 women with PCOS compared to the prevalence among representative sample of US women (NHANES III)



RELATIVE RISK FOR CHD IN WOMEN WITH SEVERE MENSTRUAL ABNORMALITIES (80% PCOS?) (Nurses' Health Study – mean age at follow-up 48 yr)



Multivariate analysis: data adjusted for age, BMI, cigarette smoking, menopausal status/hormone replacement therapy, family history of early myocardial infarction, parity, alcohol intake, physical activity level, use of aspirin, vitamins, oral contraceptives.

Surrogate markers of cardiovascular risk in young women with PCOS

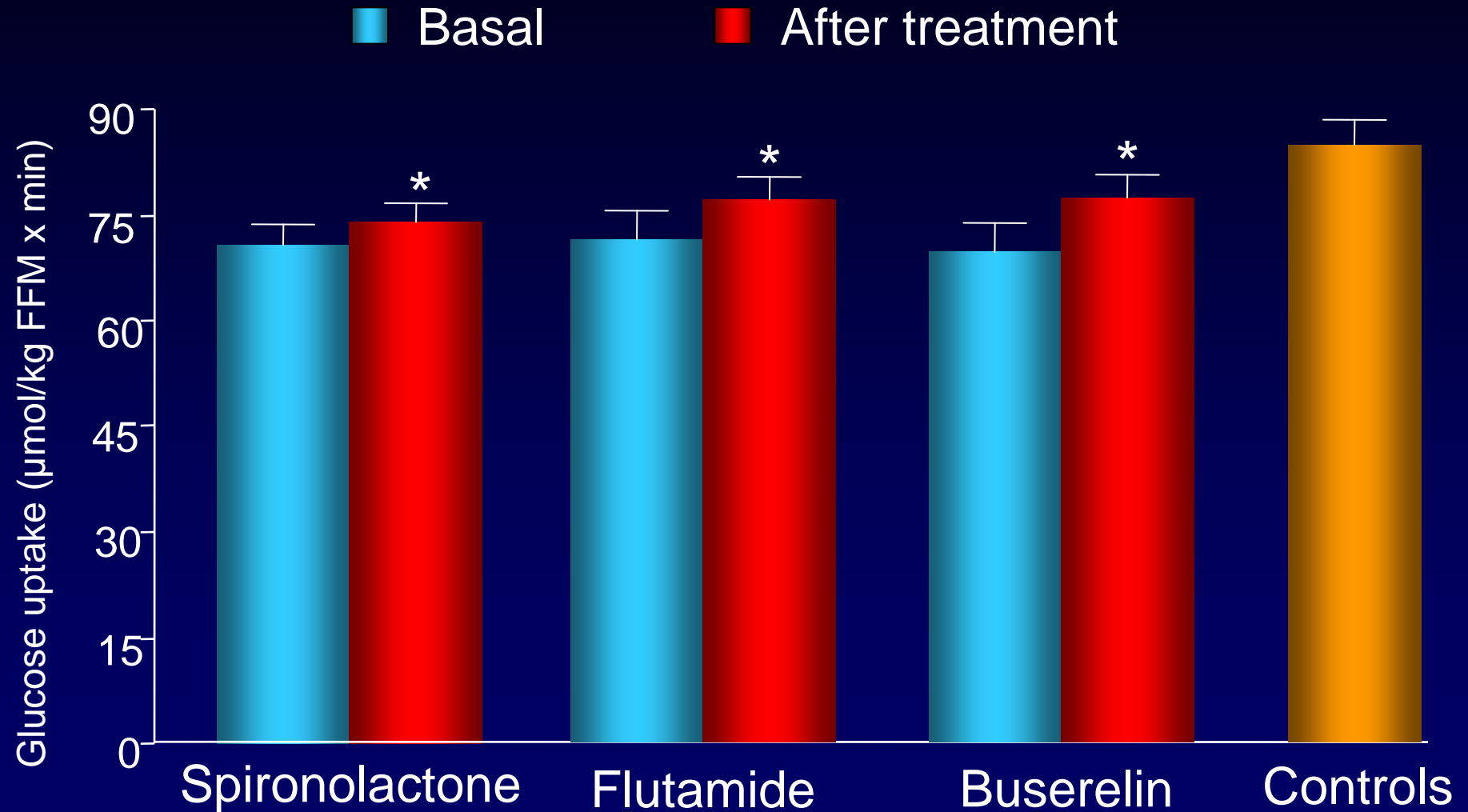
- endothelial dysfunction
- increased carotid intima-media thickness
- carotid plaques
- left ventricular hypertrophy
- diastolic dysfunction
- coronary calcifications
- increased low-grade chronic inflammation markers
- Increased oxidative stress markers

EFFECTS OF A MODERATE ANDROGEN EXCESS IN THE OVARIECTOMIZED RAT

	OVX	OVX + Testosterone	p
Serum testosterone (nmol/l)	0.4 ± 0.5	2.7 ± 0.5	0.001
Plasma insulin (mIU/l)	26 ± 2	31 ± 3	0.05
Glucose uptake (mg/kg·min)	6.3 ± 0.7	1.0 ± 0.4	0.001
Type 2 fibers in soleus muscle (%)	8 ± 1	22 ± 1	0.05
Muscle capillary density (capillaries/fiber)	5 ± 1	3 ± 1	0.05

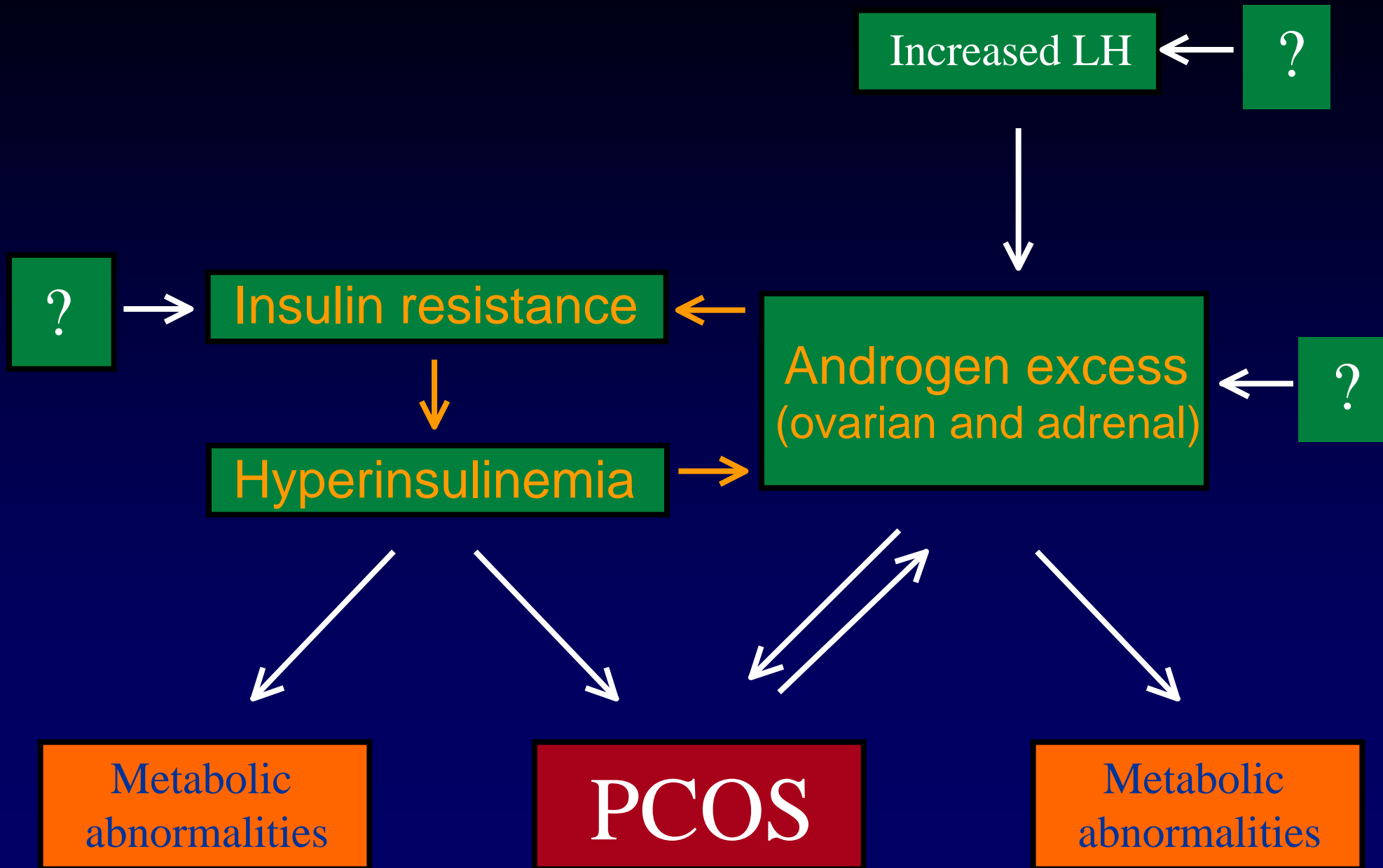
(from Holmang et al, Am J Physiol 1990)

INSULIN-MEDIATED GLUCOSE DISPOSAL IN LEAN HYPERANDROGENIC WOMEN BEFORE AND AFTER TREATMENT WITH SPIRONOLACTONE, FLUTAMIDE OR BUSERELIN



* P < 0.05 vs basal

(Moggetti et al, JCEM 1996)



POTENTIAL TARGETS OF A “PATHOGENETIC” THERAPY IN PCOS WOMEN

- Hyperinsulinemia
- Androgen excess

POLYCYSTIC OVARY SYNDROME

Potential targets of therapy

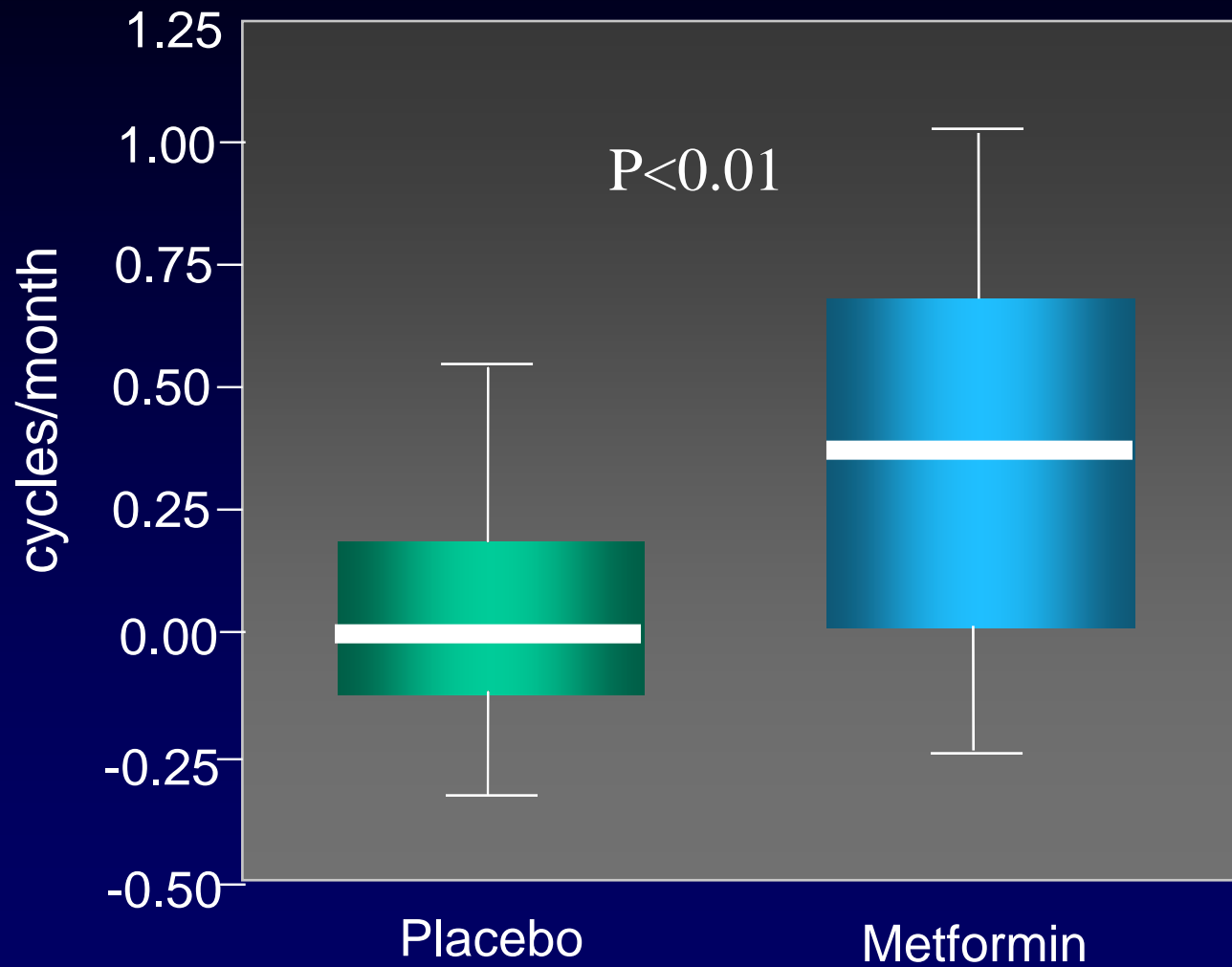
Insulin resistance

- Life style (diet, physical activity)
- Insulin sensitizing drugs (metformin, glitazones)

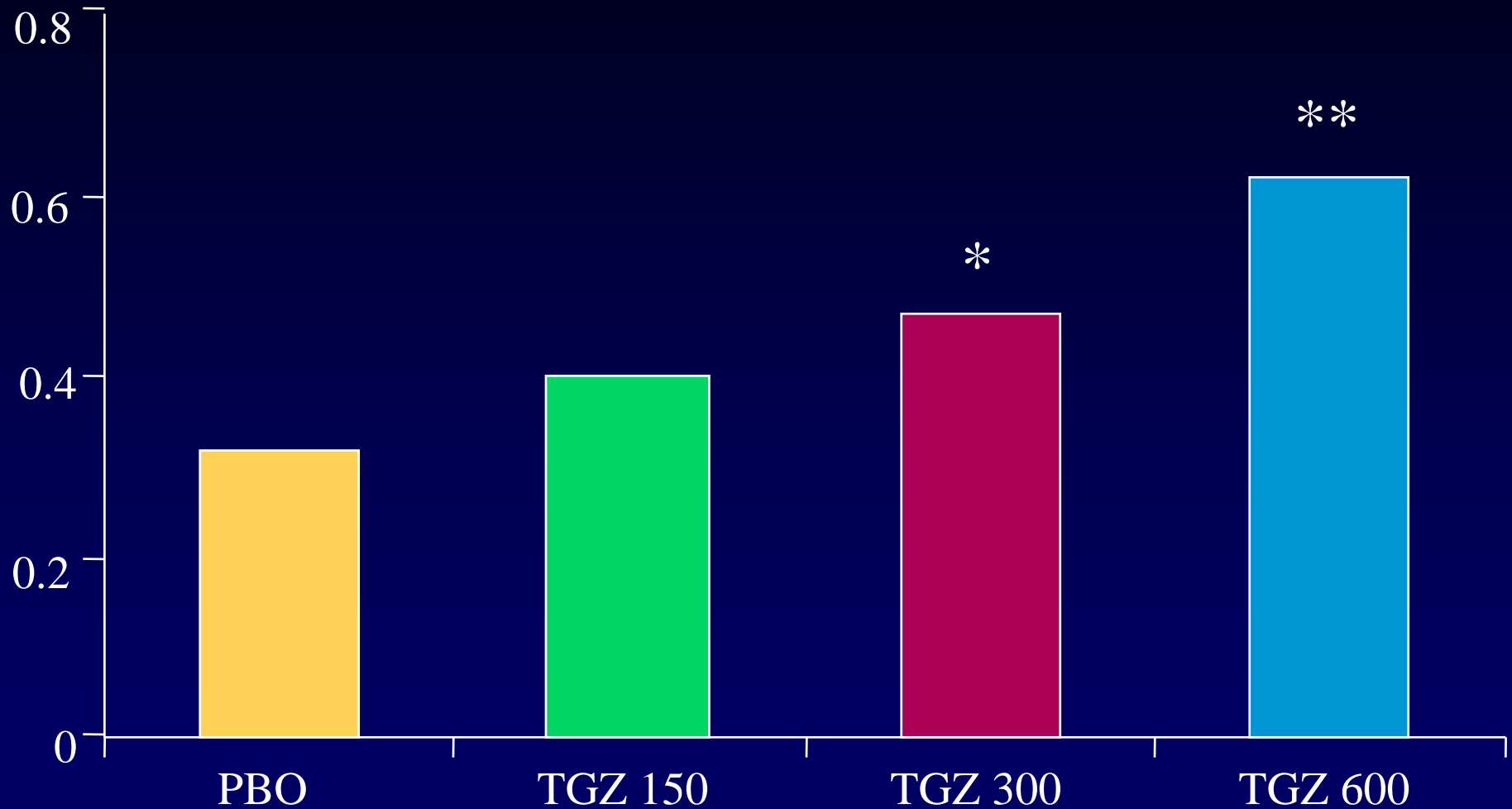
Androgen excess

- Antiandrogen drugs

BOX-PLOTS OF CHANGES IN FREQUENCY OF MENSTRUATION IN PCOS WOMEN GIVEN METFORMIN OR PLACEBO FOR 6 MONTHS



OVULATION RATE IN PCOS WOMEN GIVEN PLACEBO OR TROGLITAZONE (150-600 mg/day)



* $p < 0.02$ vs placebo
** $p < 0.0001$

(Azziz et al, JCEM 2001)

META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS TO DETERMINE EFFICACY OF INSULIN-SENSITIZING DRUGS IN PCOS WOMEN

J Lord et al, Cochrane Review, 2003

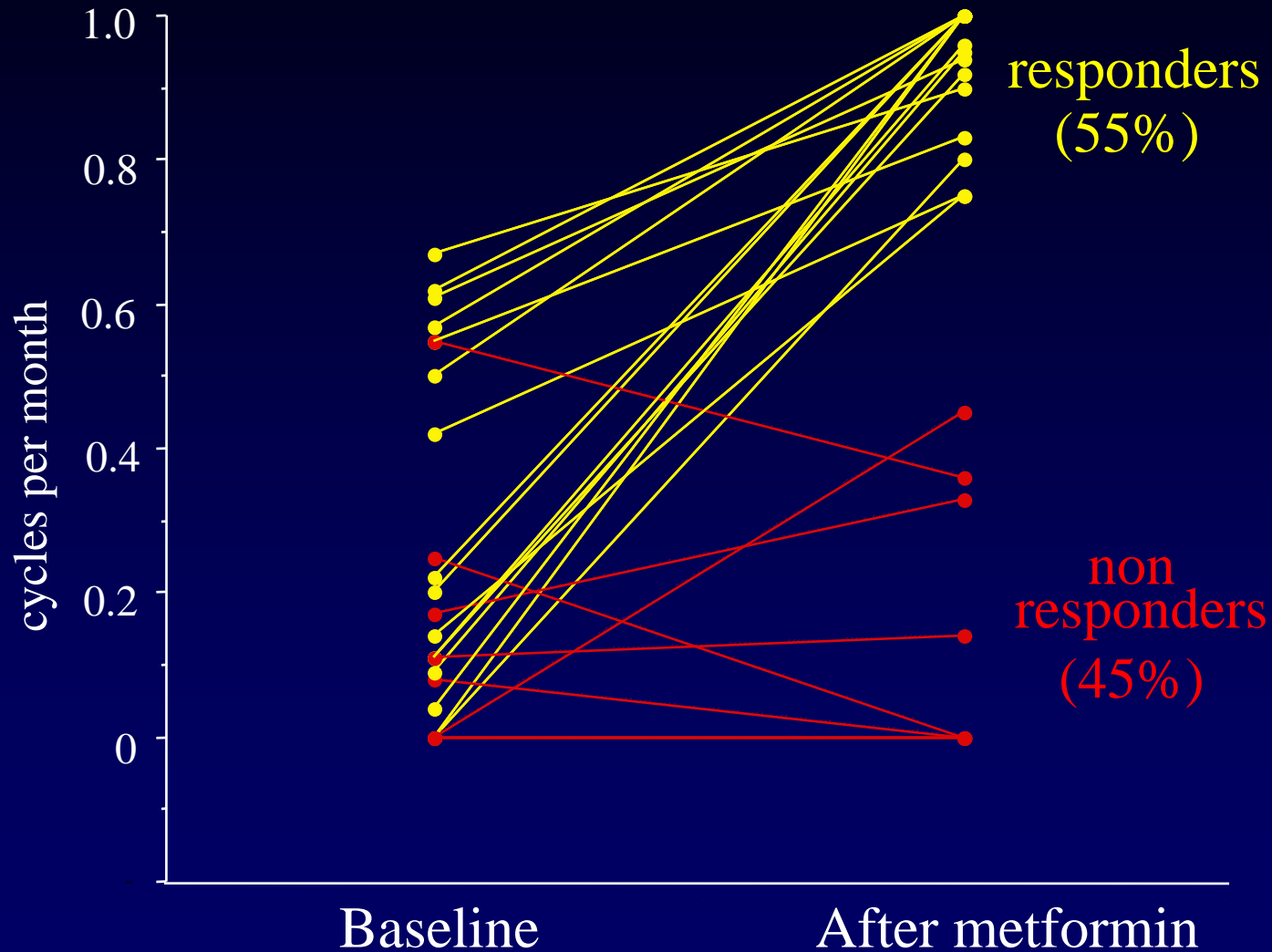
CONCLUSIONS

“Metformin is an effective treatment for anovulation in women with PCOS. Its choice as a first line agent seems justified, and there is some evidence of benefit on parameters of the metabolic syndrome.

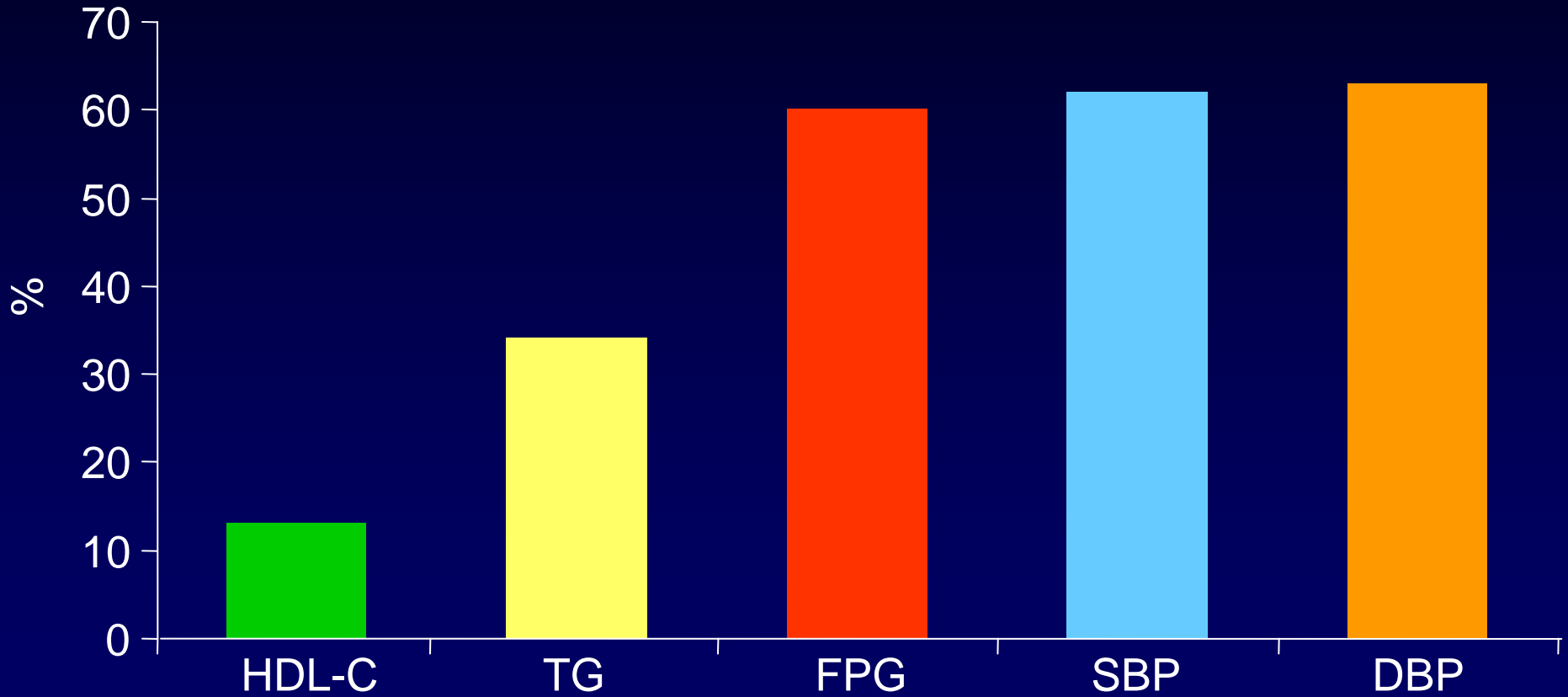
.....

It should be used as an adjuvant to general lifestyle improvements and not as a replacement for increased exercise and improved diet.”

CHANGES IN FREQUENCY OF MENSTRUATION IN INDIVIDUAL PCOS WOMEN GIVEN METFORMIN



Percentages of PCOS women having the Metabolic Syndrome in whom metabolic abnormalities reached ATP III guidelines targets after 6 months of diet plus metformin



POLYCYSTIC OVARY SYNDROME

Potential targets of therapy

Insulin resistance

- Life style (diet, physical activity)
- Insulin sensitizing drugs (metformin, glitazones)

Androgen excess

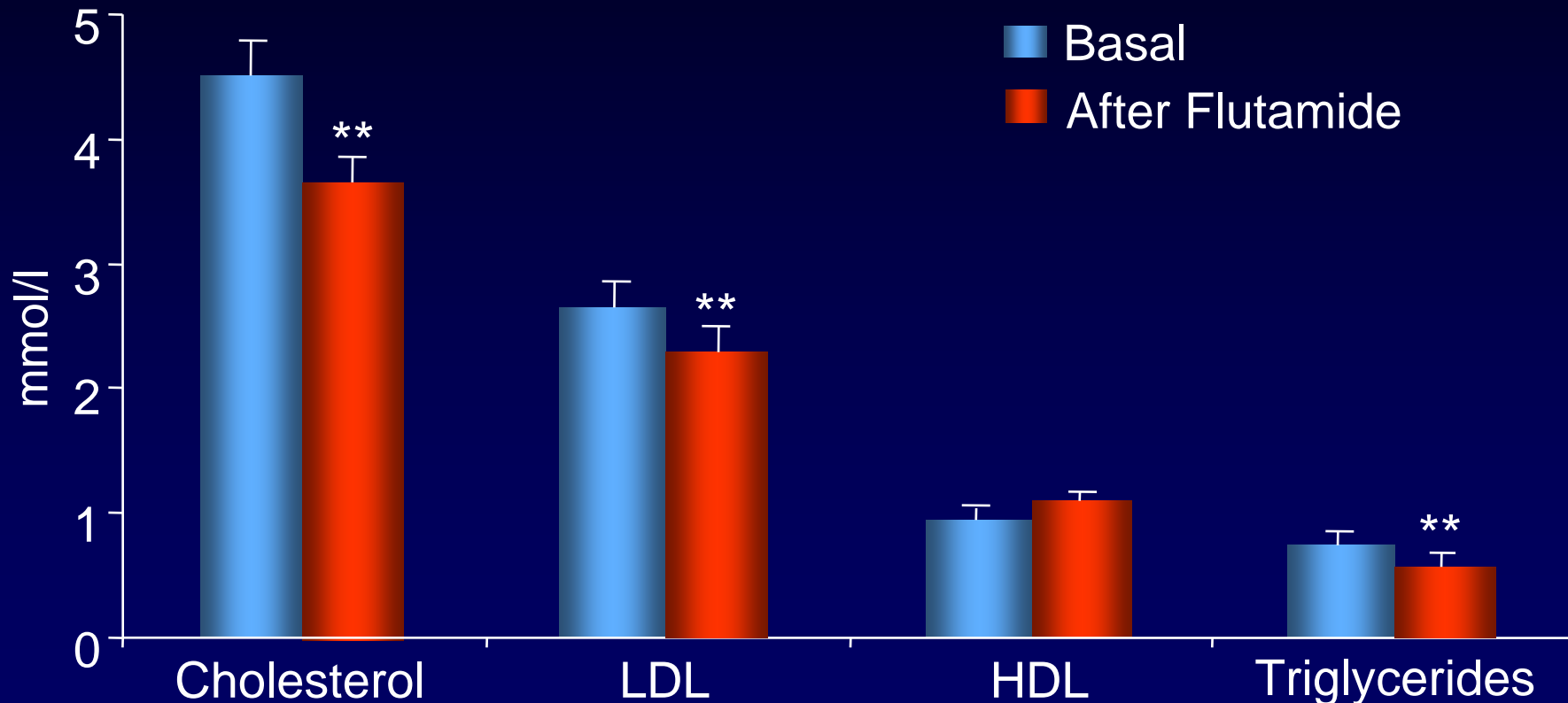
- Antiandrogen drugs

Antiandrogens in PCOS women*

- Reduction of hirsutism
- reduction of visceral fat
- reduction of LDL- and increase in HDL-cholesterol
- increase in insulin action (?)
- possible resumption of ovulation (?)

*most evidence obtained with flutamide

EFFECTS OF FLUTAMIDE (500 mg/day) ON SERUM LIPIDS IN PCOS WOMEN



**p<0.01

Diamanti-Kandarakis et al, JCEM 1998

Features improved by low-calorie diet alone or diet plus metformin (1.7 g/day) or flutamide (0.5g/day) in obese women with PCOS

	Diet	Metformin	Flutamide
BMI	X		
Visceral fat			X
Insulin resistance	X	X	X
Serum testosterone		X	X
LDL-Cholesterol			X
Menstrual cycle		X	X
Hirsutism			X

Conclusions

- Insulin resistance plays a pathogenetic role in both the endocrine and reproductive alterations of PCOS women
- These subjects often show metabolic alterations, with a probable, although not proven, increase in CV risk later in life
- Treatment should take into account the implications of these abnormalities: insulin sensitization first choice approach
- Antiandrogens offer scope for utilization beyond the symptomatic one. However, use of these drugs for a pathogenetic therapy is still experimental

