



Associazione Medici Endocrinologi

17° Congresso Nazionale AME Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

ROMA 8 - 11 novembre 2018



ITALIAN CHAPTER

Comitato Scientifico

Vincenzo Toscano, Rinaldo Guglielmi, Edoardo Guastamacchia, Franco Grimaldi

Coordinamento Centrale

Enrico Papini, Andrea Frasoldati, Roberto Attanasio, Giorgio Borretta, Nadia Cremonini

SINDROME DELL'OVAIO POLICISTICO: LA COMPAGNA DI UNA VITA

**DIAGNOSI PRECOCE, MA
TRATTAMENTO TARDIVO?**

VINCENZO TOSCANO

SAPIENZA UNIVERSITA' DI ROMA





Roma, 8-11 novembre 2018

Conflitti di interesse



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

NESSUNO



Roma, 8-11 novembre 2018

SINDROME DELL'OVAIO POLICISTICO

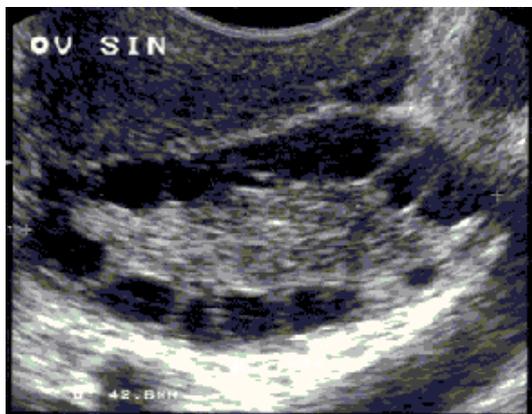
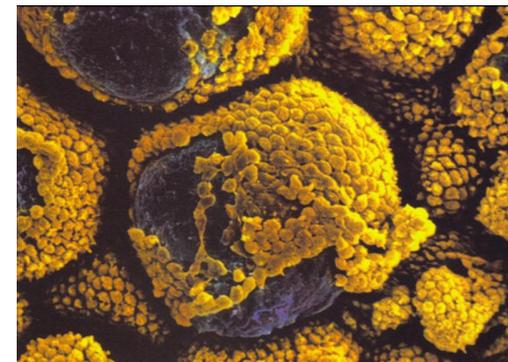


ITALIAN CHAPTER



NIH 1990

Anovulazione cronica e iperandrogenismo,
in assenza di altri disordini endocrini



ROTTERDAM 2003 (ESHRE/ASRM)

Presenza di almeno 2 delle seguenti 3
manifestazioni:

- Oligo/anovulazione
- Iperandrogenismo clinico e/o biochimico
- *Policistosi ovarica (PCO)*

Esclusione di altre patologie



SINDROME

DELL'OVAIO POLICISTICO



Roma, 8-11 novembre 2018

ANDROGEN EXCESS and PCOS SOCIETY 2006

TABLE 1

All possible phenotypes based on the presence or absence of oligo anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome (PCOS).

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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
AE-PCOS 2006 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						

presenza di iperandrogenismo clinico e/o biochimico

associato ad almeno uno dei seguenti criteri:

- ✓ - oligo-anovulazione cronica
- ✓ - ovaie policistiche all'ecografia pelvica

Esclusione di altre patologie



PREVALENZA



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

La prevalenza di PCOS in donne in età riproduttiva varia fra il 4% ed il 22%, a seconda dei criteri diagnostici utilizzati.

Azziz et al., 2004, *JCEM*, 89:2745-9

Asuncion et al., 2000, *JCEM*, 85:2434-2438

Belosi et al., 2006, *Hum. Reprod.*, 21(12): 3108-3115

Human Reproduction Vol.21, No.12 pp. 3108–3115, 2006

Advance Access publication October 19, 2006.

doi:10.1093/humrep/del306

Is the PCOS diagnosis solved by ESHRE/ASRM 2003 consensus or could it include ultrasound examination of the ovarian stroma?

C.Belosi¹, L.Selvaggi², R.Apa², M.Guido², D.Romualdi², A.M.Fulghesu³ and A.Lanzone^{1,2,4,5}

La prevalenza aumenta del 20%



PREVALENZA



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

La prevalenza fra le adolescenti non è stata indagata.

Azziz et al., 2004, *JCEM*, 89:2745-9

Asuncion et al., 2000, *JCEM*, 85:2434-2438

Belosi et al., 2006, *Hum. Reprod.*, 21(12): 3108-3115

I segni ed i sintomi della PCOS compaiono con la pubertà,
ma sono spesso sovrapponibili alle caratteristiche della pubertà fisiologica.

Diamanti-Kandarakis et al., 2008, *Pediatr Endocrinol Rev*, 5(4):904-911





IRSUTISMO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Miglior marker clinico di iperandrogenismo:
comparsa di peli terminali nelle zone in cui normalmente la donna è
glabra (tipiche del maschio).

I peli vanno distinti in:

- ✓ Vello: peli morbidi, sottili e chiari
- ✓ Peli terminali: duri, spessi e scuri





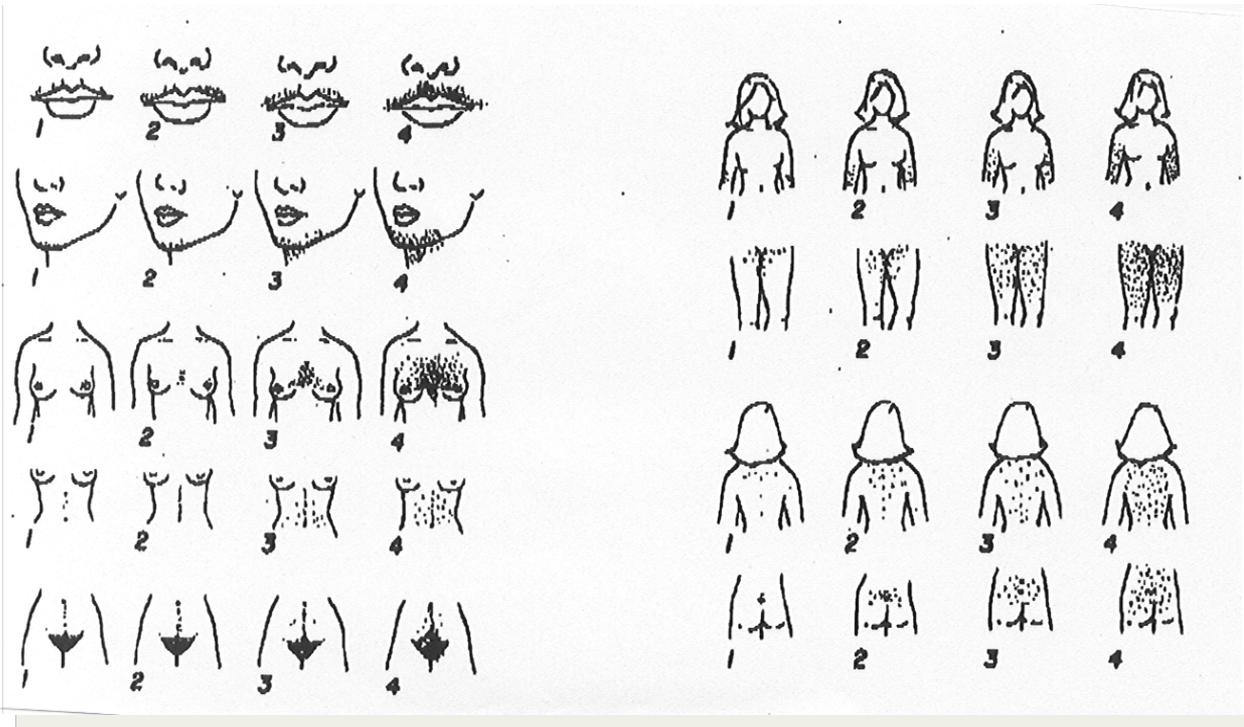
IRSUTISMO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Scala di Ferriman-Gallwey



Normalità: 0-7

Irsutismo lieve: 8-12

Irsutismo moderato: 13-18

Irsutismo grave: >19

Standardizzato in donne caucasiche adulte,
potrebbe essere meno sensibile nelle adolescenti



EZIOLOGIA



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

EXTENSIVE CLINICAL EXPERIENCE

Relative Prevalence of Different Androgen Excess Disorders in 950 Women Referred because of Clinical Hyperandrogenism

E. Carmina, F. Rosato, A. Janni, M. Rizzo, and R. A. Longo

The Journal of Clinical Endocrinology & Metabolism 91(1):2-6
Copyright © 2006 by The Endocrine Society
doi: 10.1210/jc.2005-1457

	N° di pazienti	% sul totale delle pazienti
Sindrome dell'Ovaio Policistico	685	72.1
Iperandrogenismo Idiopatico	150	15.8
Irsutismo Idiopatico	72	7.6
NCAH	41	4.3
Neoplasie Androgeno-Secernenti	2	0.2



CRITERI DIAGNOSTICI DI PCOM



ITALIAN CHAPTER

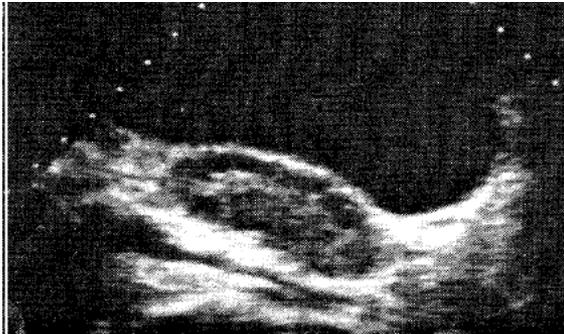
Roma, 8-11 novembre 2018



1985, Adams J,

Eco transaddominale:

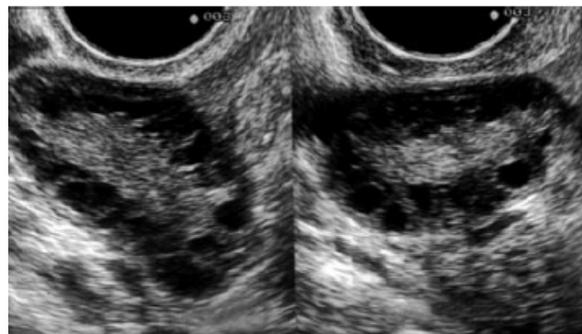
- > 10 FNPS, di 2-8 mm
- (distribuzione periferica)
- aumento dello stroma



2003, Rotterdam criteria

Eco trans-vaginale:

- in almeno 1 ovaio
- ≥ 12 FNPO di 2-9 mm o
- volume ovarico > 10 ml



2014, AE&PCOS Society,

Eco TV (sonda ≥ 8 MHz):

- ≥ 25 FNPO, di 2-9 mm o
 - volume ovarico > 10 ml
- se non è possibile una stima corretta del FNPO





DIAGNOSI DI ESCLUSIONE



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report

TABLE 5

Prevalence of thyroid dysfunction, hyperprolactinemia (Hi-Prl), androgen secreting neoplasms (ASNs), 21-hydroxylase deficient nonclassic adrenal hyperplasia (NCAH), and Cushing's Syndrome (CS) in patients with hyperandrogenism or polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. with thyroid dysfunction	% with thyroid dysfunction	No. with Hi-Prl	% with Hi-Prl	No. NCAH	% NCAH	No. CS	% CS	No. ASN	% ASN
Ferriman and Purdie 1983	83	467	0	0.00%	4	0.90% ^a						
Conway et al., 1989	84	556			58	11.00%	10	1.80% ^e				
Luciano et al., 1984	227	150			25	16.70%						
O'Driscoll et al., 1994	162	350			1	0.30%	3	0.90%	0	0.00%	2	0.60%
Moran et al., 1994	226	250					5	2.00%	1	0.40%	2	0.80%
Balen et al., 1995	87	1871	0	0.00%	25	1.30%	19	1.00%			0	0.00%
Khoury et al., 1996	89	112			17	15.20%						
Romaguera et al., 2000	228	100					1	1.00%				
Azziz et al., 2004	47	873	6	0.70%	3	0.30%	18	16.50%	0	0.00%	2	1.83%
Escobar-Morreale et al., 2004	229	109			4	3.70% ^b						
Janssen et al., 2004	230	175	36	20.60% ^c								
Glintborg et al., 2004	231	340			6	1.80% ^d	2	0.60%	1	0.29%	1	0.29%
Carmina et al., 2006	46	950					41	4.30%			2	0.21%
Legro et al., 2006	110	626	45	7.20%								
Diamanti-Kandarakis & Danidis, 2007	100	634	4	0.60%	69	10.80% ^f	0	0%	0	0%	0	0%
Total		7563	87	1.15%	212	2.80%	99	1.31%	2	0.03%	9	0.12%



Roma, 8-11 novembre 2018

The phenotype of hirsute women: a comparison of polycystic ovary syndrome and 21-hydroxylase-deficient nonclassic adrenal hyperplasia



ITALIAN CHAPTER

Marita Pall, M.D., Ph.D.,^a Ricardo Azziz, M.D., M.P.H., M.B.A.,^{a,b,c} Jorge Beires, M.D., Ph.D.,^d and Duarte Pignatelli, M.D., Ph.D.^e

Fertility and Sterility® Vol. 94, No. 2, July 2010

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TABLE 1

Clinical features of subjects.

	Obese patients with PCOS	Lean patients with PCOS	Patients with NCAH	Controls
No. of subjects	54	52	23	27
Age (y)	24 ± 7	22 ± 5	22 ± 8	26 ± 7
BMI (kg/m ²)	35 ± 6 ^a	23 ± 2 ^b	26 ± 4 ^a	22 ± 2
BMI >27 kg/m ² (%)	54/54 (100)	0/52 (0)	10/23 (43)	0/27 (0)
Degree of menstrual dysfunction				
Eumenorrhea, ovulation (%)	0/54 (0)	0/52 (0)	17/23 (74)	27/27 (100) ^a
Eumenorrhea, anovulation (%)	5/54 (9) ^{c,d}	6/52 (11) ^{c,d}	2/23 (9)	0/27 (0) ^a
Oligomenorrhea (%)	41/54 (76) ^c	41/52 (79) ^c	3/23 (13)	0/27 (0) ^a
Amenorrhea (%)	8/54 (15)	5/52 (10)	1 (4)	0/27 (0)
MFG (mean ± SD)	18 ± 5	14 ± 4 ^e	16 ± 5	5 ± 2 ^a
Maximum ovarian volume (cm ³)	10.7 ± 4.6 ^c	9.7 ± 4.2 ^c	6.1 ± 4.5	5.2 ± 2.3
Maximum no. follicles	11.9 ± 2.7 ^c	11.4 ± 2.9 ^c	8.1 ± 3.5	6.0 ± 2.8
Subjects with PCO (%)	46/52 (88) ^c	35/49 (71) ^c	5/21 (24)	1/24 (4)

Note: Values are expressed as mean ± SD. MFG = modified Ferriman-Gallwey score; NCAH = nonclassic adrenal hyperplasia; PCO = polycystic ovaries.

^a $P < .01$ compared with all other groups.

^b $P < .05$ compared with obese patients with PCOS and NCAH.

^c $P \leq .05$ compared with controls and patients with NCAH.

^d Anovulatory, luteal-phase $P < 4.0$ ng/mL.

^e $P < .01$ compared with obese patients with PCOS.

Pall. Nonclassic adrenal hyperplasia versus PCOS. Fertil Steril 2010.

In conclusion, this study suggests that nonclassic adrenal hyperplasia and PCOS present with similar clinical features and increased androgen levels. Nonclassic adrenal hyperplasia is a hyperandrogenic disease with androgen levels similar to those in obese women with PCOS but with a metabolic profile similar to that of lean women with PCOS. A few differences do exist.

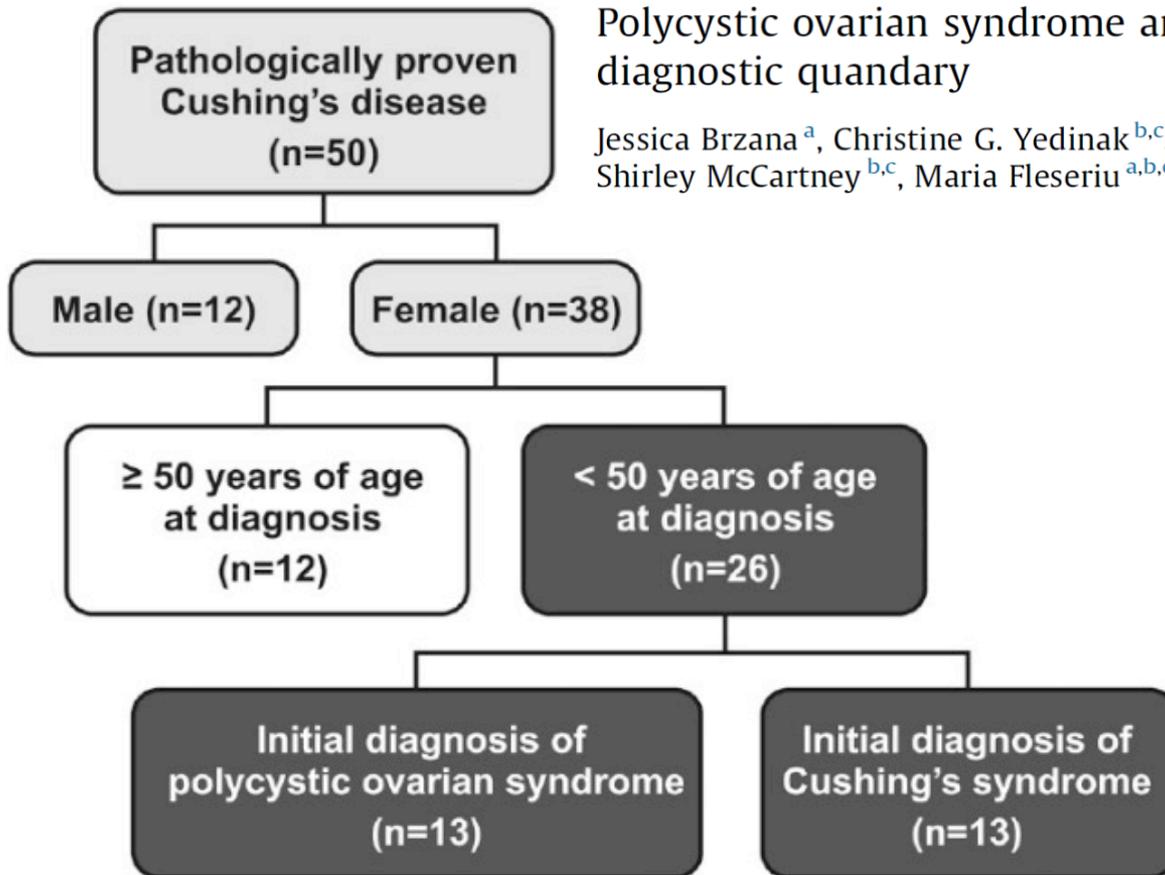


PREVALENZA DI CUSHING IN «PCOS»



ITALIAN CHAPTER

Roma, 8-11 novembre 2018



Polycystic ovarian syndrome and Cushing's syndrome: a persistent diagnostic quandary

Jessica Brzana^a, Christine G. Yedinak^{b,c}, Nadia Hameed^a, Adeline Plesiu^a, Shirley McCartney^{b,c}, Maria Fleseriu^{a,b,c,*}



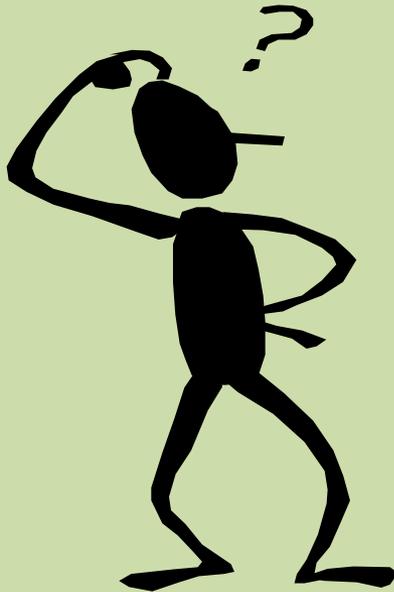
Roma, 8-11 novembre 2018



ITALIAN CHAPTER



POLYCYSTIC OVARY SYNDROME :



WHAT IS IT?

J.VAITUKAITIS , N.E.J.M. , **1983**



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



J. Endocr. (1983), **97**, 379–387 Printed in Great Britain
0022–0795/83/0097–0379 \$02.00/0

379

© 1983 Journal of Endocrinology Ltd

Is hirsutism an evolving syndrome?

Vincenzo Toscano, M. V. Adamo, Stefania Caiola, Sonia Foli, Elisa Petrangeli,
Daniela Casilli and Francesco Sciarra

*Istituto di V Clinica Medica Generale, Università degli Studi di Roma, Policlinico
Umberto I, 00100 Rome, Italy*

(Received 10 September 1982)



Table 1. *Clinical data in the five groups of hirsute patients with the number of cases shown in parentheses. The duration of hirsutism was obtained from the patient's history and the degree of hirsutism scored according to Lorenzo (1970)*

Group	Age (years)	Duration of hirsutism (years)	Degree of hirsutism (mean \pm s.d.)	Oligomenorrhoea (% of patients in group)
I (8)	12-24	1	6.25 \pm 3.8	37.5
II (12)	16-27	1-2	9.33 \pm 3.47	41.5
III (7)	14-22	2-3	11.12 \pm 2.76	44.3
IV (16)	15-30	3-5	12.75 \pm 5.18	75.0
V (17)	16-32	>5	14.88 \pm 4.72	100.0



Roma, 8-11 novembre 2018

PCOS: PATOGENESI



ITALIAN CHAPTER

Fattori genetici e ambientali

0021-972X/07/\$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(3):787-796
Copyright © 2007 by The Endocrine Society
doi: 10.1210/jc.2006-2012

CLINICAL REVIEW: Identifying Children at Risk for Polycystic Ovary Syndrome

Robert L. Rosenfield



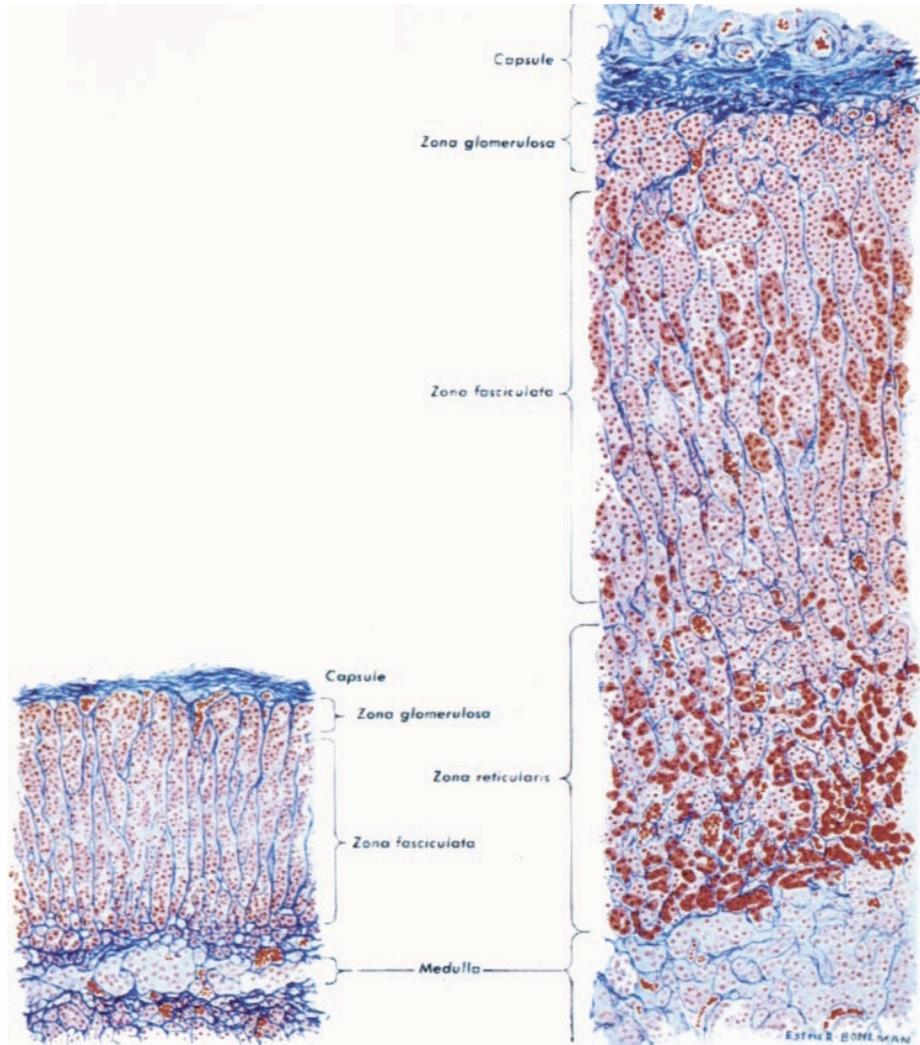


ADRENARCA



ITALIAN CHAPTER

Roma, 8-11 novembre 2018



Attivazione graduale, dall'età di 6 anni, della produzione degli androgeni da parte del surrene (zona reticolare), con incremento del DHEA e del DHEA-S

Pubarca: comparsa di peli pubici

Ibanez et al., 2000, *Endocrine Reviews*, 21(6):671-696

Bloom, Fawcett, 1986, *Textbook of histology*, ed.9. W.B: Saunders Co.,p461(323)



Roma, 8-11 novembre 2018

ADRENARCA PREMATURO



ITALIAN CHAPTER



Attivazione surrenalica precoce

Pubarca: ♂ < 9 anni, ♀ < 8 anni, ± peluria ascellare e cambiamento dell'odore del sudore, senza altri segni di maturazione sessuale



Può essere indotto dall'incremento ponderale;
l'obesità è associata a maggior incidenza di adrenarca prematuro.

Remer et al., 1999, *JCEM*, 84:3936-3944

Jabbar et al, *J Am Coll Nutr*, 10:289-296



Roma, 8-11 novembre 2018

ADRENARCA PREMATURO

Ibanez et al., 2000, *Endocrine Reviews*, 21(6):671-696



ITALIAN CHAPTER



	Gonadarca	Crescita	Età ossea	Androgeni	Gonadotropine
Pubarca prematuro idiopatico	Assente	Normale	Normale	Normali, DHEA-S =	Prepuberi
Adrenarca prematuro	Assente	Normale o lievemente accelerata	Correlata all'altezza	come nella pubertà iniziale, DHEA-S ↑ o ↑ ↑	Prepuberi
Pubertà precoce	Presente	Progressivamente accelerata	Progressivamente accelerata	Normali per età	Come nella pubertà iniziale
SAG late-onset	Assente (clitoride o pene ↑ volume)	Moderatamente-marcatamente accelerata	Moderatamente-marcatamente avanzata	Moderatamente o marcatamente elevati	Prepuberi
Neoplasie virilizanti	Assente (clitoride o pene ↑ volume)	Marcatamente accelerata	Marcatamente e progressivamente avanzata	Marcatamente elevati	Prepuberi
Iatrogeno	Assente (clitoride o pene ↑ volume)	Marcatamente accelerata	Marcatamente e progressivamente avanzata	Marcatamente elevati	Prepuberi



ADRENARCA PREMATURO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Adrenarca esagerato

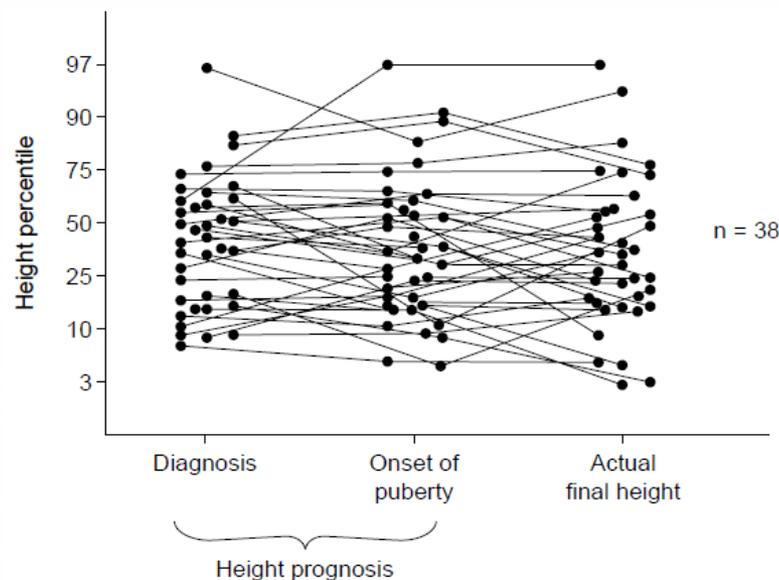
DHEA-S
130-185 mcg/dl

Androstenedione
75-99 ng/dl

Esagerata risposta
allo stimolo
con ACTH ev

Pubertà lievemente anticipata,
senza compromissione della statura
finale

Rosenfield, 2007, *JCEM*, 92(3):787-796
Ibanez et al, 1998, *JCEM*, 83:3558-3562
Ibanez et al, 1992, *JCEM*, 74:254-257
Lazar et al, 1995, *Eur J Endocrinol*, 133:403-406





ADRENARCA PREMATURO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

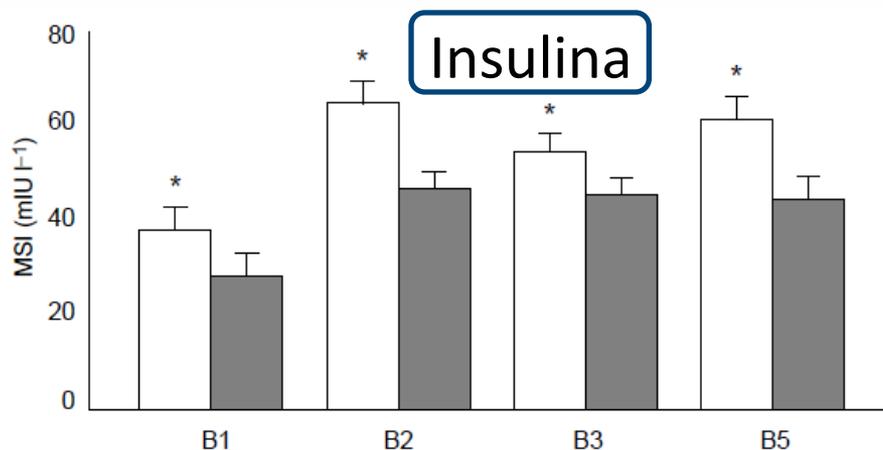
Hyperinsulinaemia, dyslipaemia and cardiovascular risk in girls with a history of premature pubarche

L. Ibáñez¹, N. Potau³, P. Chacon², C. Pascual², A. Carrascosa¹

¹ Adolescent and Endocrine Unit, Hospital Universitari Materno-Infantil Vall d'Hebron, Barcelona, Spain

² Department of Clinical Chemistry, Hospital Universitari General Vall d'Hebron, Barcelona, Spain

³ Hormonal Laboratory, Hospital Universitari Materno-Infantil Vall d'Hebron, Barcelona, Spain



Insulino-resistenza associata
all'adiposità viscerale
ed alla dislipidemia, non all'obesità.

Ibanez et al, 1997, *JCEM*, 82:2283-2288

Ibanez et al, 2003, *Clin Endocrinol*, 58:372-379

Solo il 15-20% delle pazienti con pubarca prematuro sviluppano iperandrogenismo (caratteristiche cliniche sovrapponibili alla popolazione di controllo).

Meas et al, 2002, *Clin Endocrinol*, 57:101-106



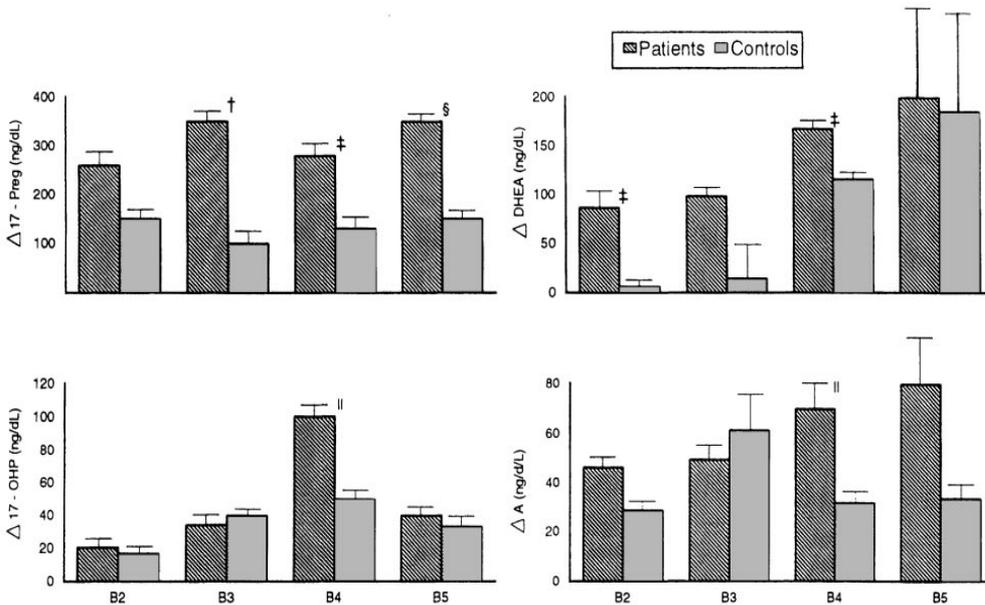
ADRENARCA ESAGERATO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Disregolazione della steroidogenesi che si manifesta con iperandrogenismo surrenalico e successivamente ovarico?



FERTILITY AND STERILITY®
Copyright © 1997 American Society for Reproductive Medicine
Published by Elsevier Science Inc.

Vol. 67, No. 5, May 1997
Printed on acid-free paper in U. S. A.

Girls diagnosed with premature pubarche show an exaggerated ovarian androgen synthesis from the early stages of puberty: evidence from gonadotropin-releasing hormone agonist testing*†

Lourdes Ibáñez, M.D.‡§ Maria E. Street, M.D¶
Neus Potau, M.D.|| Antonio Carrascosa, M.D.‡
Maria Zampoli, M.D.¶

Hospital Materno-Infantil Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain, and Clinica Pediatrica, University of Parma, Parma, Italy

Rosenfield, 2007, *JCEM*, 92(3):787-796
Ehrman et al., 1995, *End Reviews*, 16(3):322-353



PESO ALLA NASCITA

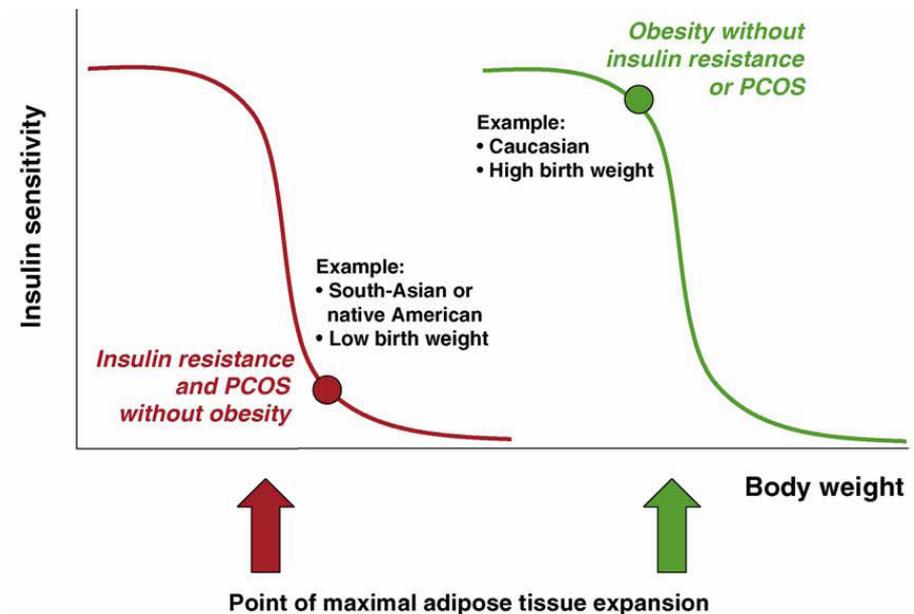
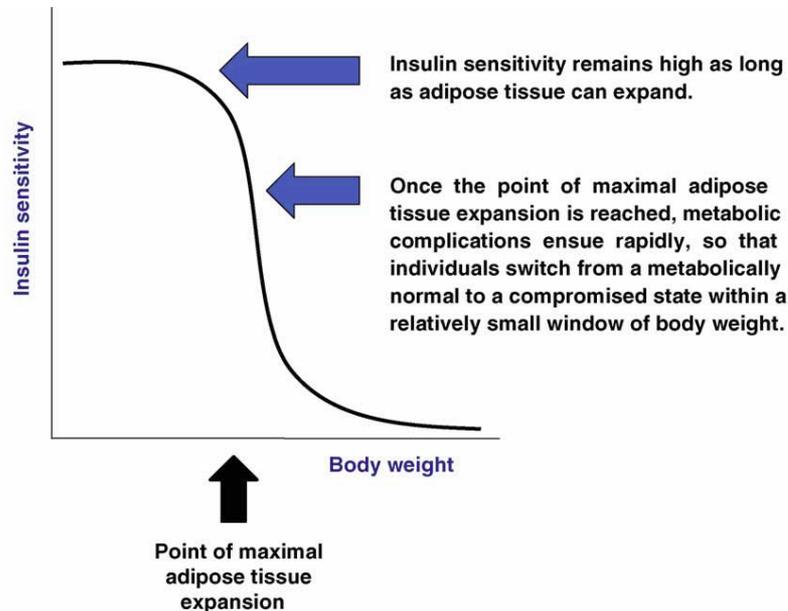
Roma, 8-11 novembre 2018

Small for gestational age (SGA/LBW)

Large for gestational age (LGA)

A rischio di pubarca prematuro e successivamente di PCOS

Alterazioni del tessuto adiposo e insulino-resistenza





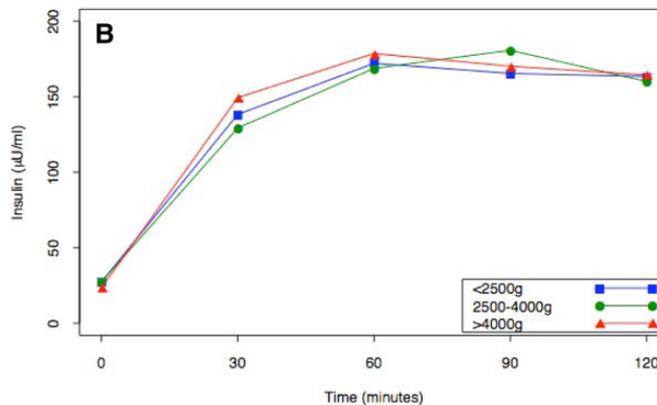
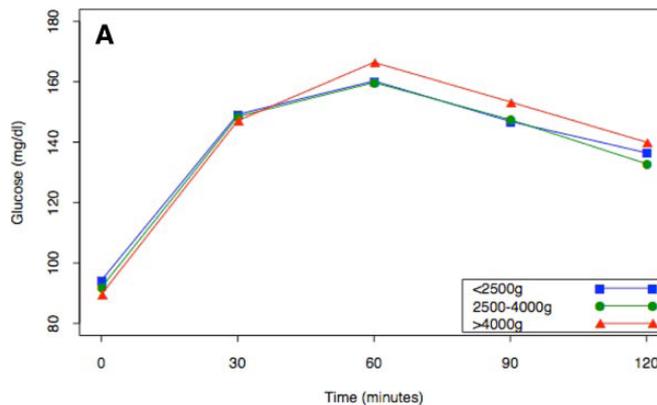
PESO ALLA NASCITA



Roma, 8-11 novembre 2018

Small for gestational age (SGA/LBW)-Large for gestational age (LGA)

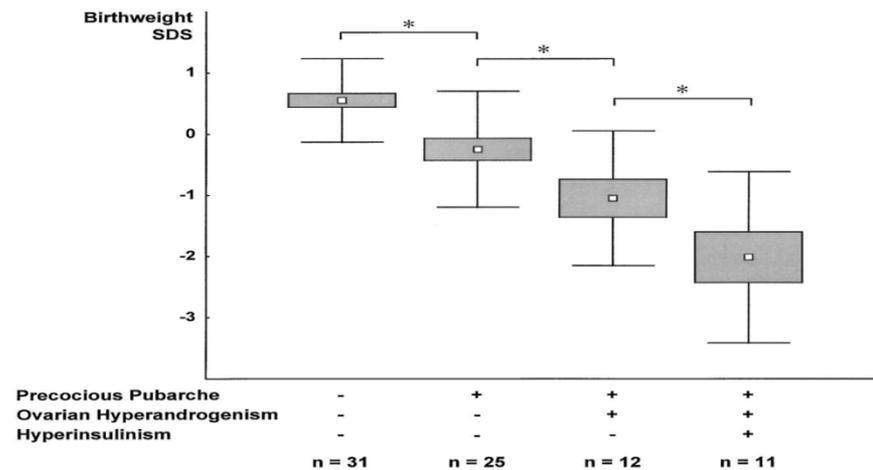
CONTRO



Legro et al., 2009, *JCEM*, 95(2):789-799

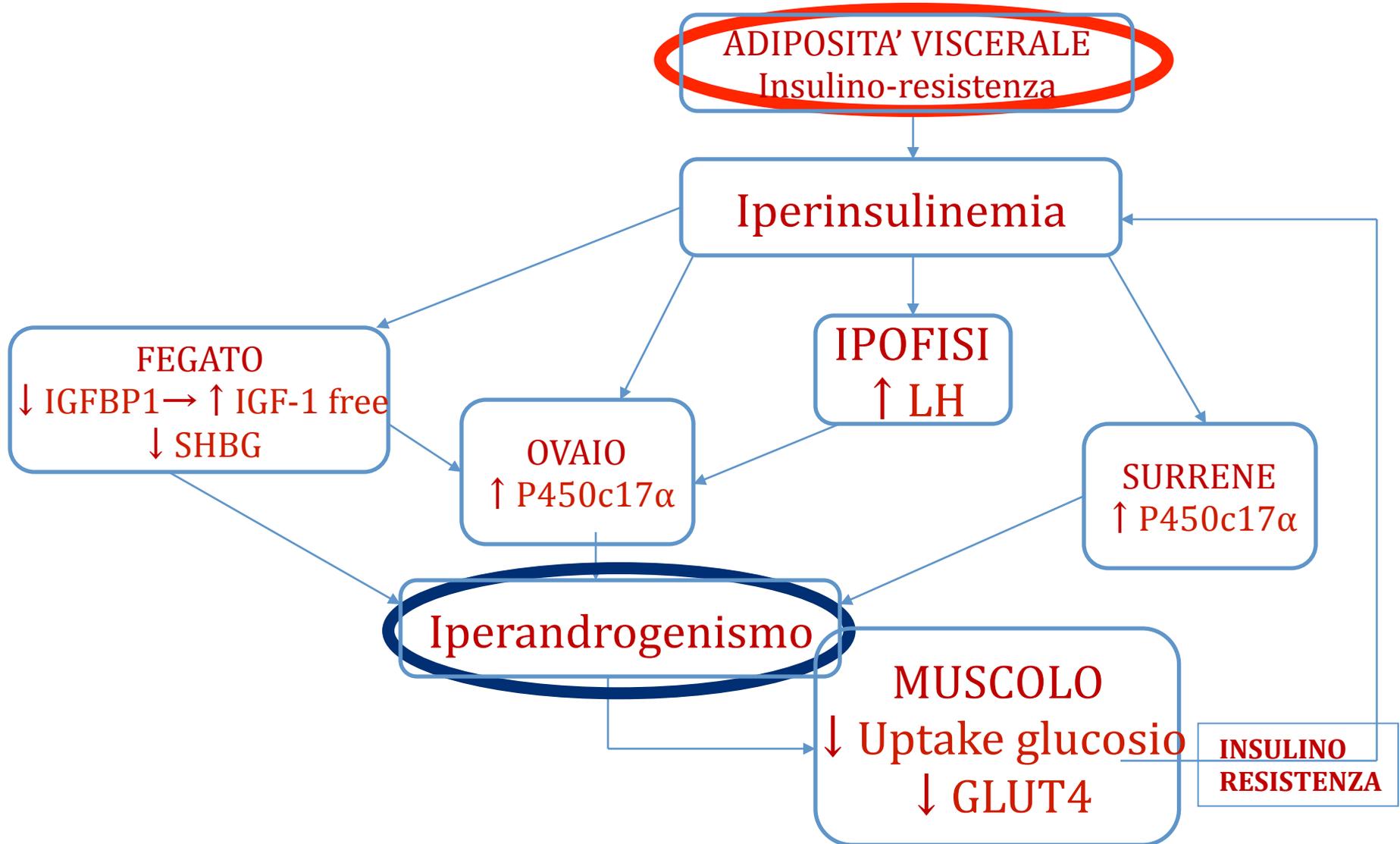
PRO

Ibanez et al, 1998,
JCEM, 83:3558-3562





IPERANDROGENISMO E INSULINO-RESISTENZA





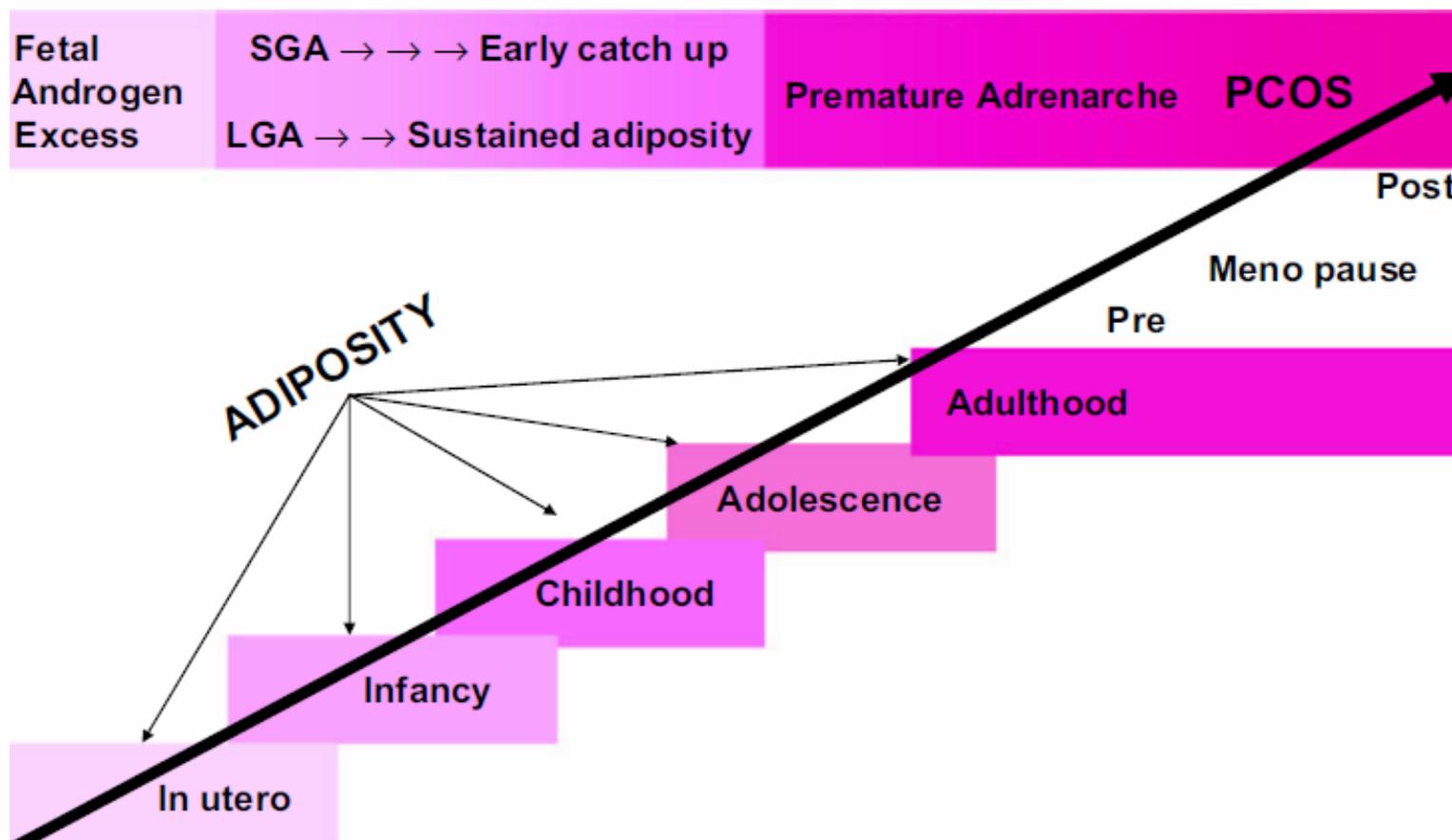
STORIA NATURALE



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

The throughout life course of PCOS



IPERTRICOSI PREPUBERALE

410

R. Balducci & V. Toscano

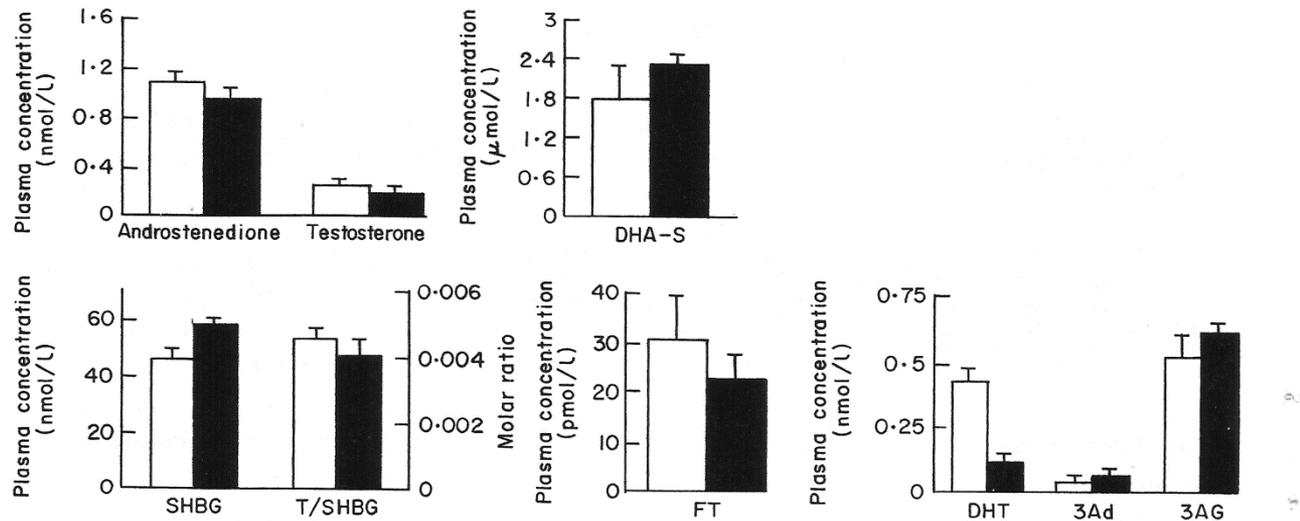


Fig. 1. Androstenedione, testosterone, dehydroepiandrosterone sulphate, free testosterone (FT), sex hormone binding globulin (SHBG), T/SHBG (molar ratio), dihydrotestosterone (DHT), 3 α -androstane diol (3Ad) and 3 α -androstane diol glucuronide (3AG) in □, patients and ■, controls.

JCI

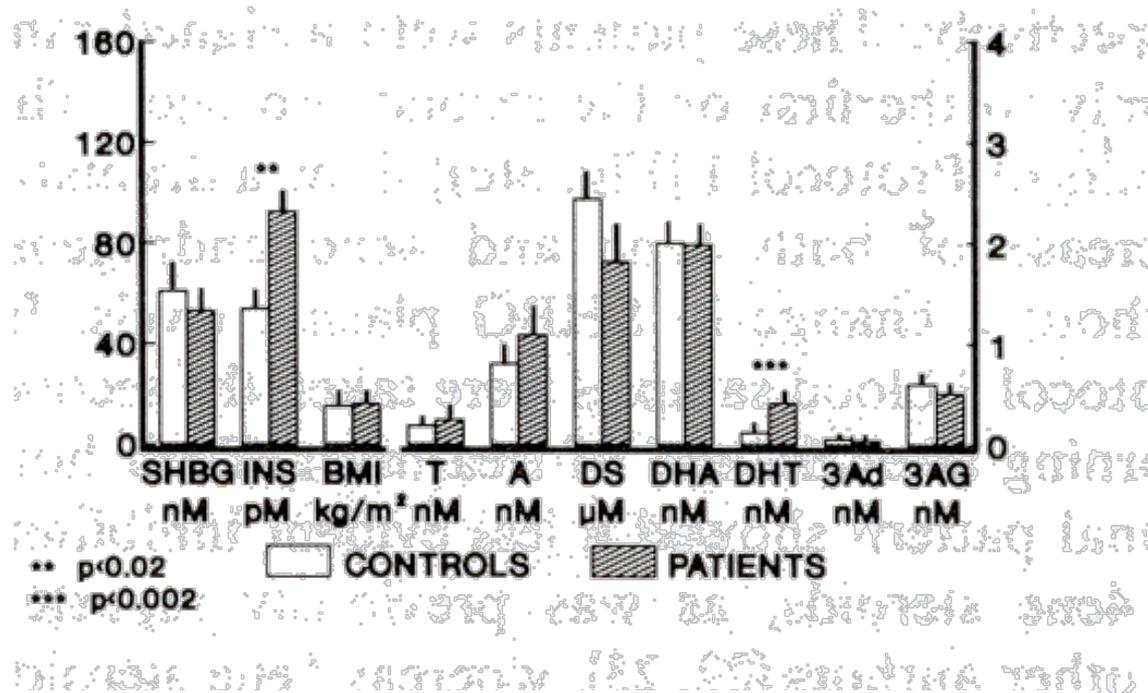
The Journal of Clinical Investigation

Circulating dihydrotestosterone may not reflect peripheral formation.

V Toscano, R Horton

J Clin Invest. 1987;79(6):1653-1658. <https://doi.org/10.1172/JCI113003>.

IPERTRICOSI PREPUBERALE





ADOLESCENZA:

IPERANDROGENISMO BIOCHIMICO



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Durante la pubertà vi sono rapide modificazioni degli ormoni gonadici e surrenalici.

Incremento degli androgeni associato a riduzione della SHBG, dovuta anche alla fisiologica insulino-resistenza.

Table 2

Longitudinal concentrations of androgens and SHBG in healthy British girls ($n = 27$) by Puberty [Tanner] Stage. Data expressed as median (IQR). Reproduced with permission from Ahmed (2008).

	Tanner stage				
	1	2	3	4	5
Age (yr)	10.2 (9.6–10.7)	11.4 (10.5–11.9)	12.2 (11.6–12.8)	13.2 (12.6–13.8)	14.9 (14.2–15.2)
Testosterone (nmol/l)	0.3 (0.3–0.5)	0.3 (0.3–0.8)	0.8 (0.5–1.1)	1.1 (0.8–1.5)	1.4 (1.1–1.6)
SHBG (nmol/l)	66 (56–94)	57 (48–69)	57 (40–71)	45 (34–66)	43 (33–61)
DHEAS (mcmol/l)	3.5 (2.4–5.2)	5.1 (2.4–7.5)	6.8 (4.5–9.6)	7.0 (4.6–10.0)	12.1 (9.0–17.7)
A4 (nmol/l)	3.3 (2.7–4.0)	4.2 (3.4–4.8)	5.8 (5.1–7.9)	6.1 (5.7–7.5)	8.7 (7.4–11.3)

Table II Early follicular phase (Day 2–6) androgen levels and diagnostic categories for PCOS.

	ALL ($n = 214$) ^a	PCOS-R			PCOS-N			PCOS-AES		
		No ($n = 168$)	Yes ($n = 46$)	P	No ($n = 204$)	Yes ($n = 10$)	P	No ($n = 203$)	Yes ($n = 11$)	P
A4 (nmol/l)	2.9 [1.0–9.3]	2.7 (2.2–3.6)	3.5 (2.9–4.6)	<0.001	2.8 (2.2–3.7)	5.8 (4.0–8.3)	<0.001	2.8 (2.2–3.7)	6.8 (4.3–9.1)	<0.001
DHEAS (μ mol/l)	3.2 [1.1–9.4]	3.2 (2.2–4.2)	3.7 (2.5–5.5)	0.034	3.2 (2.3–4.4)	4.9 (2.5–6.1)	0.079	3.2 (2.3–4.4)	5.4 (2.5–6.7)	0.029
SHBG (nmol/l)	47.9 [11.0–194.0]	50.0 (36.3–64.0)	38.9 (24.8–61.8)	0.012	48.7 (34.5–64.0)	22.9 (16.0–40.7)	0.001	48.7 (34.4–64.2)	27.9 (17.1–36.3)	0.001
TT (pmol/l)	1215 [543–3869]	1169 (940–1450)	1529 (1126–2024)	<0.001	1189 (948–1501)	2311 (1704–3289)	<0.001	1186 (945–1499)	2575 (1777–3427)	<0.001
cFT (pmol/l)	17.2 [4.5–98.3]	16.2 (11.7–21.8)	28.5 (13.1–40.4)	<0.001	16.5 (12.0–24.1)	58.5 (31.0–72.9)	<0.001	16.4 (11.9–24.1)	59.8 (34.9–71.4)	<0.001

Lynn Ahmed, 2009, PhD thesis

Hickey et al, 2011, *Hum Reprod*, 26: 1469-1477

Williams et al. 2013, *Molecular and Cellular Endocrinology*, 373: 61-67



ADOLESCENZA: IPERANDROGENISMO BIOCHIMICO



Roma, 8-11 novembre 2018

Nelle adolescenti non esistono valori di riferimento per gli androgeni

TABLE 1. Typical ranges expected for serum androgens and steroid precursors in normal females and premature adrenarche

	17PREG (ng/dl)	17PROG (ng/dl)	11-Deoxycortisol (ng/dl)	Cortisol (μ g/dl)	DHEA-S (μ g/dl)	DHEA (ng/dl)	Androstenedione (ng/dl)	Testosterone (ng/dl)
Before ACTH (0800 h)								
Children, 1–5 yr old	10–105	5–115	20–160	3–20	5–35	20–130	10–50	<20
Children, 6–10 yr old	10–200	5–115	20–160	3–20	10–115	20–345	10–75	<20
Premature adrenarche	20–350	5–115	20–160	3–20	40–130	50–600	20–75	10–35
Early pubertal girls	35–350	15–220	20–160	3–20	35–130	40–600	40–175	10–35
Adult females, follicular phase	55–360	15–150 ^a	20–160	3–20	75–255	100–850	60–200	20–60
After ACTH _{1–24} (30–60 min after $\geq 10 \mu$ g/m ² iv)								
Children, 1–5 yr old	45–350	50–270	95–300	17–45	5–35	25–100	15–70	<20
Children, 6–10 yr old	60–650	85–300	95–300	17–45	10–115	70–320	25–100	<20
Premature adrenarche	80–750	85–400	95–300	17–45	40–130	80–725	25–230	10–35
Early pubertal girls	150–750	90–400	95–300	17–45	35–130	70–725	55–230	10–35
Adult females, follicular phase	150–1070	35–160 ^a	95–300	17–45	75–255	250–1470	60–250	20–60
Conversion multipliers to SI units	0.0316 (nmol/liter)	0.0303 (nmol/liter)	0.0289 (nmol/liter)	0.0276 (μ mol/liter)	0.0271 (μ mol/liter)	0.0347 (nmol/liter)	0.0349 (nmol/liter)	0.0347 (nmol/liter)

Rosenfield RL., 2007, *JCEM*, 92(3):787-796



ADOLESCENZA: ANOVULAZIONE



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Amenorrea, oligomenorrea severa

Oligomenorrea lieve, cicli mestruali regolari:

- progesterone plasmatico (21° e 25° giorno del ciclo mestruale)
- temperatura basale
- monitoraggio ecografico

Nei primi 2 anni dopo il menarca,
i cicli mestruali sono irregolari nel 40-60% delle
adolescenti e anovulatori nel 55-80% dei casi,
per immaturità dell'asse ipotalamo-ipofisi-gonadi

Apter et al., 1977, *JCEM*, 45:1039-1048

Van Hooff et al., 1999, *Hum. Reprod.*, 14:2223-2229



ADOLESCENZA: ANOVULAZIONE



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

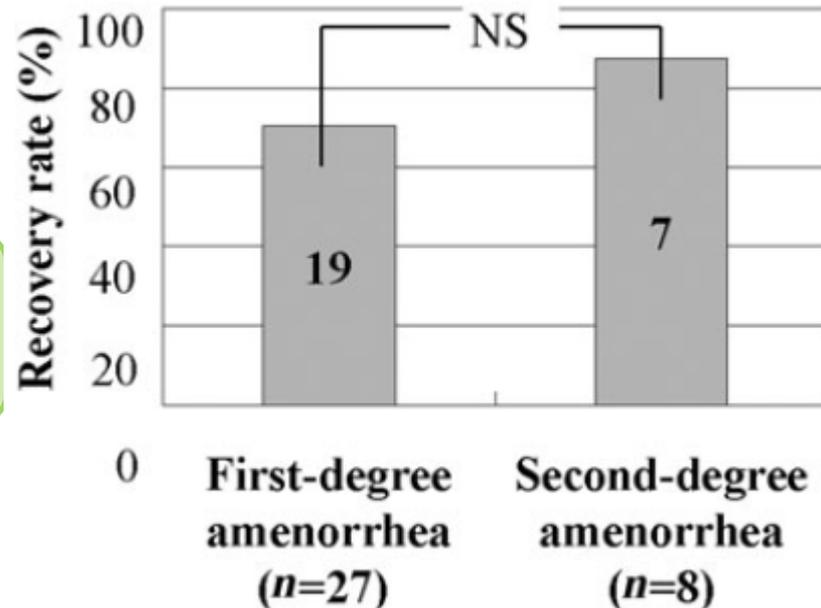
Table III. Odds ratios (95% confidence intervals) of the prevalence of oligomenorrhoea at age 18 years for girls with irregular menstrual cycles (IMC) or oligomenorrhoea at the start of the study compared with those with regular menstrual cycles (RMC) at the start of the study

Menstrual cycle pattern at start of the study	Those who started oral contraceptives (OC) recoded to menstrual cycle pattern in the year preceding OC use	Those who started OC excluded
RMC	Reference category ($n = 128$)	Reference category
IMC total group	8.3 (1.9–37) ($n = 148$) ^a	6.8 (1.4–34) ($n = 51$)
IMC subgroup mean length 35–41 days	33 (7–154) ($n = 38$)	21 (3.4–124) ($n = 13$)
IMC subgroup mean length 22–34 days	2.4 (0.4–13) ($n = 110$)	2.1 (0.3–13) ($n = 38$)
Oligomenorrhoea	63 (14–278) ($n = 67$)	31 (5.7–170) ($n = 28$)

all'età di 18 anni,
circa il 50% delle adolescenti
che a 15 anni presentavano
oligomenorrea,
presentano ancora cicli
anovulatori

Van Hooff et al., 2004, *Hum. Reprod.*, 19(2):383-392

First-degree amenorrhea = MAP test +
Second-degree amenorrhea = MAP test -



Morimatsu et al., 2009, *J Obstet Gynaecol Res*, 35(3):545-550



Roma, 8-11 novembre 2018

ADOLESCENZA: POLICISTOSI OVARICA



ITALIAN CHAPTER



Presenza di 12 o più follicoli in almeno un ovaio, che misurano 2-9 mm di diametro e/o aumento del volume ovarico (> 10 ml)

✓ Non sempre è possibile eseguire un'ecografia trans-vaginale

L'ovaio nelle adolescenti è istologicamente simile all'ovaio policistico: alto numero di follicoli antrali e aumentato volume ovarico

OVAIO MULTIFOLLICOLARE
(normale durante la pubertà)

6-10 follicoli di 4-10 mm di diametro senza
l'aumento dello stroma ovarico

Adams et al., 1985, *Lancet*, 2(8469-70):1375-1379

Merrill JA, 1963, *South Med J*, 56:225-231

Mortensen et al., *JCEM*, 91:3786-3790

Brook et al., 1988, *Br Med J*, 296:878



ADOLESCENZA: POLICISTOSI OVARICA



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Longitudinal Change of Sonographic Ovarian Aspects and Endocrine Parameters in Irregular Cycles of Adolescence

STEFANO VENTUROLI, ELEONORA PORCU, RAFFAELLA FABBRI, VALERIA PLUCHINOTTA, SAVERIO RUGGERI, SILVIA MACRELLI, ROBERTO PARADISI, AND CARLO FLAMIGNI

PCO 41%
Multifollicolare 23%
Normale 36%

Functional Significance of Polycystic-Size Ovaries in Healthy Adolescents

Monica Mortensen, Robert L. Rosenfield, and Elizabeth Littlejohn

Section of Pediatric Endocrinology, The University of Chicago, Chicago, Illinois 60637

Alta prevalenza di PCO in adolescenti sane e asintomatiche

Venturoli et al., 1995, *Pediatric Research*, 38(6): 974-980

Mortensen et al., 2006, *JCEM*, 91:3786-3790



Esistono criteri diagnostici nelle adolescenti?



GENERAL GYNECOLOGY

The diagnosis of polycystic ovary syndrome in adolescents

Enrico Carmina, MD; Sharon E. Oberfield, MD; Rogerio A. Lobo, MD

TABLE
Diagnostic criteria for polycystic ovary syndrome in adolescents

Criterion	Hyperandrogenism ^a	Chronic anovulation ^b	Polycystic ovaries ^c
Diagnosis of PCOS	+	+	+
Diagnosis of PCOS probable but not confirmed	+	+	-
Diagnosis of PCOS not possible during adolescence	+	-	+
Diagnosis of PCOS not possible during adolescence	-	+	+
Not PCOS	+	-	-
Not PCOS	-	+	-
Not PCOS	-	-	+

PCOS, polycystic ovary syndrome.

^a Hyperandrogenemia is primary criterion—acne and alopecia are not considered as evidence for hyperandrogenism—hirsutism may be considered sign of hyperandrogenism only when it has been documented to be progressive; ^b Oligomenorrhea (or documented anovulation) has to be present for at least 2 years; ^c Diagnosis of polycystic ovaries by abdominal ultrasound has to include increased ovarian size (>10 cm³).

Carmina. The diagnosis of PCOS in adolescents. Am J Obstet Gynecol 2010.

When the diagnosis cannot be confirmed, the patients should be followed up carefully into adulthood and the diagnosis should be reconsidered whenever symptoms persist. ■



Esistono criteri diagnostici nelle adolescenti?



Criteri diagnostici della PCOS nelle adolescenti presenza di 4 criteri fra i seguenti 5
Iperandrogenismo clinico: irsutismo e acne persistenti e di grado rilevante
Iperandrogenismo biochimico: testosterone totale > 50 ng/dl e rapporto LH/FSH > 2
Insulino-resistenza e iperinsulinemia: acanthosis nigricans, adiposità viscerale e alterata tolleranza glucidica
Oligomenorrea persistente a più di due anni dal menarca
Ovaio policistico all'ecografia

ASRM PAGES

Sultan C, Paris F, 2006, *Fertil Steril*, 86(1):S6

Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group

Conclusions (Agreement)

- Criteria for the diagnosis of PCOS in adolescents differ from those used for older women of reproductive age (level B).
- Groups at risk (e.g., obese, hirsute, irregular menses) should be identified, but physicians should be cautious of overdiagnosing PCOS (level B).
- Individual PCOS manifestations in adolescents (e.g., obesity, hirsutism, irregular menses) (level B) should be treated.

Knowledge Gaps/Recommended Future Research

- Absence of longitudinal studies through adolescence.
- Absence of specific diagnostic criteria for identifying PCOS early in adolescence.
- Absence of normative values for a number of biochemical markers during adolescence.
- Assessment of value of intervention in PCOS early in adolescence.
- Lack of clarity as to whether the severity of symptoms during adolescence predicts the extent of the disorder in later life.



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Esistono criteri diagnostici nelle adolescenti?



ITALIAN CHAPTER



ENDOCRINE SOCIETY 2013

Viene suggerito di porre la diagnosi in presenza di **persistente oligomenorrea** e **iperandrogenismo clinico e/o biochimico**, dopo aver escluso altre possibili cause.

La presenza di **anovulazione** e **ovaie policistiche** non è sufficiente alla diagnosi, perché potrebbero essere fisiologiche in alcune fasi della maturazione riproduttiva.

Legro et al, 2013, *JCEM*, 98(12): 4565-4592



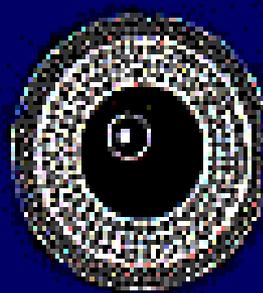
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POLICISTOSI OVARICA

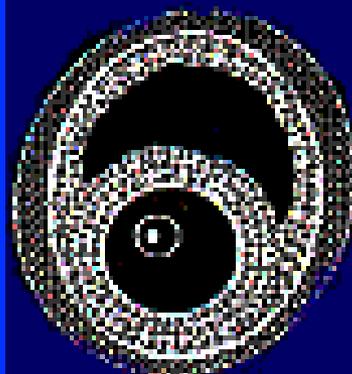
IPOSTESI PATOGENETICHE



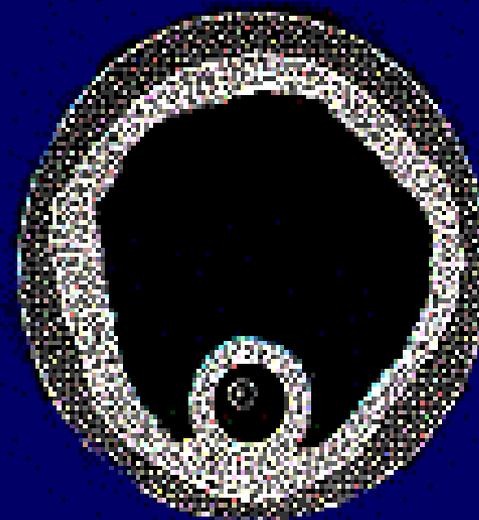
ITALIAN CHAPTER



**Follicolo
pre-antrale**



**Follicolo
antrale
precoce**



**Follicolo
pre-ovulatorio**



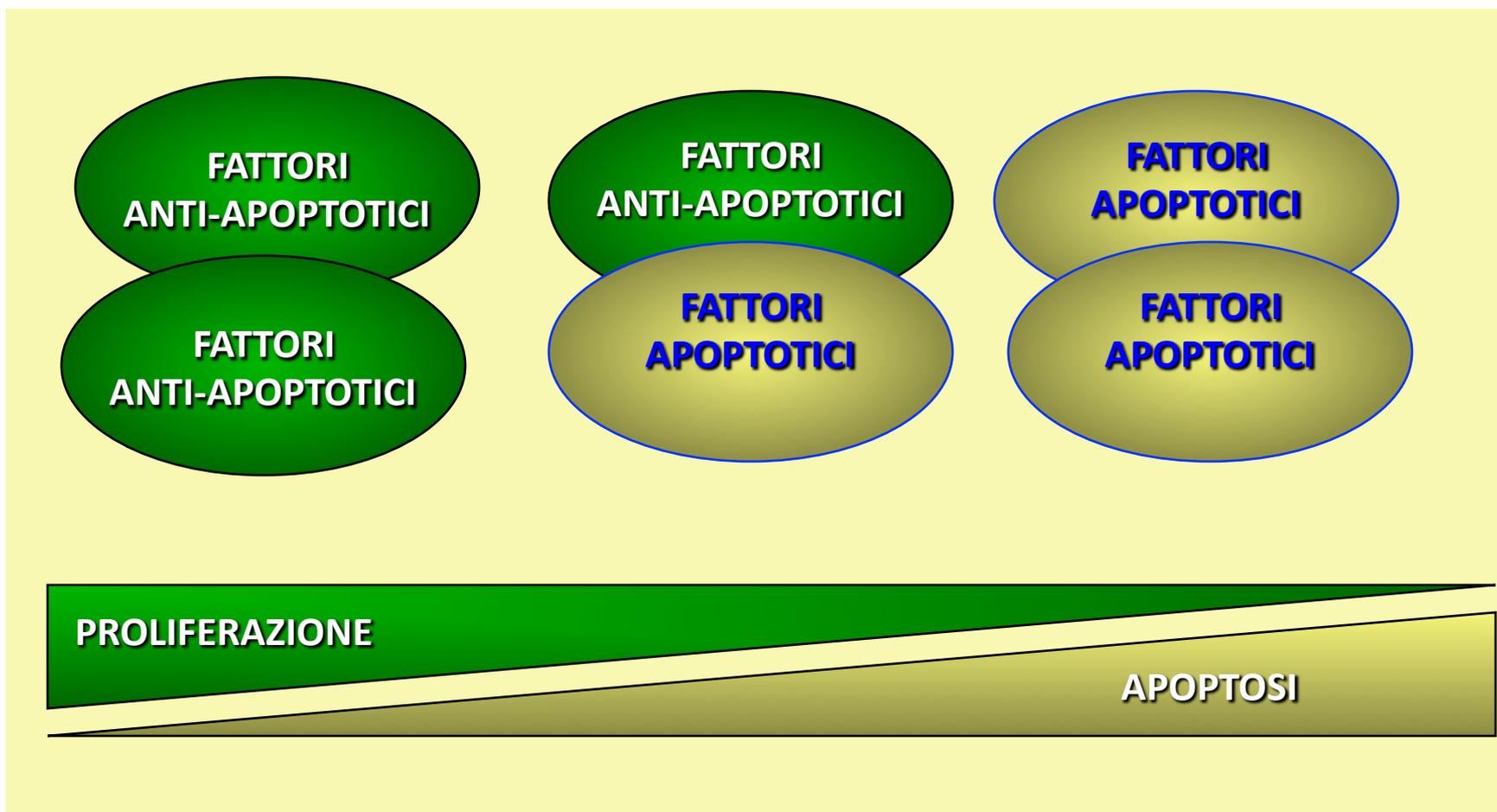
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POLICISTOSI OVARICA

IIPOTESI PATOGENETICHE



ITALIAN CHAPTER





Roma, 8-11 novembre 2018

PCOS: TENTATIVO DI DEFINIZIONE



ITALIAN CHAPTER



PERDITA DI EQUILIBRIO FRA

FATTORI APOPTOTICI

E

FATTORI ANTI APOPTOTICI



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



J. Endocr. (1983), **97**, 379–387 Printed in Great Britain
0022–0795/83/0097–0379 \$02.00/0

379

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Is hyperandrogenism an evolving syndrome?

Vincenzo Toscano, M. V. Adamo, Stefania Caiola, Sonia Foli, Elisa Petrangeli,
Daniela Casilli and Francesco Sciarra

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(Received 10 September 1982)



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



- COME SPIEGARE QUESTO ANDAMENTO EVOLUTIVO?**

- COME L'ALTERATO METABOLISMO DEGLI ANDROGENI IN PERIFERIA PUÒ COINVOLGERE LA PRODUZIONE GHIANDOLARE DEGLI ANDROGENI STESSI E QUINDI CREARE UN MECCANISMO AUTO-MANTENENTESI?**



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



➤ **DUPLICE APPROCCIO:**

- **SPERIMENTALE (TRATTAMENTO CON DHT DELL'ANIMALE DA ESPERIMENTO)**
- **CLINICO (FOLLOW-UP DI SITUAZIONI CLINICHE DI IPERANDROGENISMO CHE POTEVANO ESSERE ESPRESSIONE DI:
 - **ISOLATA IPERPRODUZIONE PERIFERICA DI ANDROGENI IN ASSENZA DI IPERPRODUZIONE GHIANDOLARE**
 - **IPERPRODUZIONE DI ANDROGENI DAL SURRENE PRIMA DELL'ATTIVAZIONE PUBERALE DELL'OVAIO****

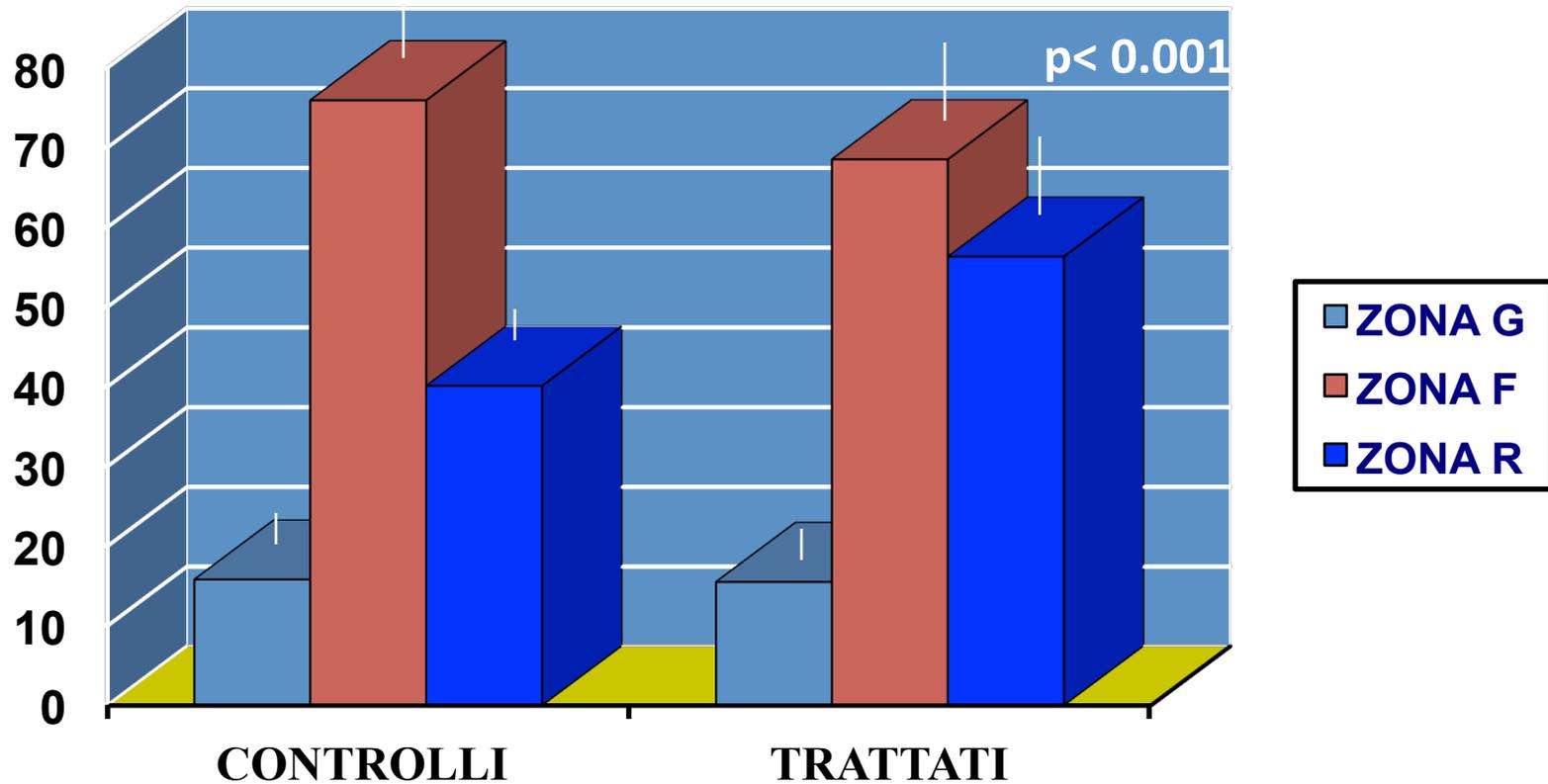


Roma, 8-11 novembre 2018

EFFETTI DEL DHT SUL VOLUME DELLE DIVERSE ZONE DELLA CORTECCIA SURRENALICA DI CAVIA



ITALIAN CHAPTER



V. Toscano et al
J. Ster. Biochem, 1990

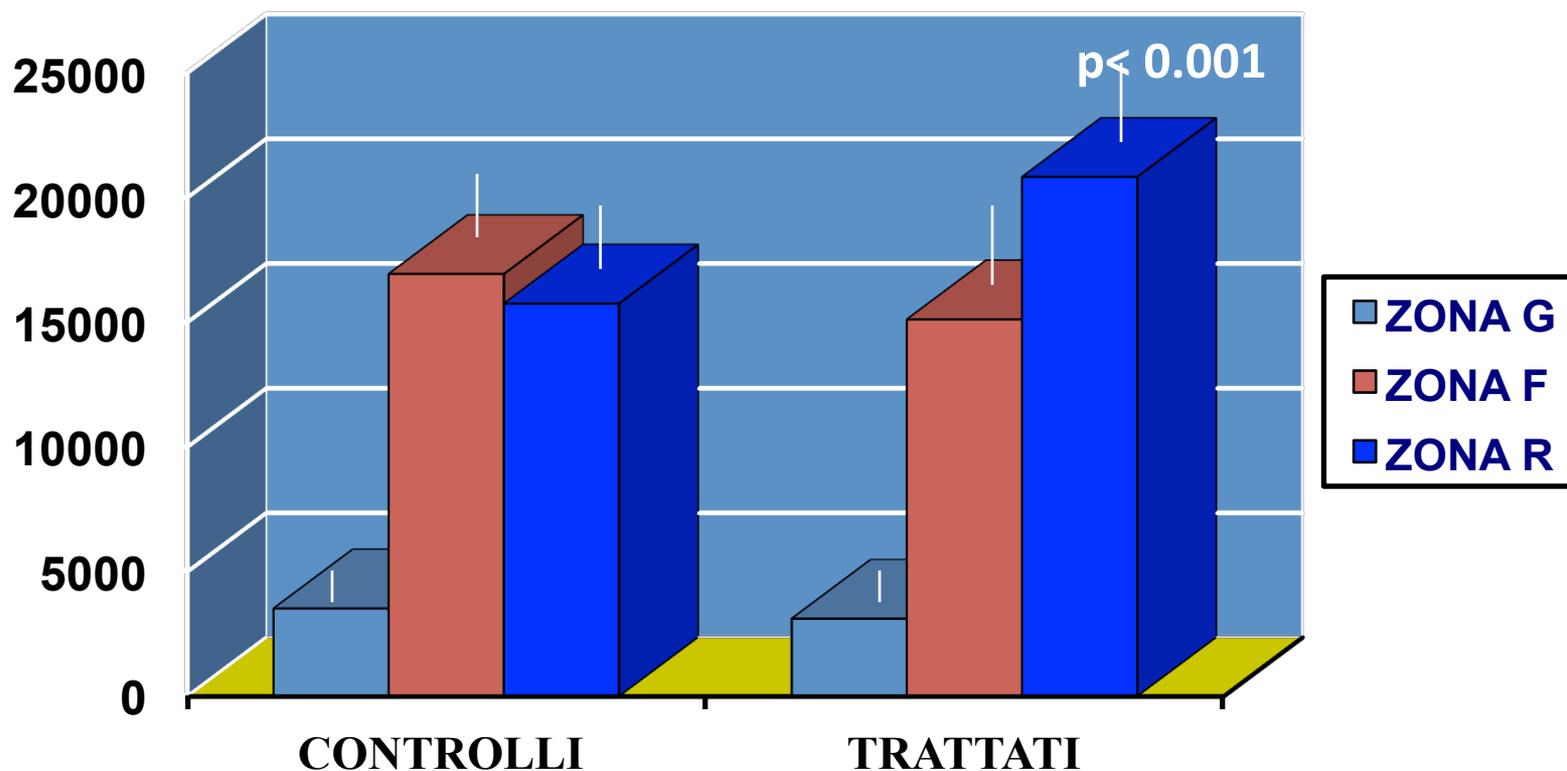


Roma, 8-11 novembre 2018

EFFETTI DEL DHT SUL VOLUME DELLE CELLULE DELLE DIVERSE ZONE DELLA CORTECCIA SURRENALICA DI CAVIA



ITALIAN CHAPTER



V. Toscano et al
J. Ster. Biochem, 1990

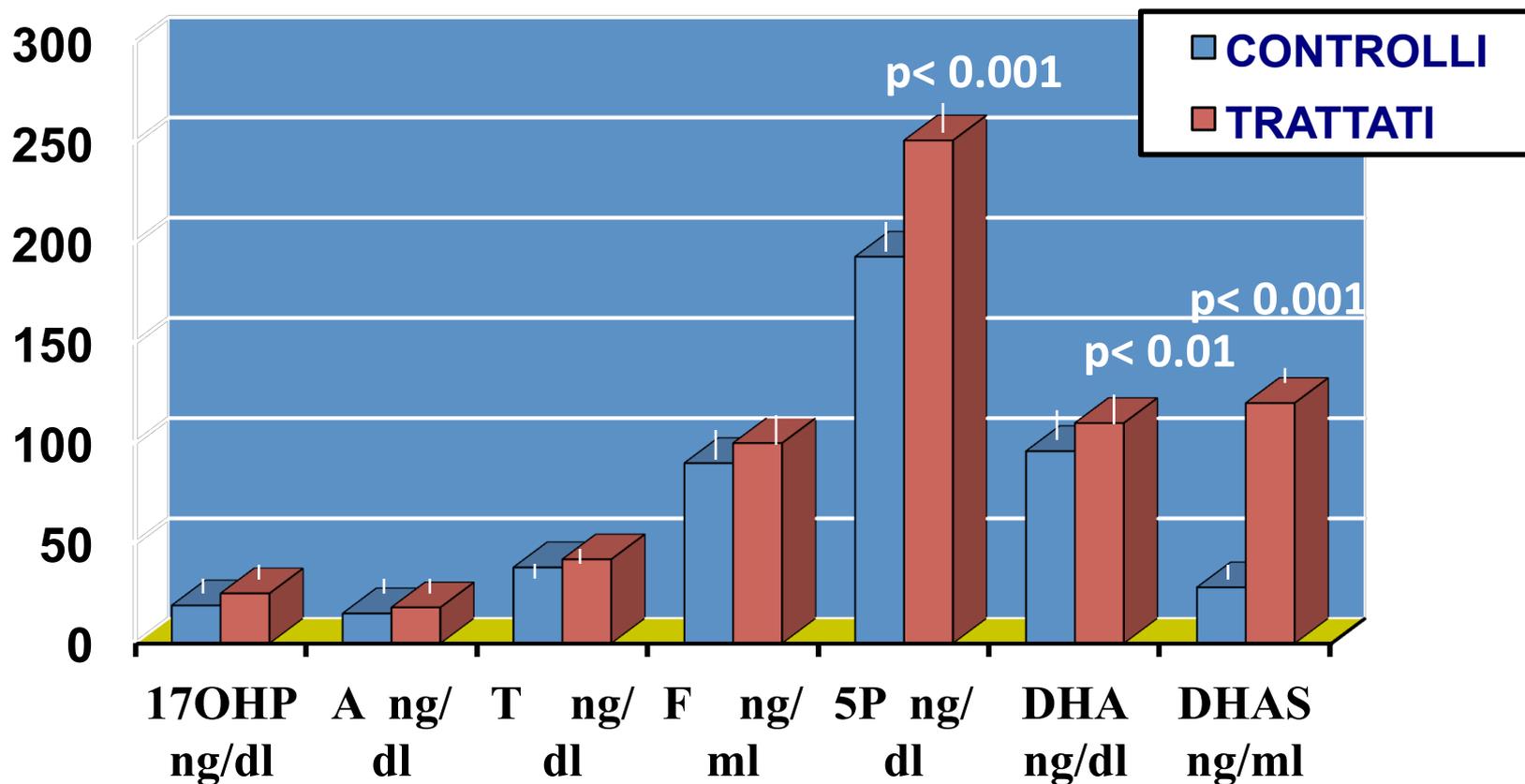


Roma, 8-11 novembre 2018

EFFETTI DEL DHT SUI LIVELLI PLASMATICI DEGLI STEROIDI 4ENE E SU QUELLI 5ENE NELLE CAVIE



ITALIAN CHAPTER



V. Toscano et al
J. Ster. Biochem, 1990



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



**IL TRATTAMENTO CON DHT NELLE CAVIE INDUCEVA OLTRE
L'IPERPLASIA DELLA RETICOLARE DEL SURRENE ANCHE:**

- ↘ UNA IPERPLASIA DELLE CELLULE TECALI CON ASPETTO DA IPERATTIVITA' STEROIDO-SINTETICA**
- ↘ ATTIVA PROLIFERAZIONE FOLLICOLARE FINO ALLO STADIO ANTRALE (INDOTTO DA DHT O DAGLI AUMENTATI LIVELLI DI STEROIDI SURRENALICI)**

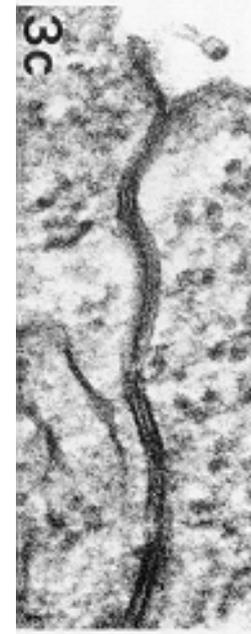
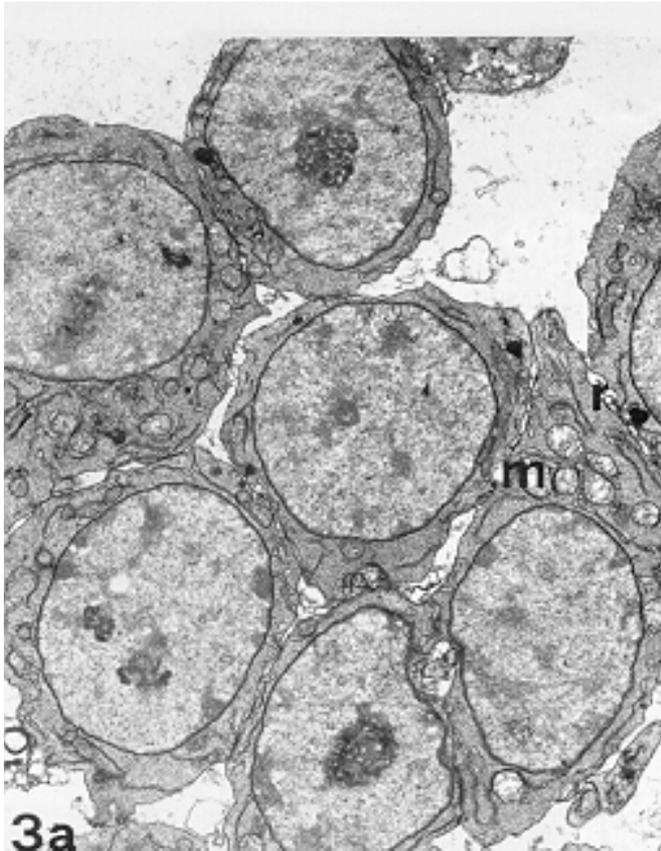


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CELLULE DELLA GRANULOSA DI TOPO TRATTATO CON DHA



ITALIAN CHAPTER



G. Familiari et al
Cell Tissue Res, 1985

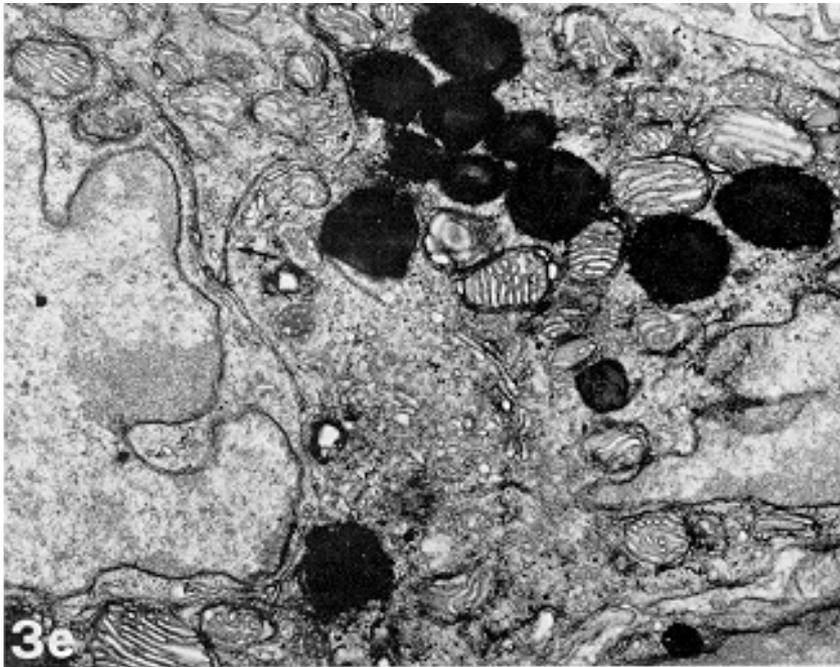


Roma, 8-11 novembre 2018

CELLULE DELLA TECA DI TOPO TRATTATO CON DHA



ITALIAN CHAPTER



G. Familiari et al
Cell Tissue Res, 1985



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



IL TRATTAMENTO CON TESTOSTERONE O DHT NELLA SCIMMIA **INDUCE:**

- **PROLIFERAZIONE E CRESCITA DEI FOLLICOLI PRE-ANTRALI**
- **AUMENTO DELLE CELLULE DELLA GRANULOSA E DELLA TECA, CON INCREMENTATA PRODUZIONE DI ANDROGENI, E AUMENTATA ESPRESSIONE DELL'mRNA dell'AR SULLE CELLULE DELLA GRANULOSA**
- **RIDOTTA APOPTOSI DELLE CELLULE DELLA GRANULOSA**
- **IPERTROFIA STROMALE**
- **AUMENTATA ESPRESSIONE SULLE CELLULE DELLA GRANULOSA DELL'mRNA DEL RECETTORE DELL'FSH**

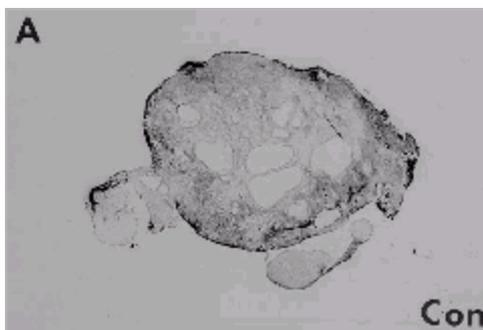


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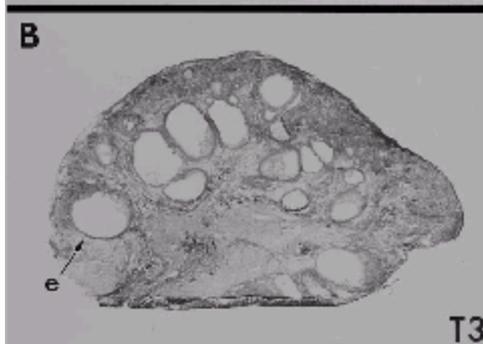
SEZIONI OVARICHE DI SCIMMIA TRATTATA CON T O DHT



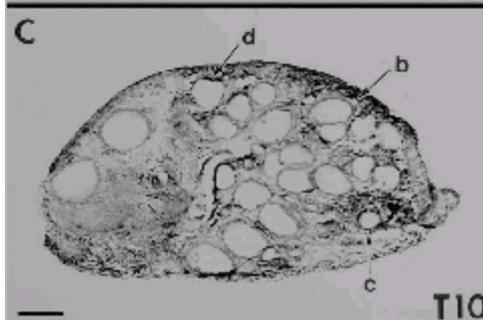
ITALIAN CHAPTER



CONTROLLO



TRATTATO x 3 gg



TRATTATO x 10 gg

K.A. Vendola et al
JCI, 1998



Roma, 8-11 novembre 2018

EFFETTI DEL TESTOSTERONE IN F TO M TRANGENDER



ITALIAN CHAPTER



Results of the pathologic examination of endometrium, myometrium, and ovaries in the 12 female-to-male patients.

Patient no.	Age (y)	Endometrium	Myometrium	Ovary
1	26	Secretive	Fibrosis	Corpus luteum
2	37	Active	Normal	Multifollicular
3	22	Active	Fibrosis	Multifollicular
4	26	Active	Fibrosis	Multifollicular
5	37	Active	Normal	Multifollicular
6	20	Active	Normal	Multifollicular
7	31	Active	Fibrosis	Multifollicular
8	34	Active	Fibrosis	Multifollicular
9	31	Secretive	Hypertrophy	Corpus luteum
10	33	Active	Normal	Multifollicular
11	20	Active; squamous metaplasia	Normal	Multifollicular
12	20	Active	Hypertrophy	Multifollicular

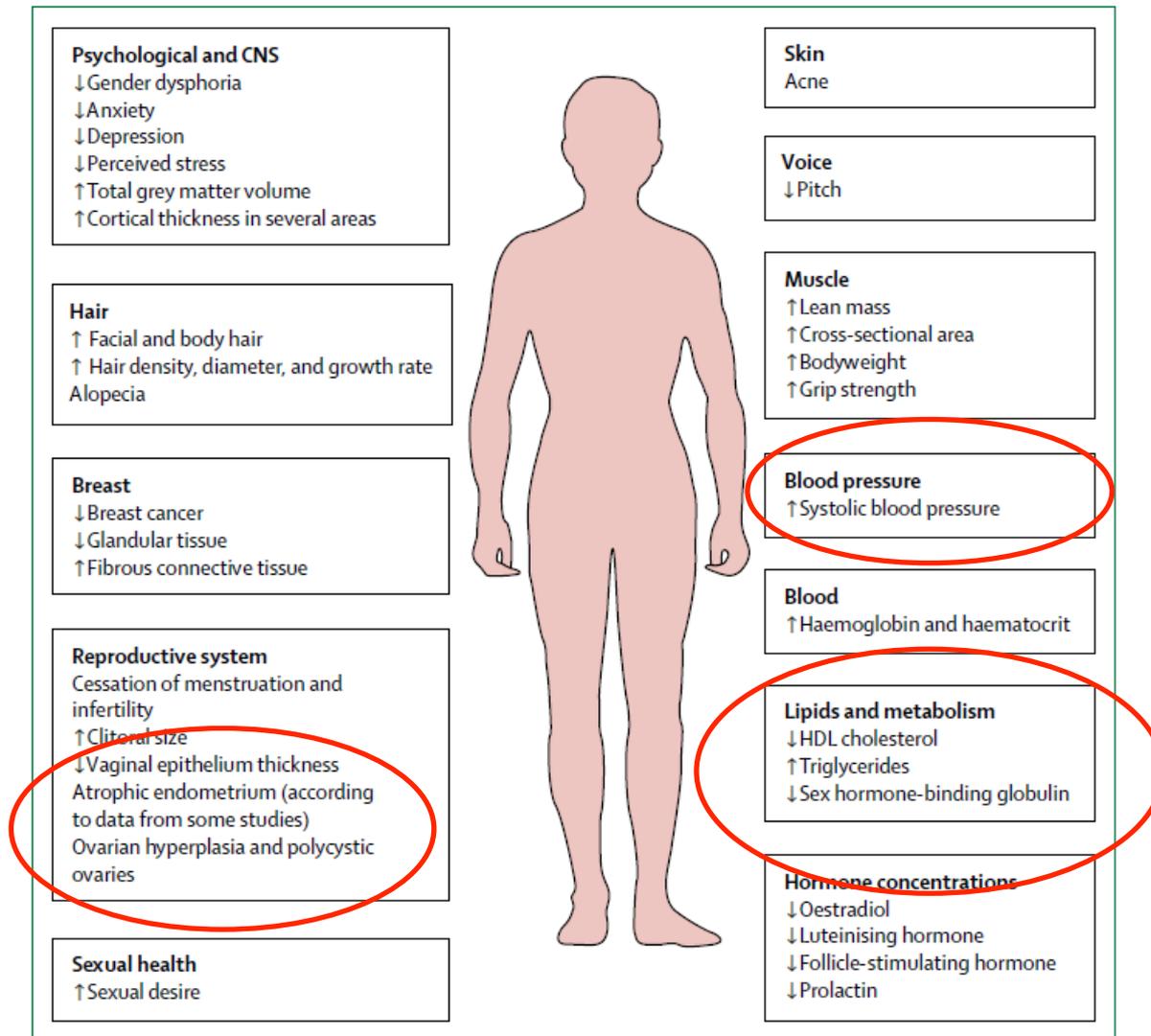


Figure: Effects of testosterone therapy in transgender men



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



Testosterone therapy seems to be quite safe in the short term, based on results from many studies. Nonetheless, testosterone decreases HDL cholesterol, increases triglycerides, might increase systolic blood pressure, and might increase the incidence of diabetes and metabolic syndrome. The long-term consequences of these changes are not known.



TABLE 1

Hormone concentrations before and after androgenic treatment (combination testosterone and aromatase inhibitor).

Hormone	Before treatment (n = 22)		After treatment (n = 22)		P value
	Median	Mean ± SD	Median	Mean ± SD	
AMH ($\mu\text{g/L}$)	3.5	4.4 ± 4.4	0.3	1.4 ± 2.1	.000 ^a
Inhibin B (ng/L)	11.0	17.9 ± 12.2	11.0	16.8 ± 13.7	.44
T (nmol/L)	1.0	1.1 ± 0.24	14.5	17.8 ± 9.6	.000 ^a
A (nmol/L)	4.5	4.8 ± 2.8	5.7	7.0 ± 3.4	.002 ^a
DHEAS ($\mu\text{mol/L}$)	6.3	6.1 ± 2.1	7.0	7.4 ± 2.7	.005 ^a
E ₂ (pmol/L)	30.0	32.8 ± 13.1	20.0	33.2 ± 24.7	.151
SHBG (nmol/L)	43.0	42.0 ± 14.2	28.5	29.9 ± 9.2	.001 ^a
LH (U/L)	0.32	0.36 ± 0.18	0.33	0.49 ± 0.88	.39
FSH (U/L)	1.7	1.9 ± 1.1	3.4	3.3 ± 1.8	.001 ^a

Note: AMH = antimüllerian hormone.

^a Statistically significant difference between measurements before and after treatment.

Caanen. AMH in female-to-male transsexuals. *Fertil Steril* 2015.



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



CHE RUOLO GIOCA IN TUTTO QUESTO
L'ALTERAZIONE METABOLICA E QUALE
E' IL RUOLO DELL'INSULINA ?

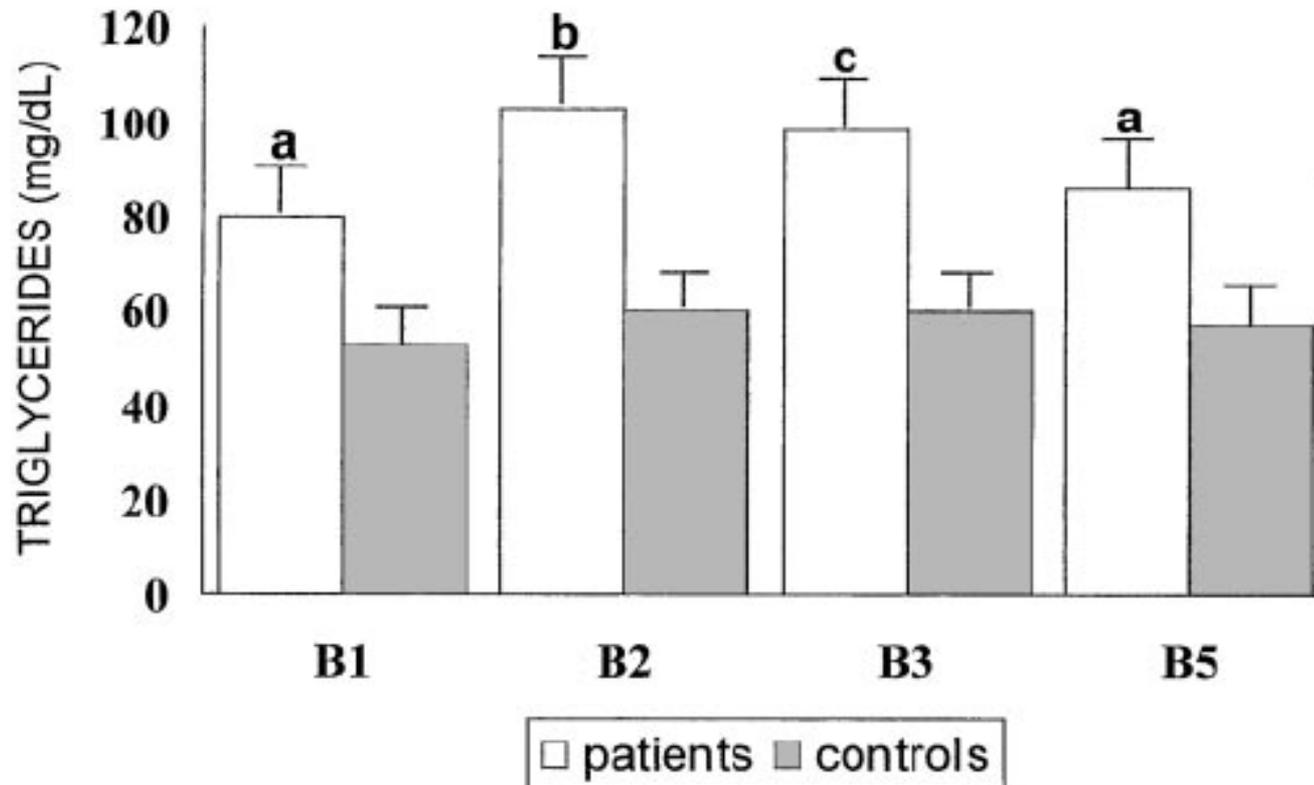


FIG. 14. Serum triglyceride levels in premature adrenarche patients and controls throughout all stages of pubertal development. B1 to B5, Tanner breast stages 1 to 5. ap = 0.01; bp = 0.006, and cp = 0.001 vs. controls. [Modified with permission from L. Ibáñez *et al.*: *Diabetologia* 41:1057–1063, 1998 (278).]



	AGA n = 40	SGA n = 23
Birthweight (Kg)	3.21 ± 0.03	2.13 ± 0.08
Birthweight SD score	0.0 ± 0.1	-2.9 ± 0.1**
Age (yr)	14.0 ± 0.3	13.9 ± 0.3
Age at menarche (yr)	12.1 ± 0.1	12.2 ± 0.2
Height (cm)	158.0 ± 1.1	152.4 ± 1.5*
Body Mass Index (Kg/m ²)	21.8 ± 0.4	20.8 ± 0.6
DHEAS (µg/dL)	136 ± 9	282 ± 25**
Androstenedione (ng/dL)	177 ± 9.9	229 ± 18*
Insulin (µU/mL)	11 ± 0.8	18 ± 2.7*
Glucose (mg/dL)	80 ± 2	79 ± 3
Estradiol (pg/mL)	21 ± 3.3	22 ± 4.4

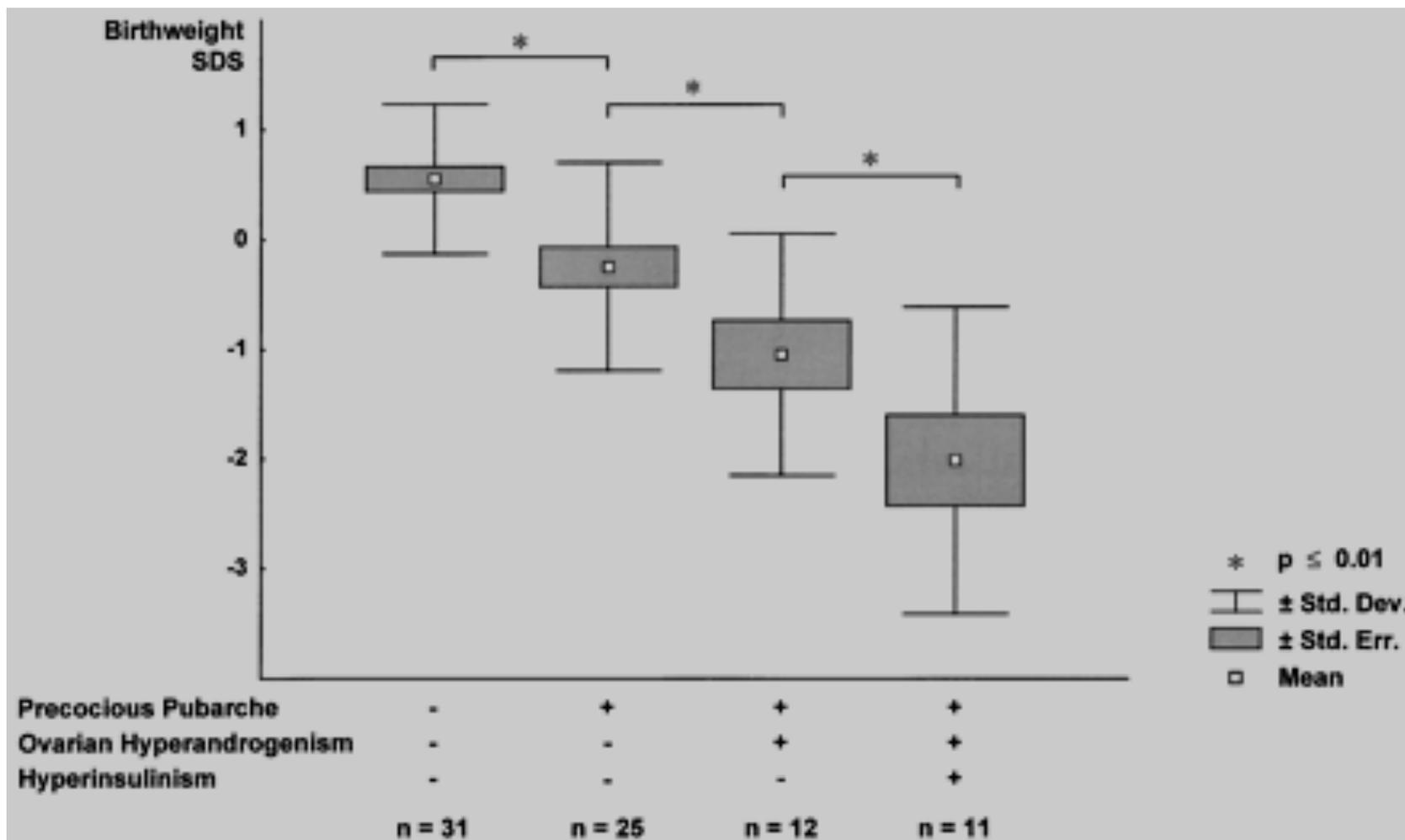
*p < 0.01; **p ≤ 0.0001

When compared to AGA adolescents, the SGA girls were found to have strikingly increased serum DHEAS concentrations (see Figure), as well as higher androstenedione and fasting insulin levels, while glycemia and serum estradiol were similar.



ITALIAN CHAPTER

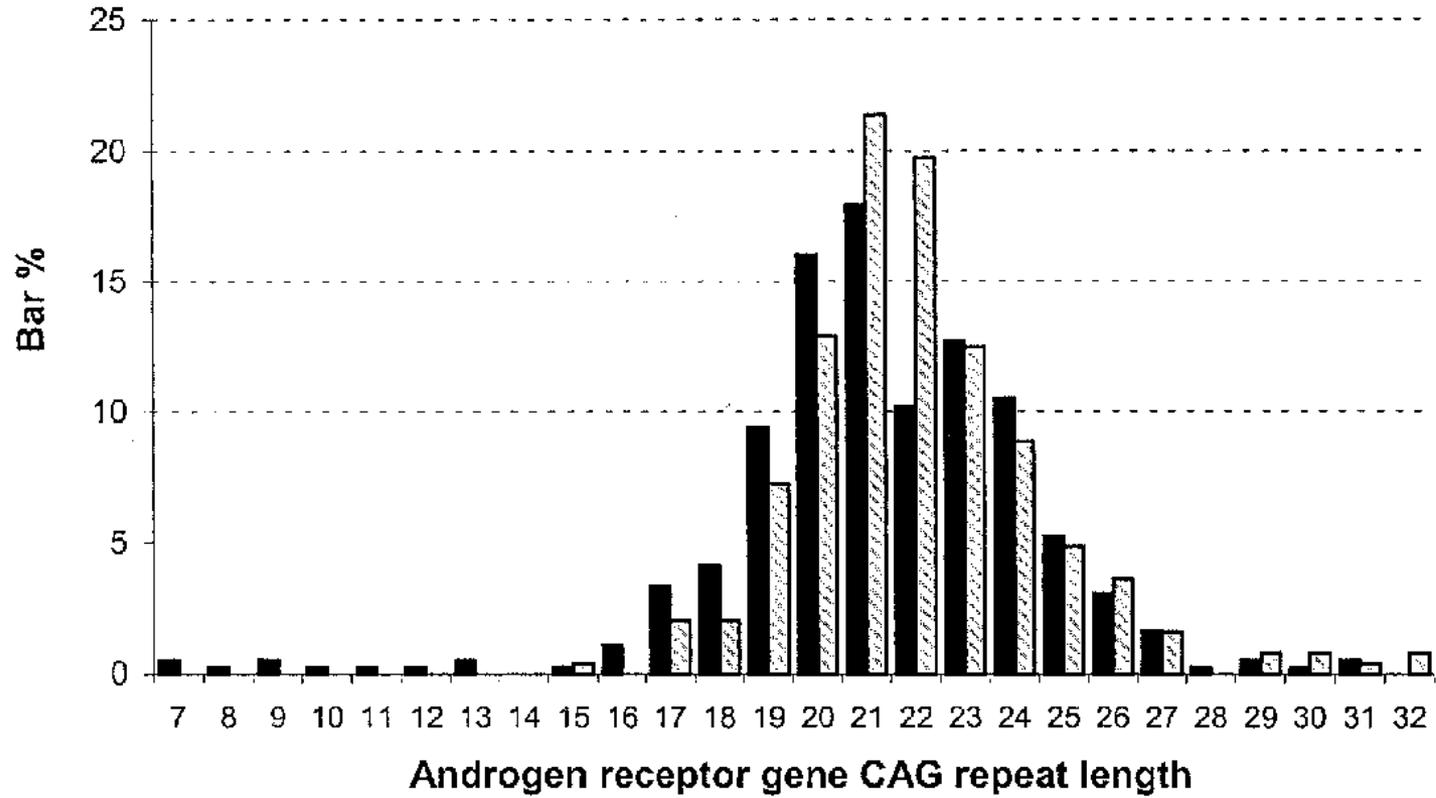
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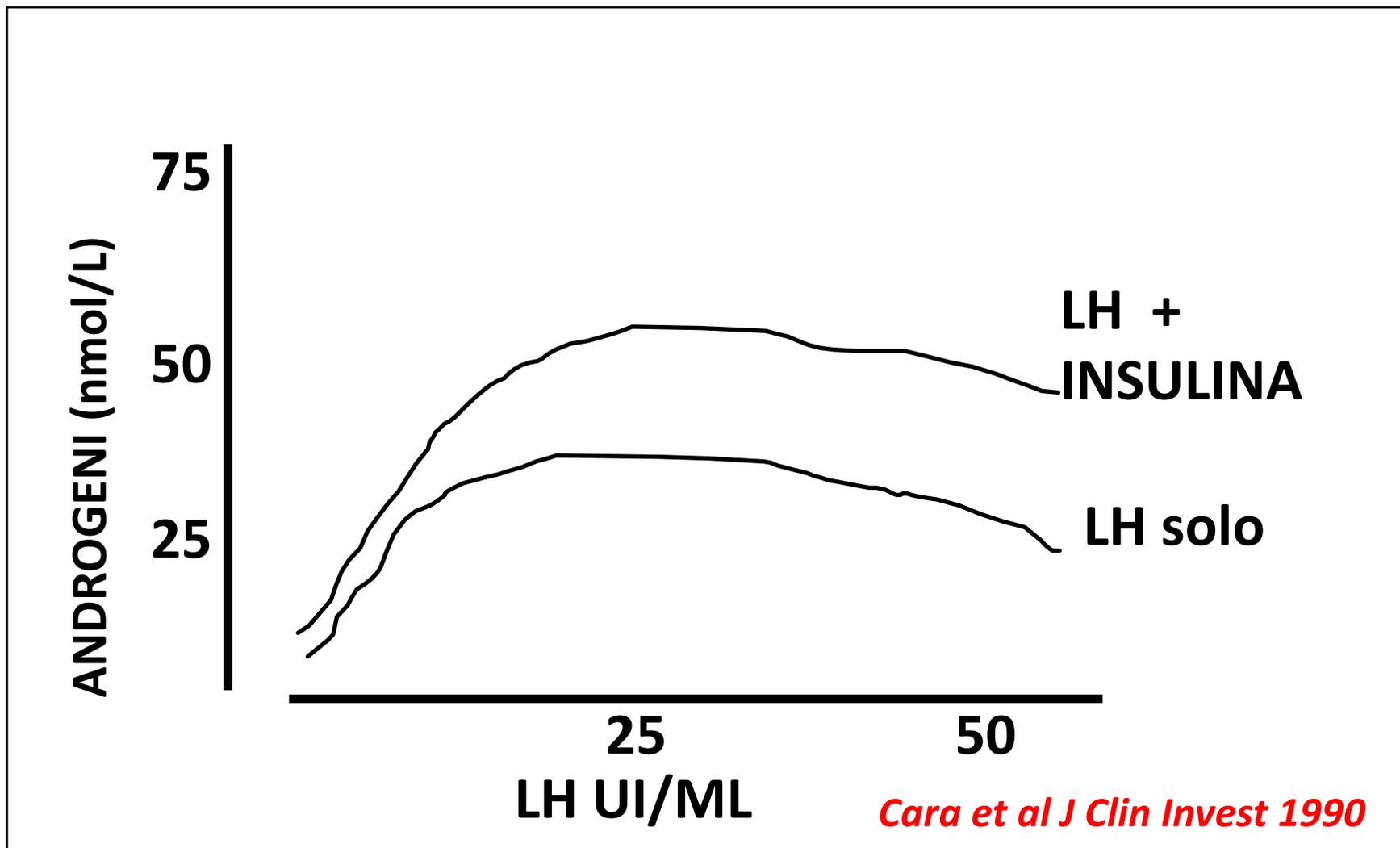
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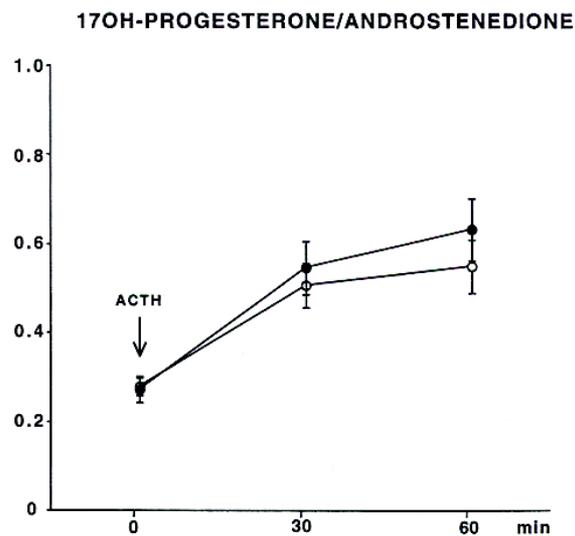
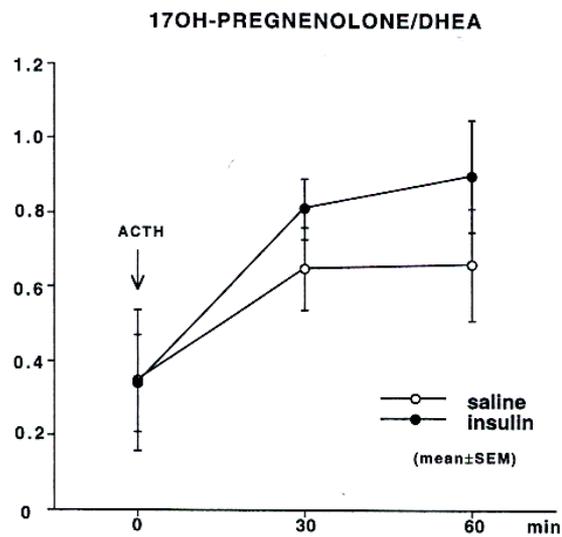
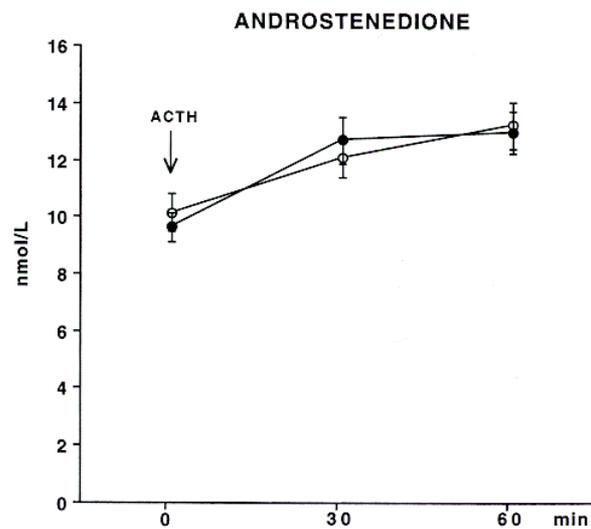
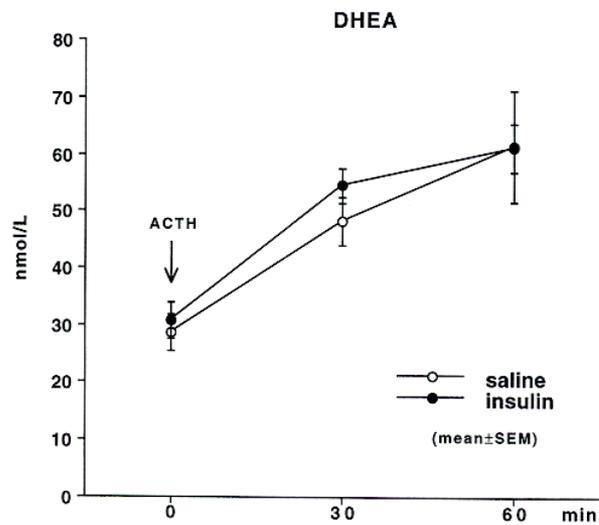
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IPERTRICOSI PREPUBERALE E PUBARCA PREMATURO E INSULINA

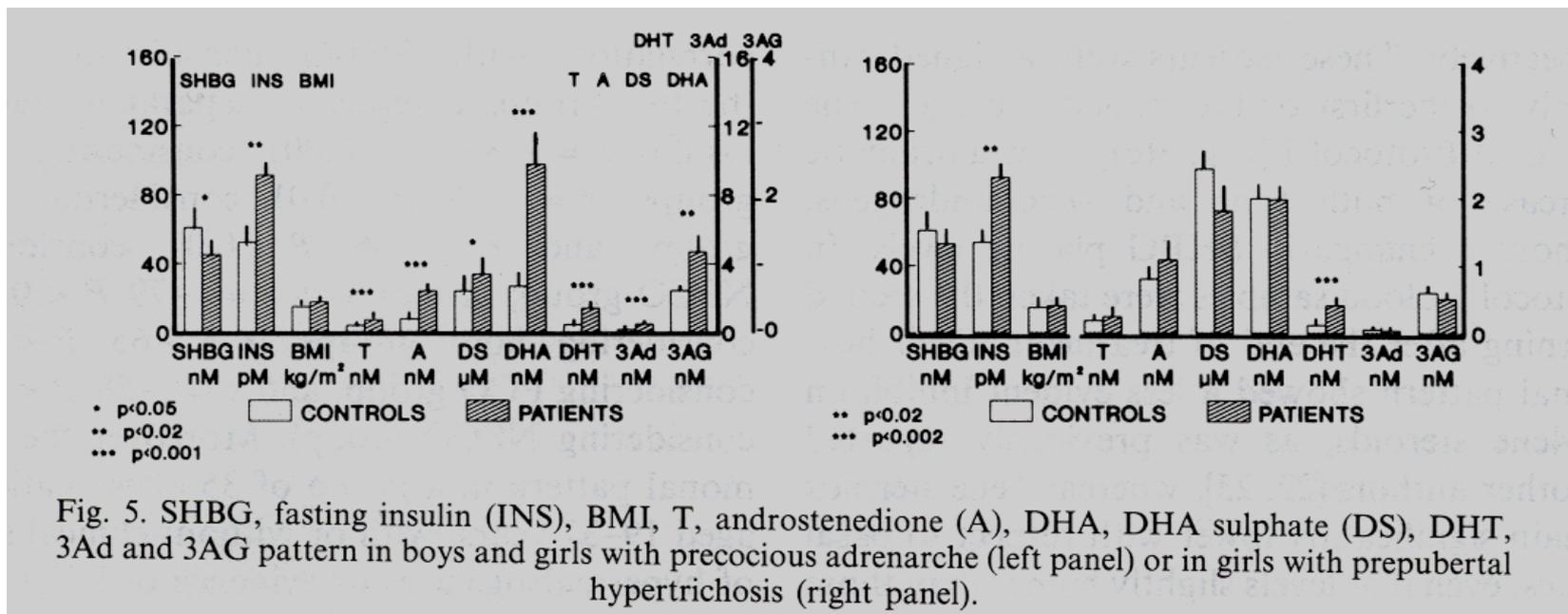


ITALIAN CHAPTER



PUBARCA PREMATURO

IPERTRICOSI PREPUBERALE





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ITALIAN CHAPTER



↘ **COME QUESTE 2 FORME PATOLOGICHE
POTEVANO CORRELARE FRA LORO ?**

↘ **COME POTEVANO POI ESSERE CORRELATE CON
LO SVILUPPO DELLA PCO ?**

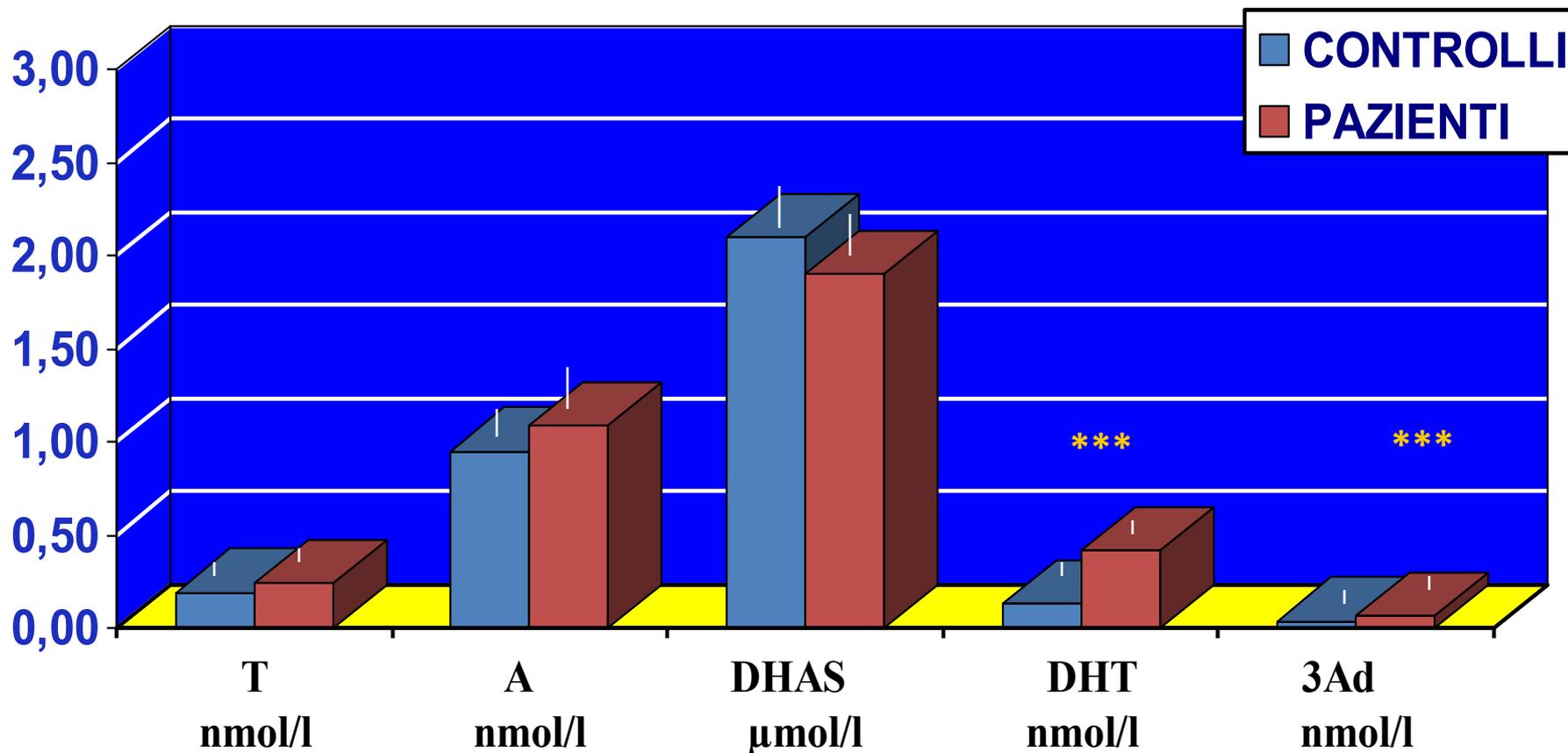


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IPERTRICOSI PREPUBERALE



ITALIAN CHAPTER



R. Balducci et al
Clin Endocr, 1990

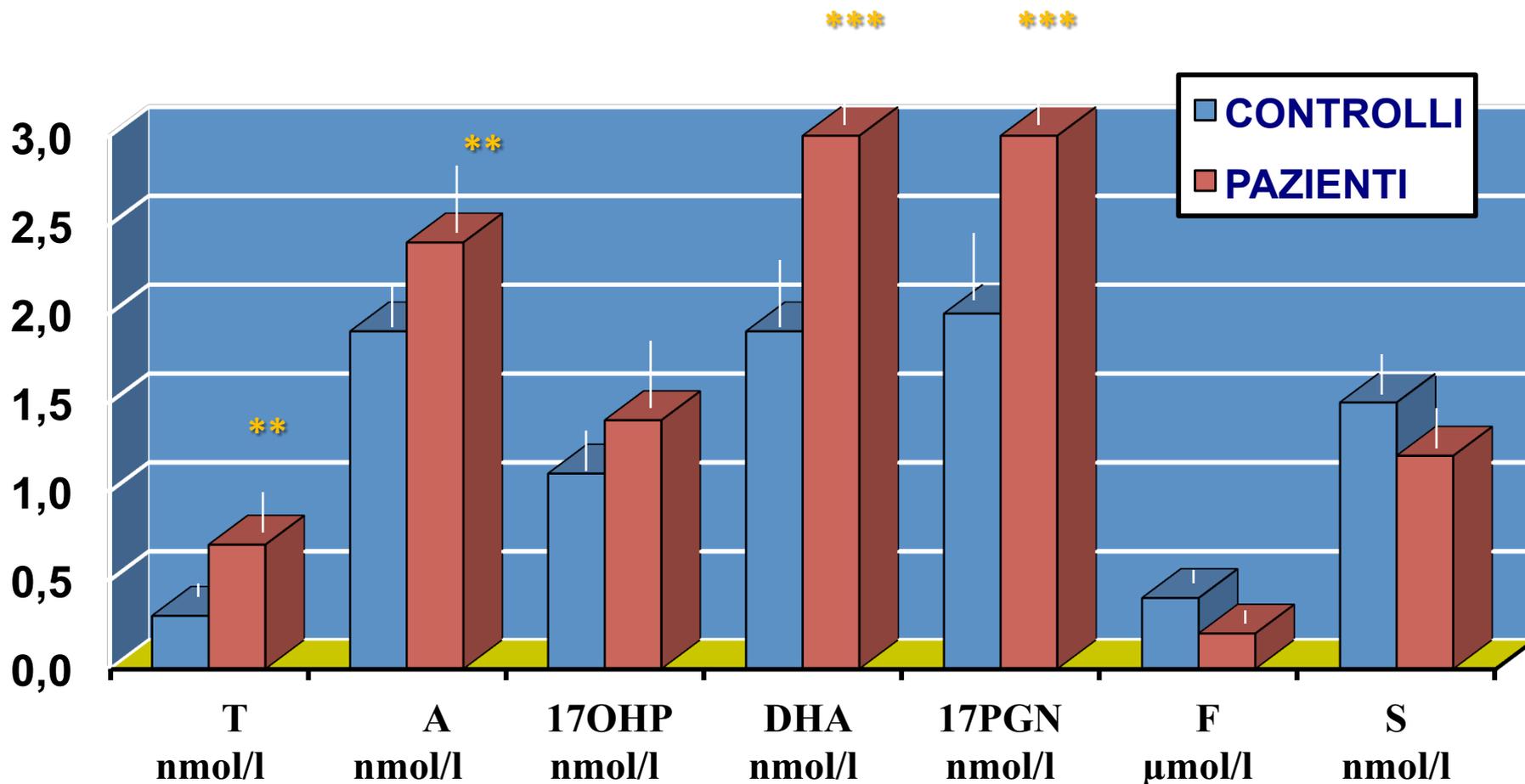


PUBARCA PRECOCE



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R. Balducci et al
J.C.E.M., 1994

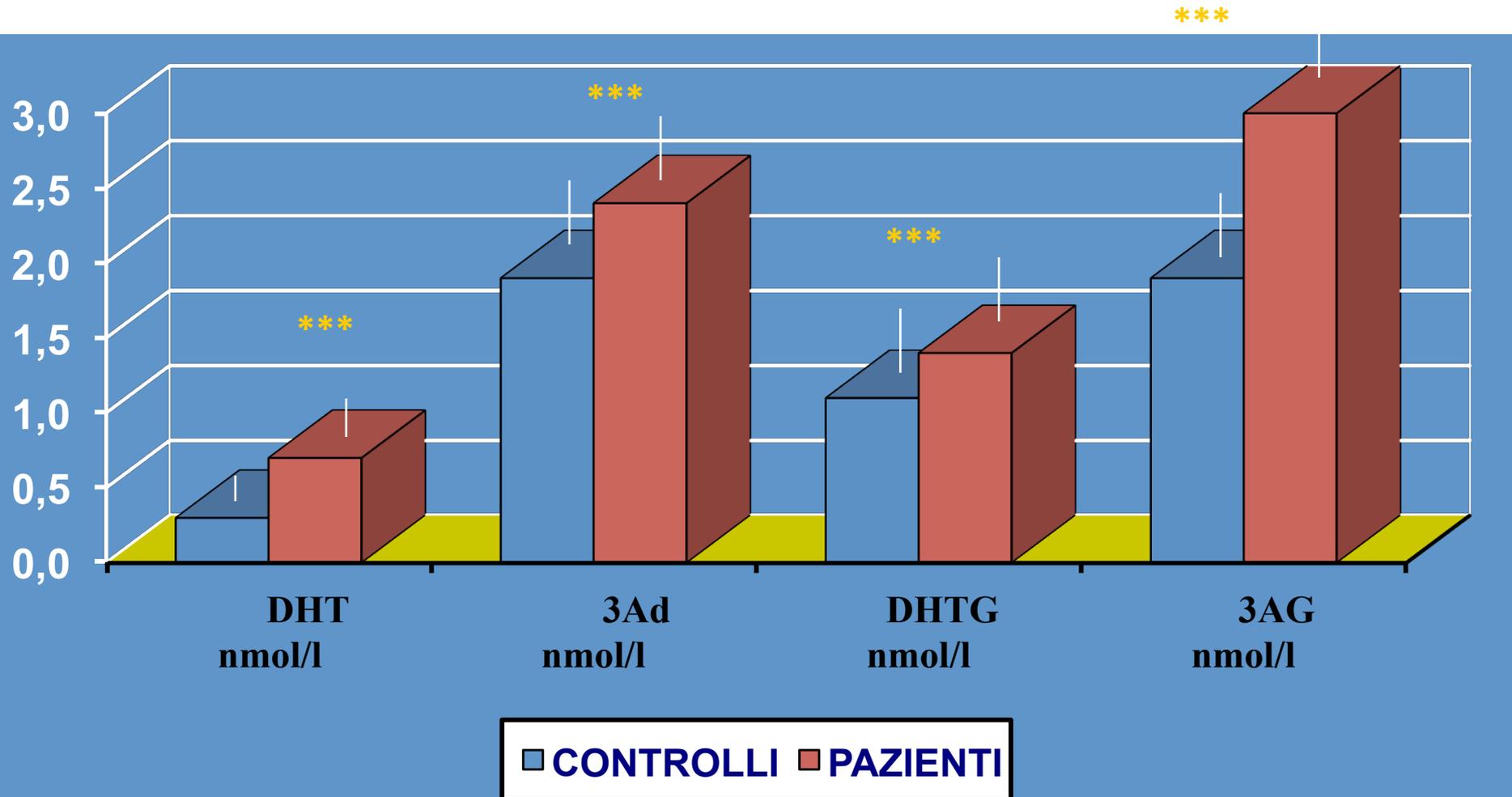


PUBARCA PRECOCE



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R. Balducci et al
JEI, 1992



STUDIO PROSPETTICO



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- ↘ **77 BAMBINE CON PP SEGUITE FINO A 4 ANNI DOPO IL MENARCA, VALUTANDO LO SVILUPPO DI IRSUTISMO**

- ↘ **ETA' DEL PUBARCA:**
 - ✓ **PP TIPICO $6.7 + 0.9$ ANNI (70)**
 - ✓ **PP DA SAG NC 21OH $6.6 + 0.4$ ANNI (7)**

- ↘ **IPERTRICOSI PREPUBERALE:**
 - ✓ **46/70 PAZIENTI (66%)**

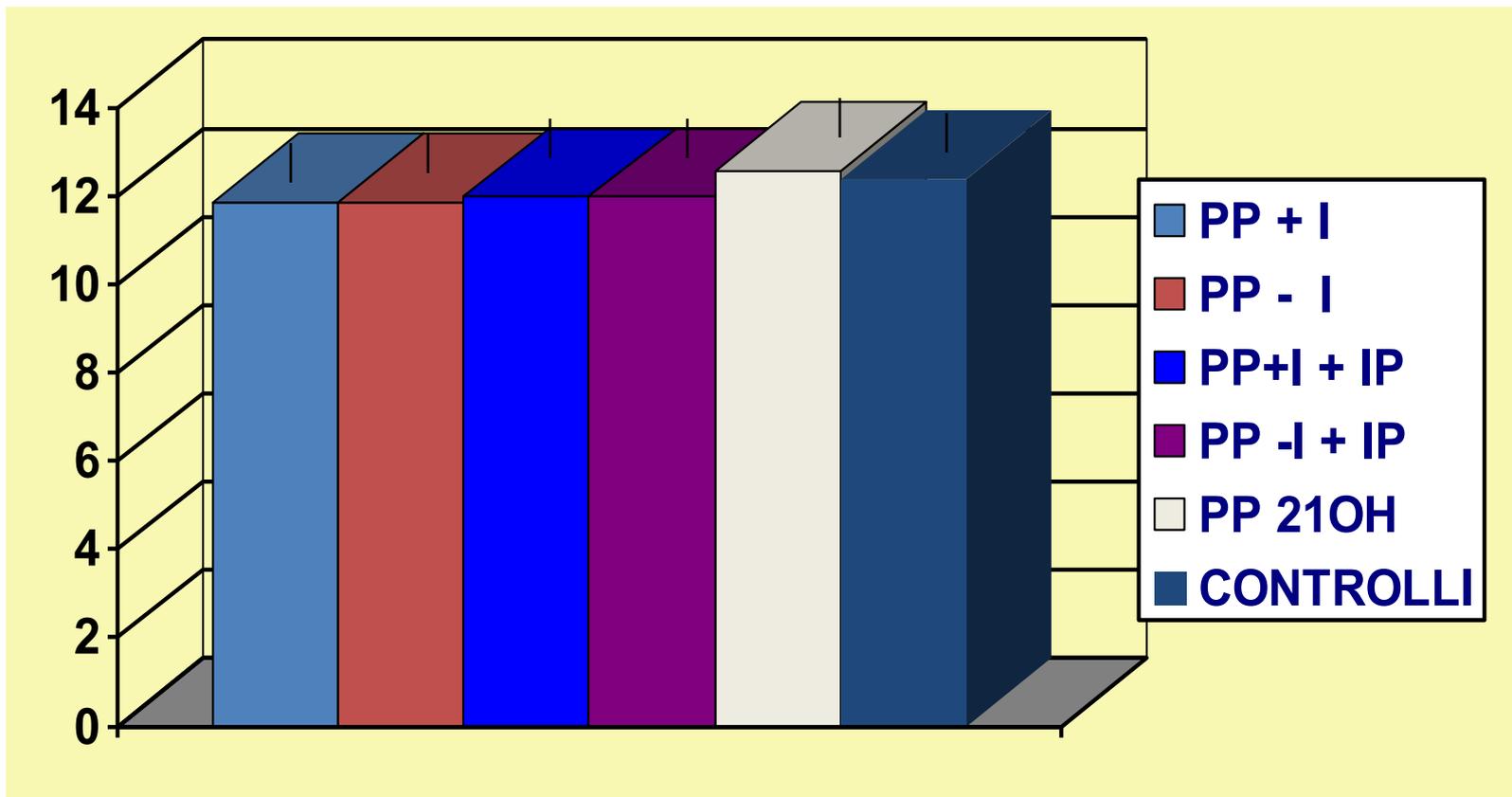


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ETA' DEL MENARCA



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V. Toscano et al
Steroids, 1998

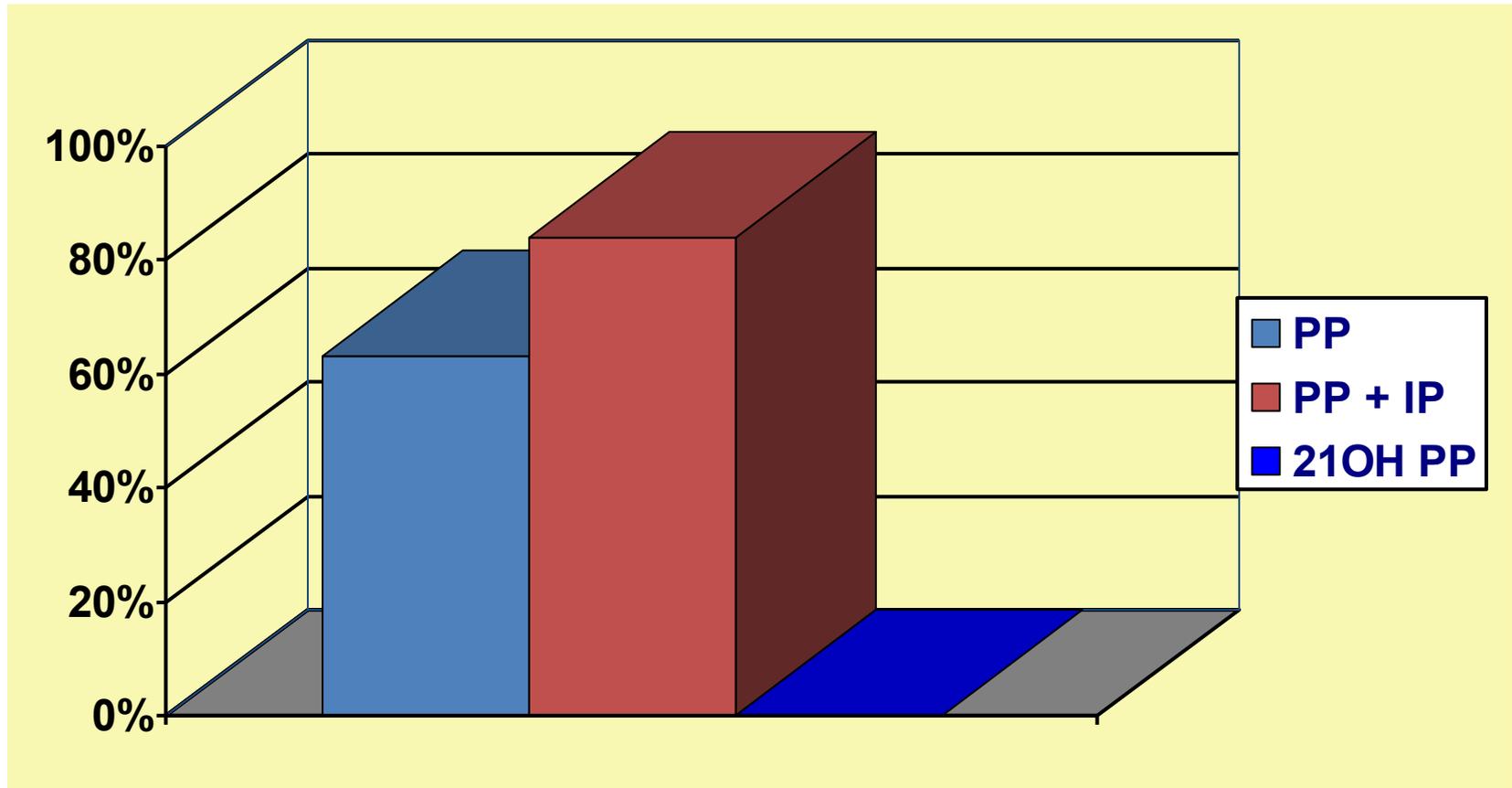


SVILUPPO DI IRSUTISMO



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V. Toscano et al
Steroids, 1998

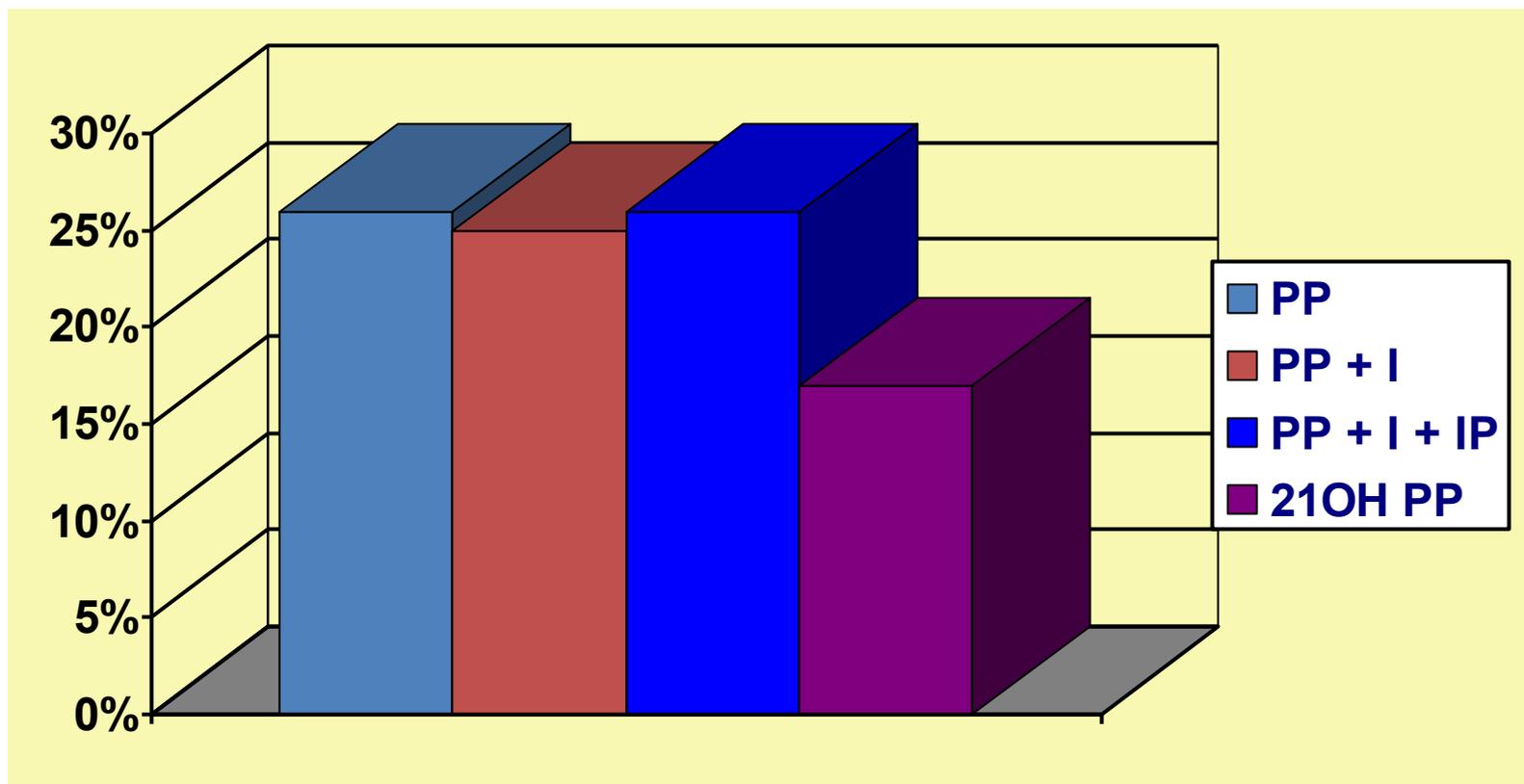


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SVILUPPO DI OLIGOAMENORREA



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V. Toscano et al
Steroids, 1998

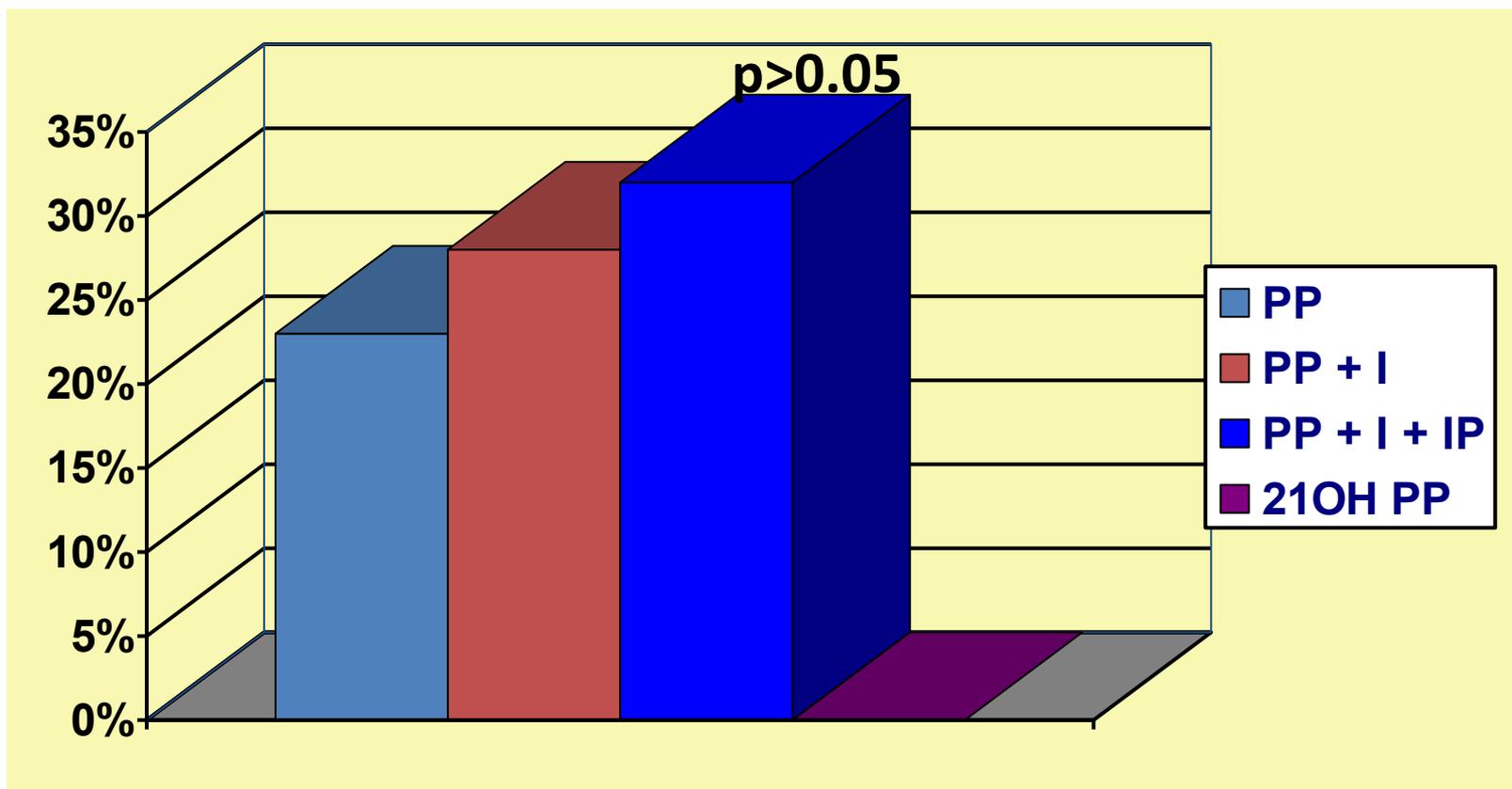


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SVILUPPO DI PCO



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V. Toscano et al
Steroids, 1998



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Is hyperandrogenism an evolving syndrome?

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(Received 10 September 1982)



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POLYCYSTIC OVARY SYNDROME: WHAT IS IT?



ITALIAN CHAPTER



**UNA SINDROME EVOLUTIVA CON INIZIO NEONATALE/
PREPUBERALE IN CUI L'INIZIALE DISTURBO
ENDOCRINO DEL METABOLISMO PERIFERICO DEGLI
ANDROGENI LOCALIZZATO A CARICO DEL RECETTORE
ANDROGENICO/ UNITA' PILO-SEBACEA SI COMPLICA
PROGRESSIVAMENTE, INVESTENDO SURRENI E
OVAIO, LA CUI FUNZIONE VIENE ULTERIORMENTE
COMPROMESSA DAL DISTURBO METABOLICO
CONCOMITANTE.**

Grazie



E Hopper - Rooms by the sea '51