Minicorso Linee Guida 2

Linee Guida irsutismo
Moderatori:
M. Caputo, R. Castello

1. **Real clinical practice**
   M.G. Deiana
2. **Iperandrogenismo: valutazione clinica**
   I. Tenuti
3. **Iperandrogenismo: valutazione biochimica**
   M. Caputo
4. **Sindrome dell'ovaio policistico nell'adolescente**
   G. Spiazzi
5. **Terapia farmacologica**
   A. Salcuni
6. **Terapia "cosmetica"**
   E. Perosino
7. **Take home messages**
   R. Castello

QUALI ?

QUANTE ?

Lorenza, 16 anni

Giunge alla nostra osservazione a Luglio u.s

An. Familiare: familiarità per diabete mellito di tipo 2 (madre, nonna materna e paterna), ipertensione arteriosa, tireopatia nodulare.

Nega familiarità per neoplasie, malattie cardiovascolari ed eventi tromboembolici.

An. Fisiologica:

Peso alla nascita 2.2 kg. Normale sviluppo.

Pubarca 9 anni. Menarca a 10 anni e sei mesi.

Nega allergie. Non fuma.

An. Patologica Remota: ipotiroidismo subclinico, per cui le è stata prescritta L-tiroxina 50 μg/die.

Lorenza, 16 anni

- ✓ Lamenta irsutismo dal menarca ma peggioramento da circa due anni (irsutismo ingravescente)

- ✓ Incremento ponderale di circa 15 kg negli ultimi tre anni

- ✓ Cicli mestruali regolari fino a 10 mesi fa, amenorrea da Gennaio 2017
- ✓ Non rapporti sessuali

Lorenza, 16 anni

Esame Obiettivo:

Peso: 79 kg, h 163 cm; BMI 29,7 kg/m^2

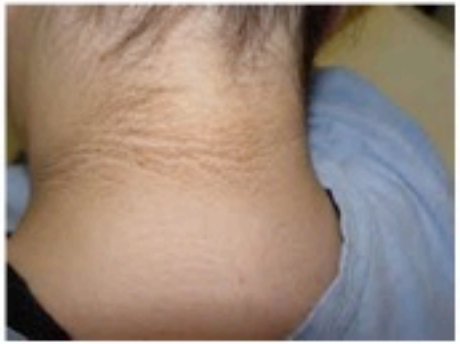
CV 92 cm, CF 108 cm.

PA 125/85 mmHg.

Acanthosis nigricans retronucale.

Non galattorrea.

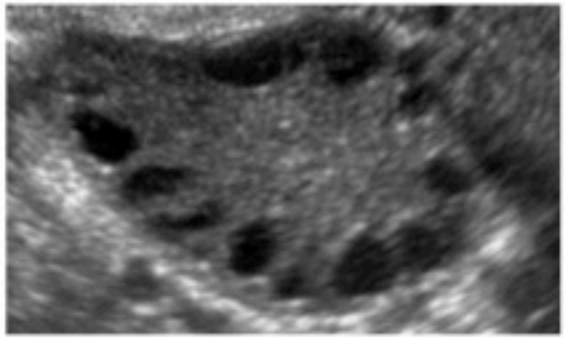
Strie rubrae addominali.

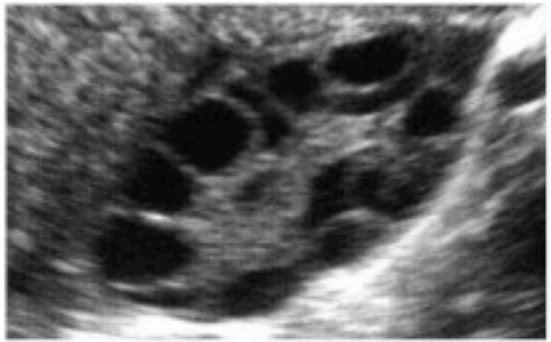


Lorenza, 16 anni

Ecografia pelvica sovra-pubica eseguita in amenorrea:

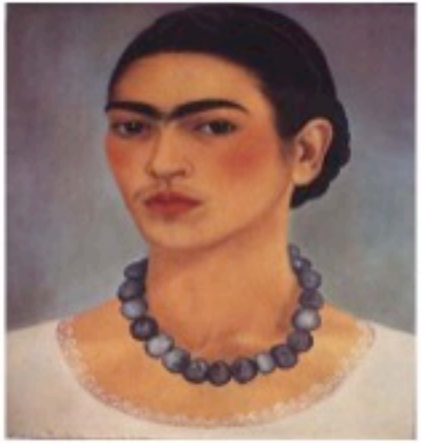
«ovaie aumentate di dimensioni (sx mm 41x23; dx mm 39x21) con aspetti ecostrutturali di tipo policistico»





IPERANDROGENISMO

«Sindrome clinicamente eterogenea determinata da un eccesso di androgeni circolanti o da una ipersensibilità tessutale agli androgeni»



CAUSE E PREVALENZA DELL 'IPERANDROGENISMO IN ETÀ FERTILE

Da tutte le cause	~10%
- PCOS	5-7%
- Irsutismo idiopatico	2-3%
- Iperandrogenismo surrenalico funzionale	1-2%
- Deficit enzimatici	~ 0.1%
- Tumori	assai rari

Best Practice & Research Clinical Obstetrics and Gynaecology 37 (2016) 98–118

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

9

Androgen excess: Investigations and management

Daria Lizneva, MD, PhD [a, b, c], Larisa Gavrilova-Jordan, MD [a], Walidah Walker, MS [a], Ricardo Azziz, MD, MPH [a, d, *]

[a] Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta State University, 1120 15th Street, 30912 Augusta, GA, USA

Diagnosis of AE in women

Hyperandrogenism or AE in women can be evident clinically (by the presence of hirsutism and/or androgenic alopecia) or biochemically, through the measurement of androgens, total, free, or in precursor/metabolite forms, in the circulation or other body fluids (eg, urine, saliva, etc.).

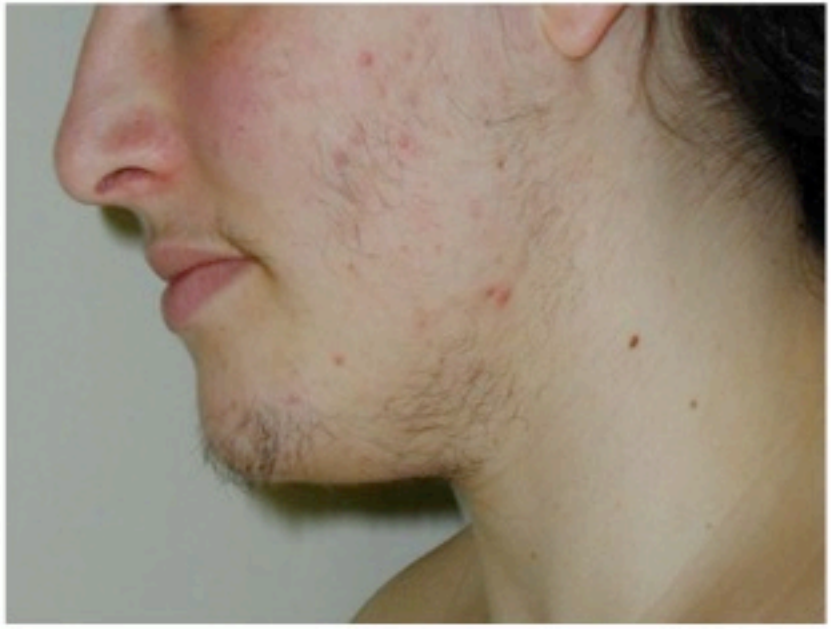
- ✓ Irsutismo
- ✓ Acne
- ✓ Alopecia
- ✓ Acanthosis

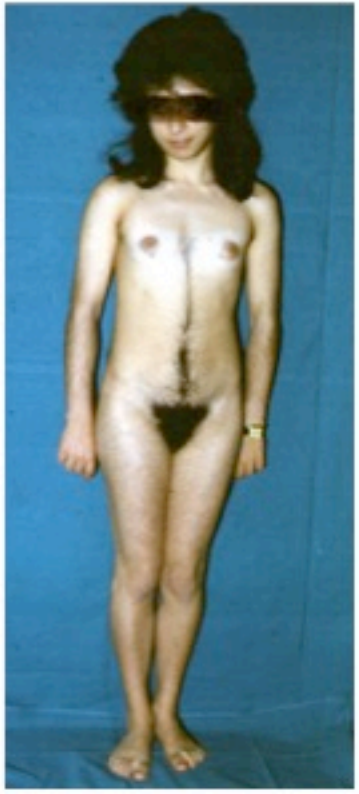
COSA SI INTENDE PER IRSUTISMO?

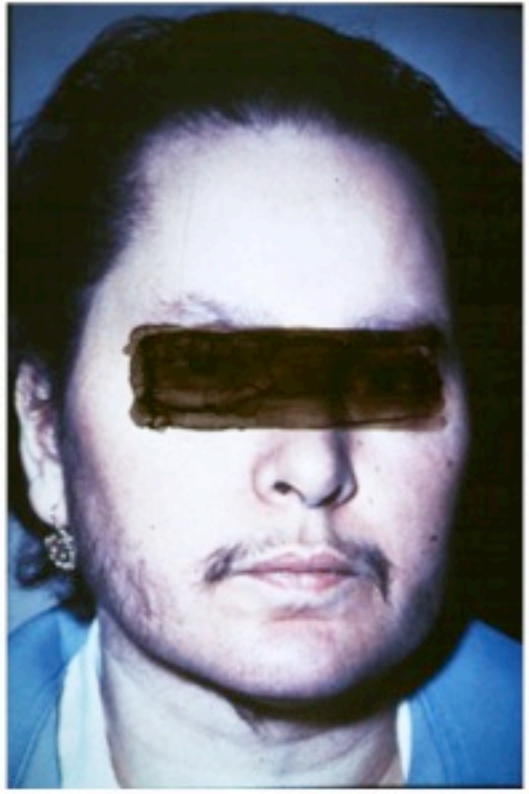
Comparsa di **PELI** in *zone in cui normalmente la donna è glabra* (dd: **IPERTRICOSI**: eccessiva crescita di peli in sedi e con caratteristiche normali per la donna).

L'**IRSUTISMO** è il *miglior marcatore della presenza di IPERANDROGENISMO*: sindrome clinicamente eterogenea determinata da un eccesso di androgeni circolanti o da una ipersensibilità tessutale agli androgeni

COSA SI INTENDE PER IRSUTISMO?







TIPOLOGIA DI PELI

VOL. 101, NO. 5, PART 1, MAY 2003

I peli vanno distinti in:

***PELI TERMINALI** (duri, spessi e scuri)*

***VELLO** (peli morbidi, sottili e chiari)*

The Evaluation and Management of Hirsutism

Ricardo Azziz, MD, MPH

There are three general types of hair.[12] Lanugo is a dense, soft unmedullated hair over the surface of the fetus that is shed sometime late in gestation or early postpartum. Vellus hairs are soft, short (generally less than 2 mm in length), fine, unmedullated, and usually nonpigmented, and cover the apparently hairless areas of the body. Terminal hairs are long, coarse, medullated (ie, having a denser core of compacted melanocytes), and pigmented. This hair makes up the eyebrows, the eyelashes, the scalp hair, the pubic and axillary hair, etc.

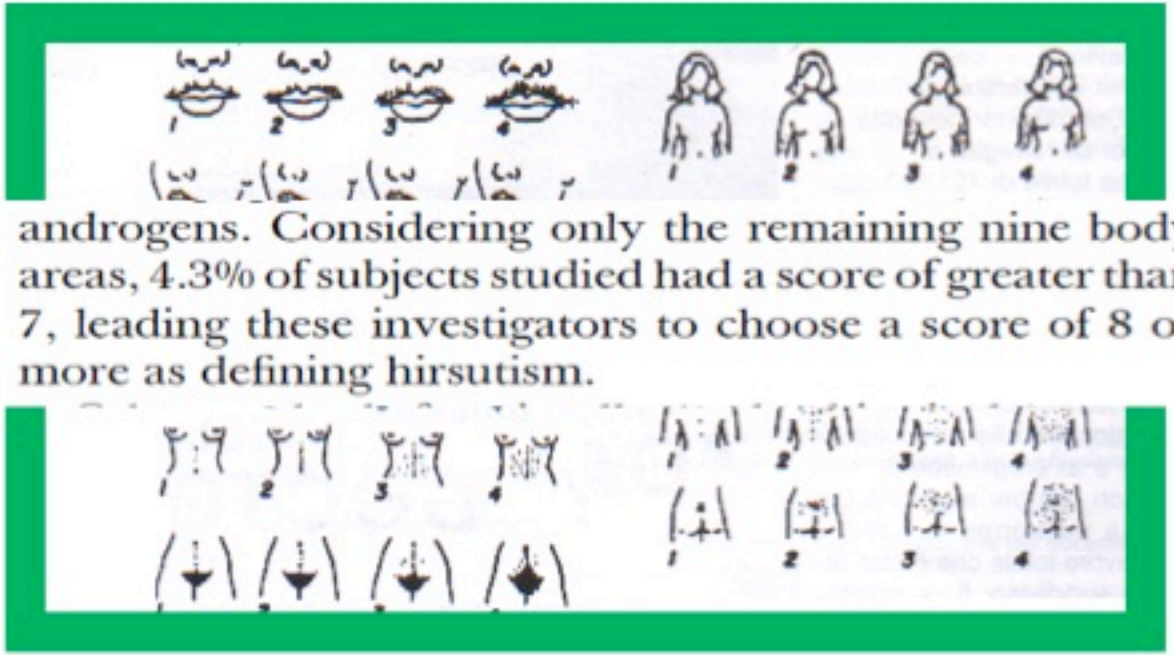
METODI PER LA QUANTIFICAZIONE DELL'IRSUTISMO

METODI	MISURA
Punteggio di FERRIMAN-GALLWEY (semi-quantitativo)	clinica
Diametri del pelo (Dopo asportazione)	microscopica
Densità dei peli (dopo rasatura)	fotografica
Velocità di crescita dei peli (dopo rasatura)	fotografica

Quante scale per valutare l'iperandrogenismo vengono utilizzate?

- 1
- 3
- > 5

SCHEMA PER LA VALUTAZIONE CLINICA SEMI-QUANTITATIVA DELL'IRSUTISMO



androgens. Considering only the remaining nine body areas, 4.3% of subjects studied had a score of greater than 7, leading these investigators to choose a score of 8 or more as defining hirsutism.

Punteggio "visuale" per la valutazione dell'irsutismo secondo Ferriman & Gallwey

Ad ogni area si attribuisce un punteggio tra 0 (cute glabra) e 4 (elevata presenza di peli terminali)

1 Labbro superiore-guancia
2 Mento- regioni mandibolari
3 Dorso superiore
4 Torace anteriore – petto
5 Addome superiore
6 Addome inferiore
7 Dorso inferiore
8 Braccio
9 Avambraccio
10 Coscia
11 Gamba

T Punteggio totale = Somma da 1 a 11
TC Punteggio "corretto" = Totale esclusi 9 ed 11

da Ferriman e Gallwey, modificato da Hatch et al, Am J Obstet Gynecol 1981

Clinical Review & Education

JAMA Clinical Guidelines Synopsis

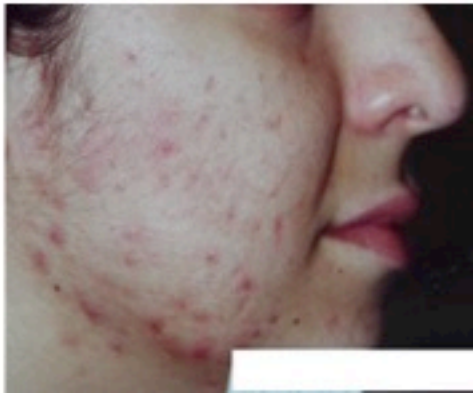
Management of Acne Vulgaris

Carly J. Roman, MD; Adam S. Cifu, MD; Sarah L. Stein, MD

January 10, 2017

Summary of the Clinical Problem

About 50 million people in the United States have acne.[1] Acne affects 85% of all adolescents and about 12% of adult women.[2,3] Acne is a chronic inflammatory condition presenting as comedones (blackheads and whiteheads), papules, pustules, and nodules. It is caused by androgen-induced sebum production, follicular hyperkeratinization, and colonization of the folliculosebaceous unit by the *Proprionibacterium acnes* bacterium.[4] Follicles become impacted with sebum because of follicular keratinization and then become distended, forming comedones. *Proprionibacterium acnes* growth in the follicle results in cytokine release, causing inflammatory lesions.[5] Although it is a benign condition, acne can have considerable morbidity, including pain and discomfort, permanent scarring, and depression and anxiety resulting in poor self-esteem.[2]



DOI: 10.1111/j.1468-3083.2011.04374.x JEADV

GUIDELINES

European Evidence-based (S3) Guidelines for the Treatment of Acne

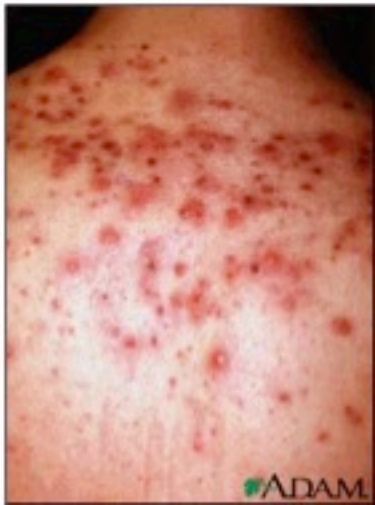
A. Nast,[1,*] B. Dréno,[2] V. Bettoli,[3] K. Degitz,[4] R. Erdmann,[5] A. Y. Finlay,[6] R. Ganceviciene,[7] M. Haedersdal,[8] A. Layton,[9] , J.L. López-Estebaranz,[10] F. Ochsendorf,[11] C. Oprica,[12] S. Rosumeck,[1] B. Rzany,[1] A. Sammain,[1] T. Simonart,[13] N.K. Veien,[14] M.V. Živković,[15] C.C. Zouboulis,[16] H. Gollnick,[17]

I.7 Clinical features and variants

Layton/Finlay

Acne (synonym 'acne vulgaris') is a polymorphic, inflammatory skin disease most commonly affecting the face (99% of cases). Less frequently it also affects the back (60%) and chest (15%).[2] Seborrhoea is a frequent feature.[3]

The clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions (IL), to aggressive fulminate disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms.



Management of acne: Canadian clinical practice guideline

CMAJ, February 2, 2016, 188(2)

Yuka Asai MD MSc, Akerke Baibergenova MD PhD, Maha Dutil MD MEd, Shannon Humphrey BSc MD, Peter Hull MMed PhD, Charles Lynde BSc MD, Yves Poulin MD, Neil H. Shear BASc(Hons) MD, Jerry Tan BSc MD, John Toole BSc MD, Catherine Zip MD

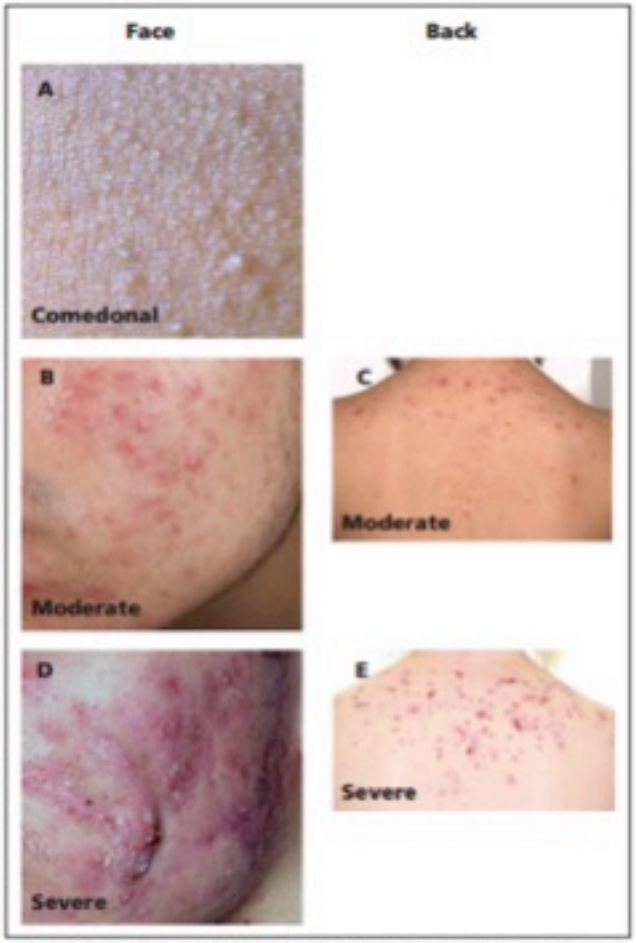
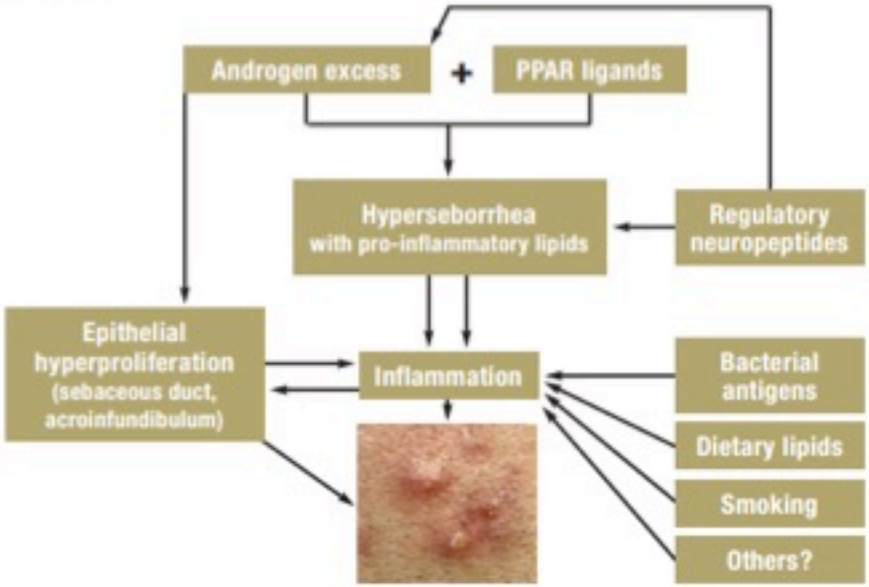


Figure 1: Representative photos of acne categories. (A) Comedonal facial acne. (B) Moderate inflammatory facial acne. (C) Moderate inflammatory acne of the back. (D) Severe facial acne. (E) Severe inflammatory acne of the back.

Not All Acne Is Acne Vulgaris

Harald P. Gollnick, Christos C. Zouboulis

FIGURE 2



Modern aspects of the pathogenesis of acne. Androgens, lipid ligands of the peroxisome proliferation-activating receptor (PPAR), regulatory neuropeptides with hormonal and non-hormonal activity and environmental factors led to hyperseborrhea, epithelial hyperproliferation in the sebaceous duct and acroinfundibulum and to expression of pro-inflammatory chemokines/cytokines, which stimulate the development of comedones and inflammatory acne lesions (from [4])

SCALE DI GRAVITÀ DELL' ACNE

- **SCALA FOTOGRAFICA di LEEDS** = 10 foto
- **GAGS** (Global Acne Grading System) con una conta numerica delle lesioni (1-18 lieve/ 19-30 moderata/31-38 severa/>39 molto severa)
- **Analisi di immagine** per conteggio computerizzato delle lesioni
- **Kligman-Plewig-Cook-Allen-Smith-Dreno** dai 4 a 8 gradi per complessità
- Scala **CADI** (Cardiff Acne Disability Index) relativa alla qualità di vita

Resident's Page

Scoring systems in acne vulgaris

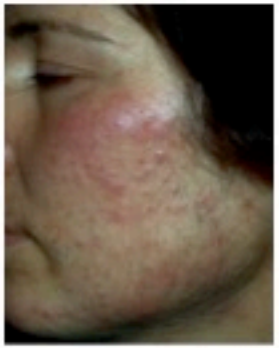
Balaji Adityan, Rashmi Kumari, Devinder Mohan Thappa

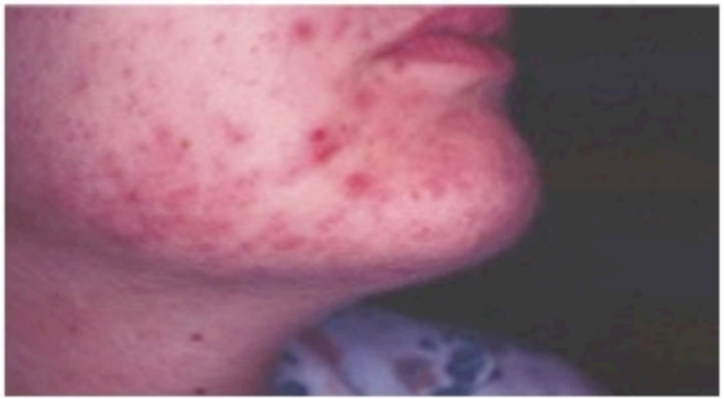
CONCLUSION

Assessment of the severity of acne vulgaris continues to be a challenge for dermatologists. No grading system has been accepted universally. An ideal grading system would

VALUTAZIONE DEL GRADO DI ACNE:
Scala di Lucky

Grado	tipo	lesione
0	assente	assente
1	minore	comedoni = 2 mm
2	medio	comedoni 10 - 20 mm
3	moderato	comedoni > 20 mm o foruncoli < 20mm
4	severo	foruncoli > 20 mm
5	cistico	lesioni infiammatorie





SCALE DI GRAVITÀ DELL' ACNE

TENDENZA ATTUALE ALLA DISTINZIONE IN:

LIEVE/MODERATA/SEVERA

COMEDOCICA, PAPULO-PUSTOLOSA, NODULO-CISTICA

ALOPECIA

Processo di diminuzione della qualità (colore, spessore) e della quantità di capelli o la loro scomparsa. Perdita di capelli a chiazze

SCALE DI RAPPRESENTAZIONE

RAPPRESENTAZIONE DI ALOPECIA:

- ***1977 SCALA di LUDWIG*** (**3 gradi** che misurano il grado di diminuzione della densità di capelli sul cuoio capelluto delle donne)
- ***1994 Savin*** (più condivisa nel mondo scientifico, suddivide i 3 livelli della scala Ludwig in sottofasi)
- ***1999 Olsen*** (pattern di diradamento frontale ad "albero di Natale")
- ***2006 SINCLAIR***

FEMALE PATTERN HAIR LOSS

Female pattern hair loss

Female pattern hair loss (FPHL) is a thinning of hair, primarily in the sagittal area of the scalp, caused by miniaturization of the hair follicles (a process whereby the scalp terminal hairs become smaller and

Fig. 3. Ludwig classification of female pattern of hair loss (androgenic alopecia) (reproduced with permission [50]).

PULL TEST

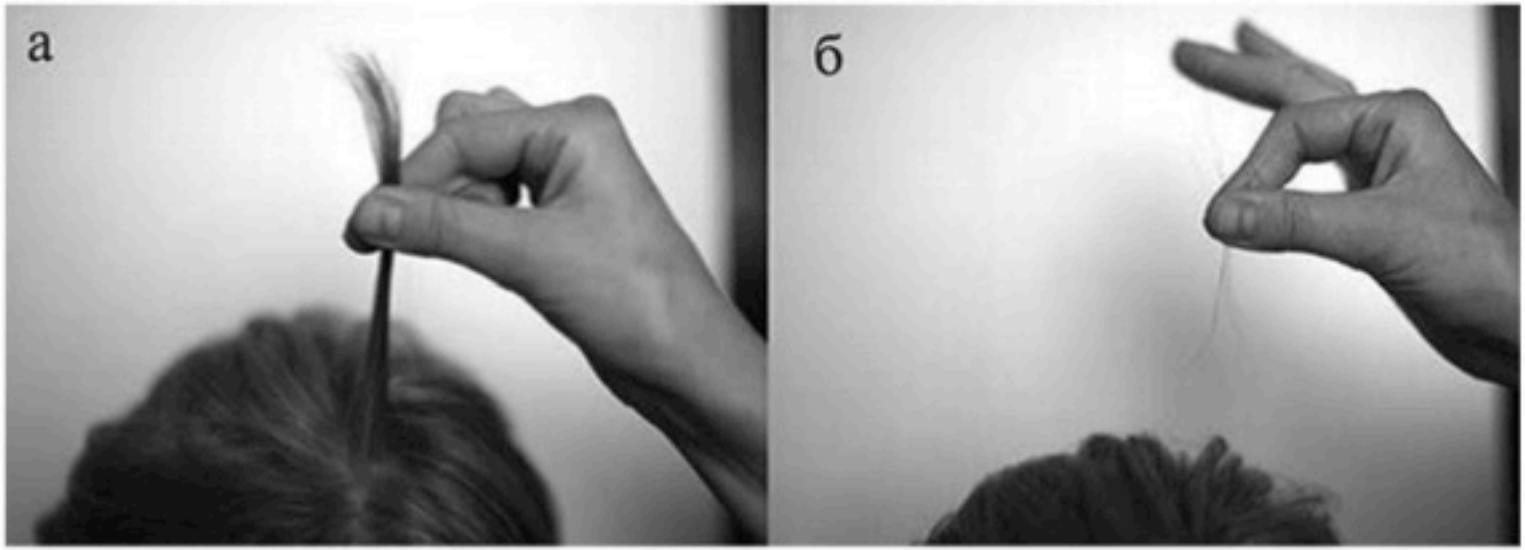
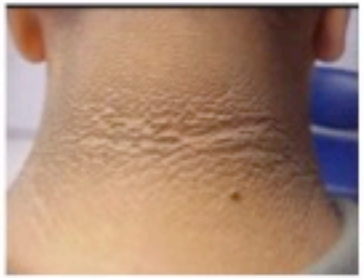


Fig. 4. Hair pull test for the detection of hairs in telogen (photo courtesy of Dr. Daria Lizneva). The patient should not have washed or brushed her hair for at least 24–48 hours before the test. Approximately 50 hairs are grasped and gently tugged outward by the examiner. The easy extraction of more than six (i.e., >10% of hairs grasped) suggests the presence of excess numbers of hairs in telogen. ***Note***: There are three phases of hair growth: *Anagen*, which represents the phase of active growth; *catagen*, which rep-

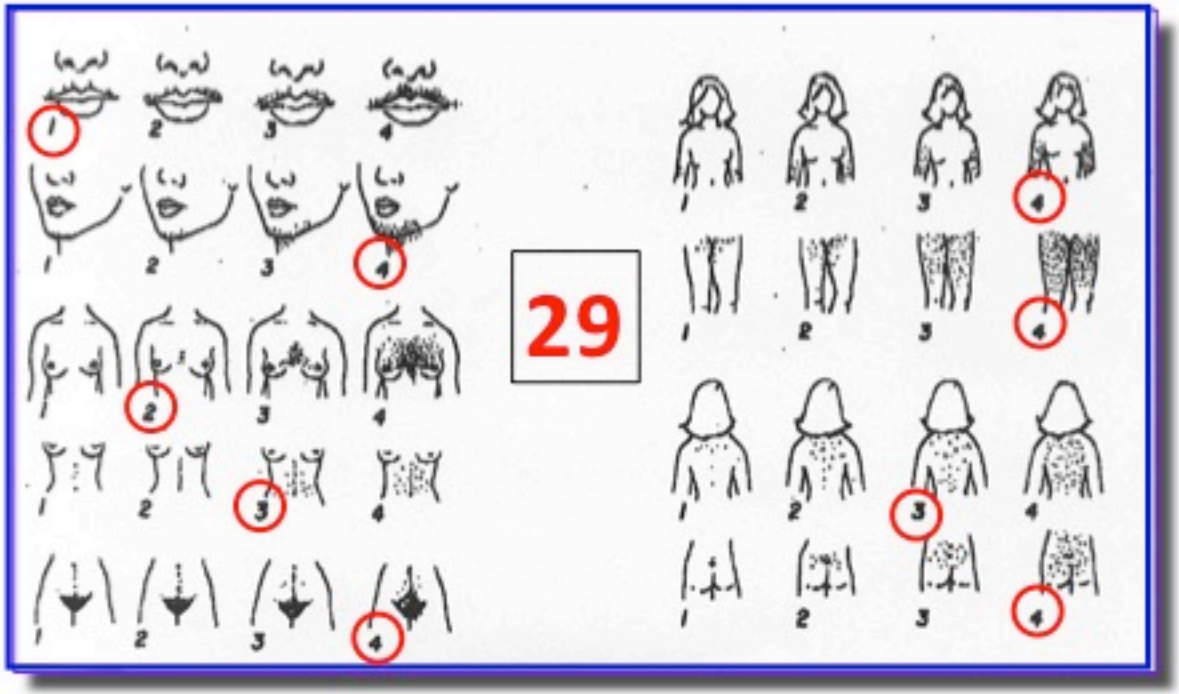
ACANTHOSIS NIGRICANS

L'**Acanthosis nigricans** è una manifestazione cutanea caratterizzata da zone iperpigmentate, mal delimitate, che compaiono tipicamente a livello delle pieghe cutanee (collo, ombelico, inguine, ascelle). La pelle si presenta ispessita e vellutata, di colore più scuro (dal brunastro al nero) rispetto alle zone circostanti.



RITORNIAMO ALLA NOSTRA LORENZA

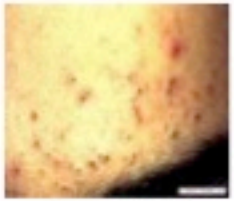
VALUTAZIONE DEL GRADO DI IRSUTISMO
Scala di Ferriman-Gallwey

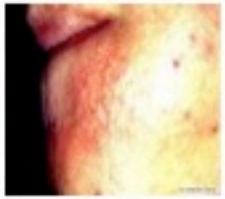


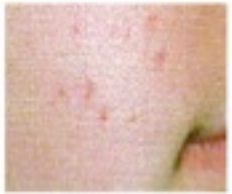
Normalità :	0-7	Irsutismo moderato:	13-18
Irsutismo lieve :	8-12	Irsutismo grave:	>19

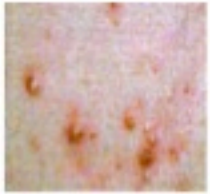
VALUTAZIONE DEL GRADO DI ACNE: Scala di Lucky

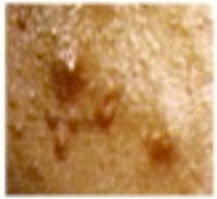
Grado	tipo	lesione
0	assente	assente
1	minore	comedoni = 2 mm
2	medio	comedoni 10-20 mm
3	moderato	comedoni > 20 mm/foruncoli < 20mm
4	severo	foruncoli > 20 mm
5	cistico	lesioni infiammatorie

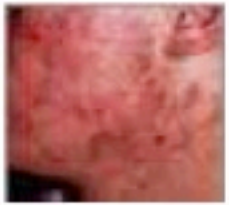

Comedoni aperti


Comedoni chiusi


Papule


Pustole


Noduli


Cisti

VALUTAZIONE DELL'ALOPECIA

Scala di Ludwig

Assente

Tipo I.	Diradamento percettibile dei capelli sulla corona, limitato ad una linea situata 1-3 centimetri dietro la linea frontale
Tipo II.	Rarefazione pronunciata dei capelli sulla corona
Tipo III.	Diradamento molto avanzato su tutta l'area interessata nel tipo I e II

MAP TEST

- Chi sa in cosa consiste?
- Quante modalità esistono per eseguire il MAP test?

Lorenza.. amenorrea, strie rubrae, irsutismo ingravescente/acne

Quali esami avreste richiesto?

1) PRL, Testosterone Totale, SHBG, DHEA-S, 17-OH Progesterone, TSH.

1) + Test di Nugent.

TSH, PRL, Testosterone Totale e Libero, 17-OHProgesterone, ACTH, Cortisolo.

Lorenza.. sovrappeso con acanthosis e familiarità per DM2: quali esami avreste richiesto?

- Glicemia e insulinemia basale
- OGTT per glicemia e insulinemia 0’ e 120’
- HbA1c

Esami ematici:

PRL 13,07 ng/mL,

TSH 1,91 mcUI/mL,

17OHP 7 nmol/L,

testosterone 0.53 ng/mL, SHBG 8,7 nmol/L → FAI 21,1

DHEAS 332 μg/dL.

Test di Nugent→ Cortisolo < 22 nmol/L

Dopo carico orale con 75 g di glucosio

Tempo 0'

glicemia 69 mg/dL, insulina 49,3 UI/L HOMA-IR 8,3

Tempo 120'

glicemia 92 mg/dL, insulina 231,3 UI/L

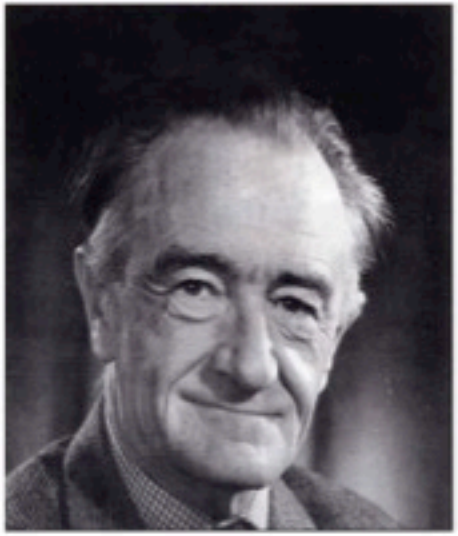
Abbiamo escluso la SAG late-onset?

SI

NO

IPERANDROGENISMO: VALUTAZIONE BIOCHIMICA

Marco Caputo



"Prima di chiedere un esame, decidete cosa fare se è:
(1) positivo o (2) negativo.
Se le risposte coincidono, **non chiedetelo proprio !**"

"Cosa ci dice che non sapevamo già?
E il fatto di saperlo cosa ci cambia?"

Archibald Leman Cochrane

(1909 - 1988)

Iperandrogenismo biochimico

In nessuna linea guida esiste una esplicita definizione di "**iperandrogenismo biochimico**".

Sospetta PCOS e Lab

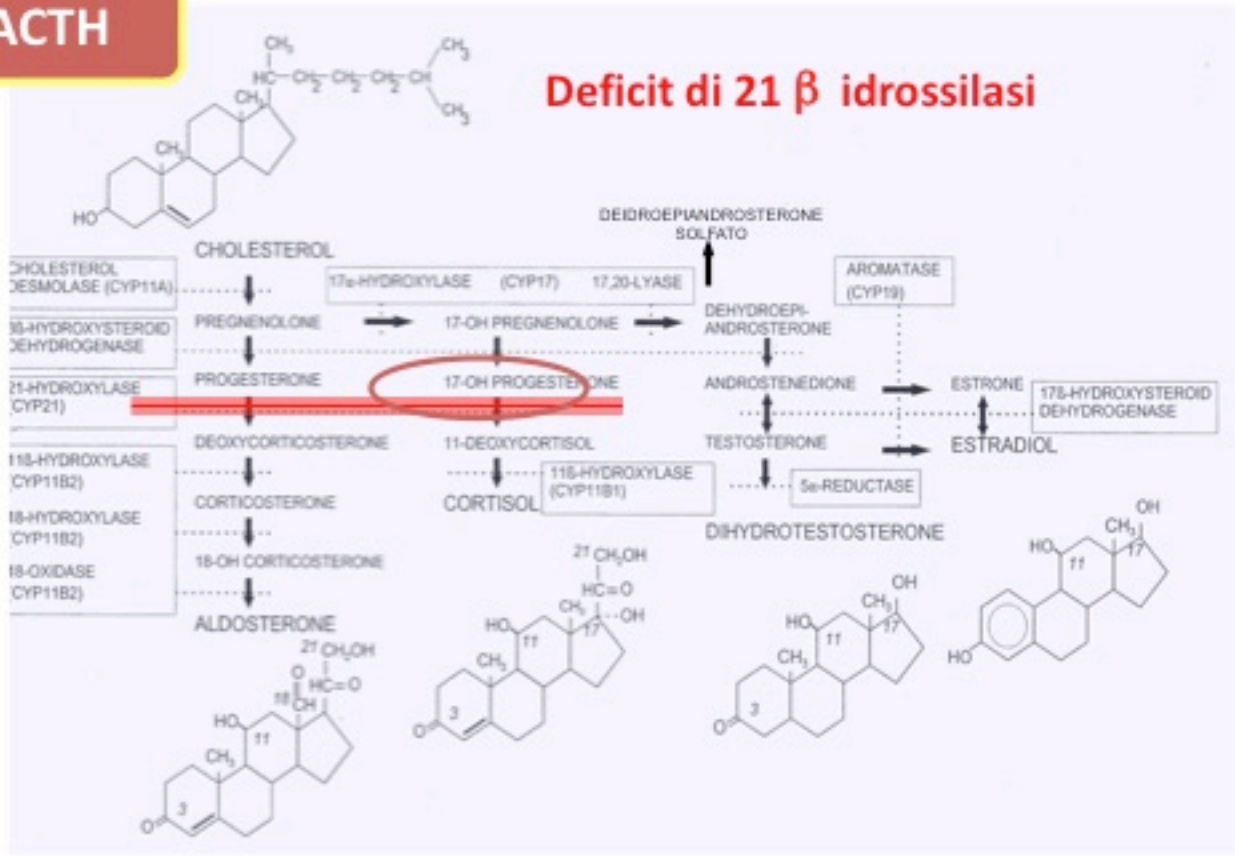
1. **Quando:**
   a. se mancano segni **clinici** di iperandrogenismo;
   b. nel sospetto di neoplasia androgeno-secernente
2. **Come:**
   a. Testosterone totale (solo)
   b. TT + DHEAS

Diagnosi di esclusione
(se richiesto dal quadro clinico)

1. Cushing:
   - Test di Nugent; Cortisolo salivare
2. Iperprolattinemia:
   - prolattinemia
3. Distiroidismi:
   - TSH (reflex)
4. **SAG (late-onset):**
   - 17-OH P e stimolo con ACTH

ACTH

Deficit di 21 β idrossilasi



MINERALCORTICOIDI | GLUCOCORTICOIDI | **ANDROGENI** | ESTROGENI

17- OH PROGESTERONE (17-OHP)

INTERVALLO RIFERIMENTO: 1,21 – 3,03 nmol/L 40 - 100 ng/dL

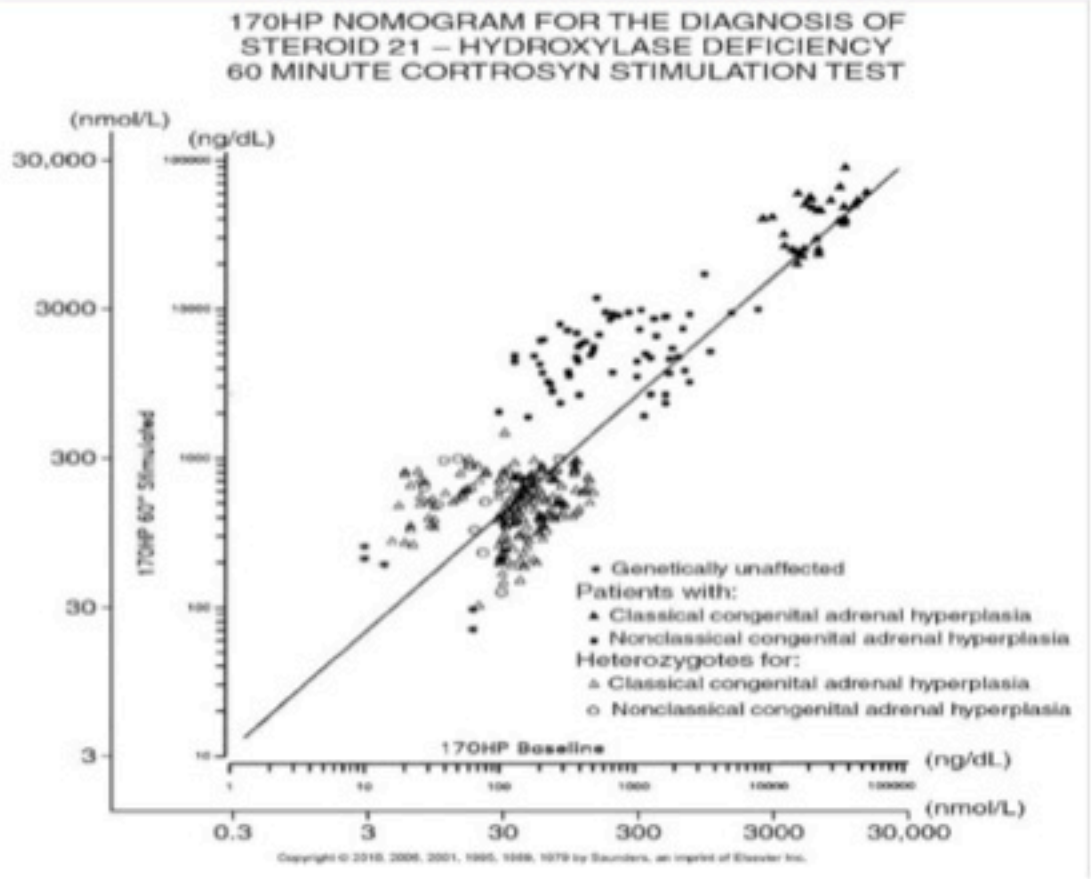
17-OHP ≥ 6 nmol/L (200 ng/dL) → Deficit di 21 β idrossilasi ?

- **Test di stimolo con ACTH (250 μg e.v.):**

  MA **SOLO** NEI PAZIENTI CON 17-OHP **≥ 6 nmol/L** (200 ng/dL)

  CUT OFF DECISIONALE: 17-OHP **> 18.1** nmol/L (600 ng/dL)

- Valutazione, **in fase follicolare precoce**
- Studio genetico per confermare la diagnosi


170HP NOMOGRAM FOR THE DIAGNOSIS OF
STEROID 21 – HYDROXYLASE DEFICIENCY
60 MINUTE CORTROSYN STIMULATION TEST
(nmol/L)
(ng/dL)
30,000
3000
300
30
3
170HP 60' Stimulated
• Genetically unaffected
Patients with:
▲ Classical congenital adrenal hyperplasia
• Nonclassical congenital adrenal hyperplasia
Heterozygotes for:
△ Classical congenital adrenal hyperplasia
○ Nonclassical congenital adrenal hyperplasia
170HP Baseline
(ng/dL)
(nmol/L)
0.3
3
30
300
3000
30,000

SINDROMI ADRENOGENITALI NON CLASSICHE

- **SAG NC DA DIFETTO DI HSD3B2**
- **SAG NC DA DIFETTO DI CYP11B1**

} **0,2-0,7 % delle irsute**

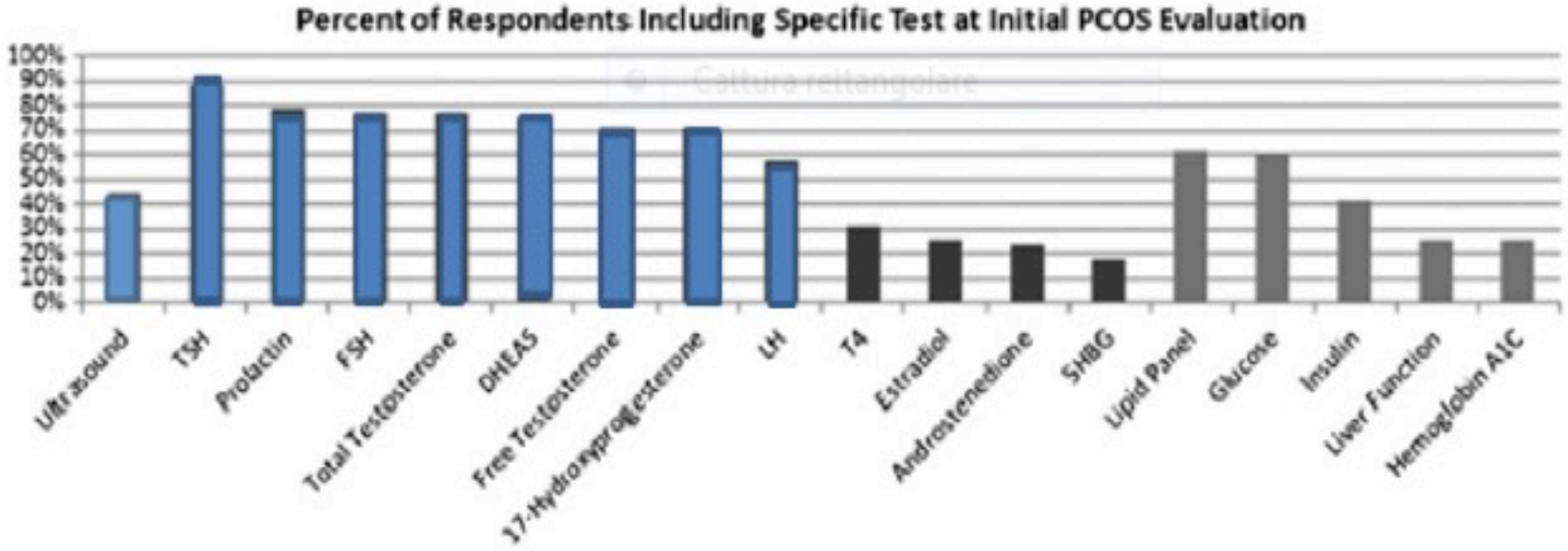
- **SAG NC DA DIFETTO DI CYP21B** ⟹ **1-3 % delle irsute**

Per ottenere risultati rapidi si utilizza l'amplificazione PCR, in grado di rilevare simultaneamente la presenza delle 10 mutazioni rinvenute in circa il 95% degli alleli mutati per deficit della 21-idrossilasi.
L'analisi genetica di CYP21 NON SERVE PER LA DIAGNOSI ma può essere utile per:

- Confermare la base genetica del difetto;
- Aiutare nel counseling genetico;
- Chiarire una minoranza di casi borderline.

Quali esami nel sospetto di PCOS?

A.E. Bonny et al. / J Pediatr Adolesc Gynecol 25 (2012) 259–261



Alternative ?

Testosterone biodisponibile → http://www.issam.ch/freetesto.htm

Indice Androgeni Liberi F.A.I. →

$$\frac{\text{Testosterone totale}}{\text{SHBG}} \times 100$$

Domanda:

Voi lo fate (lo fareste) il F. A. I. ?

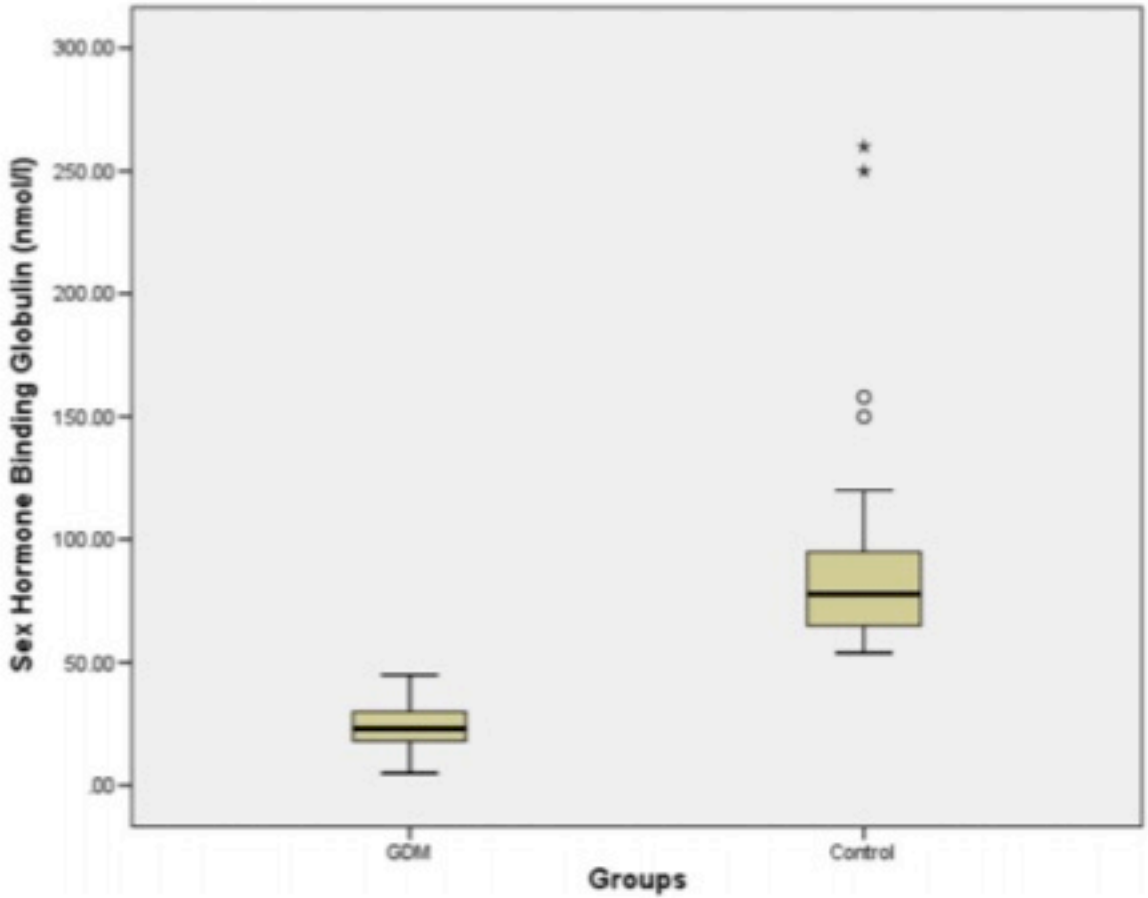
SI.

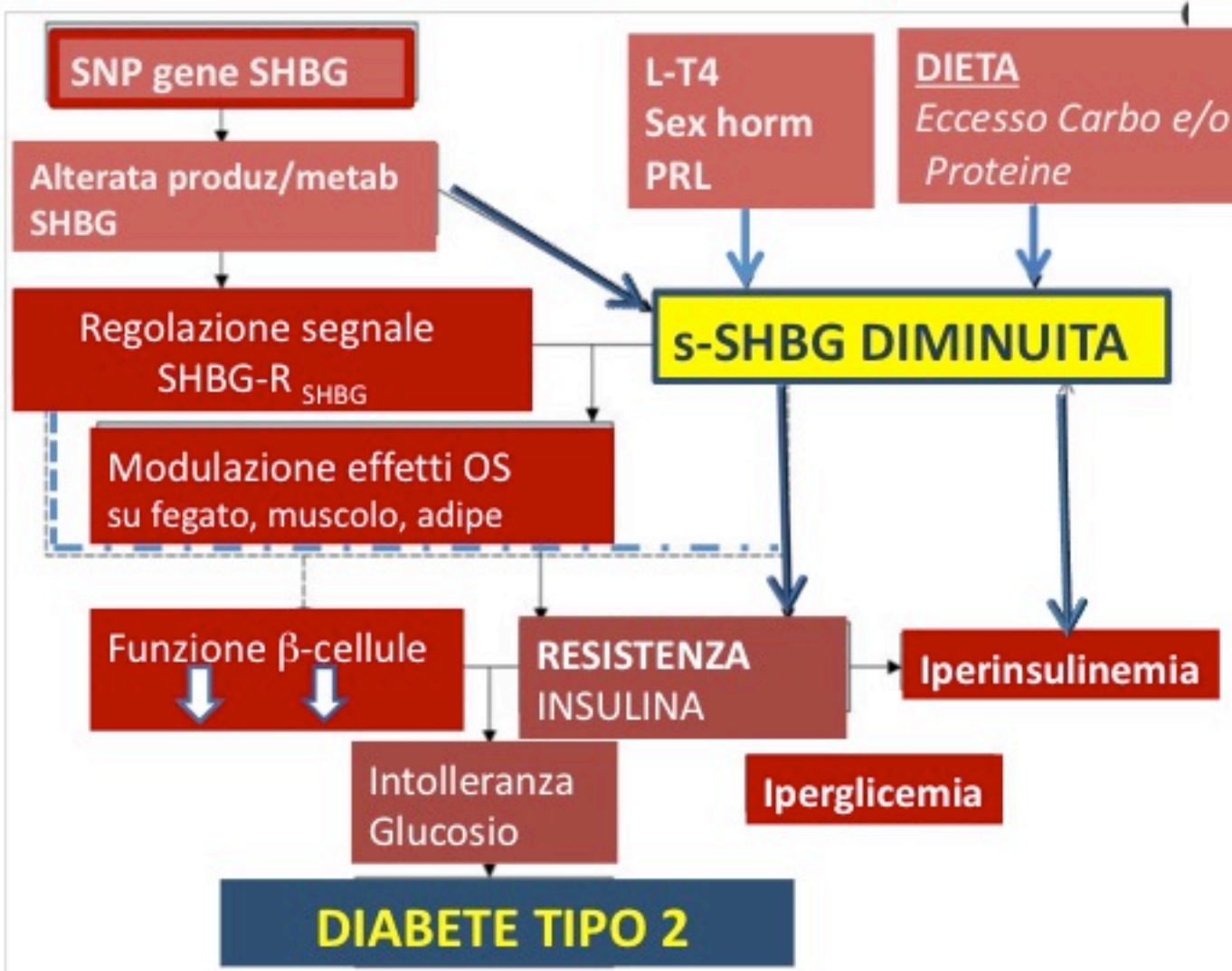
NO.

Tawfeek *et al. BMC Women's Health* (2017) 17:18
DOI 10.1186/s12905-017-0373-3

RESEARCH ARTICLE

Sex hormone bin
valuable biochem
gestational diabe





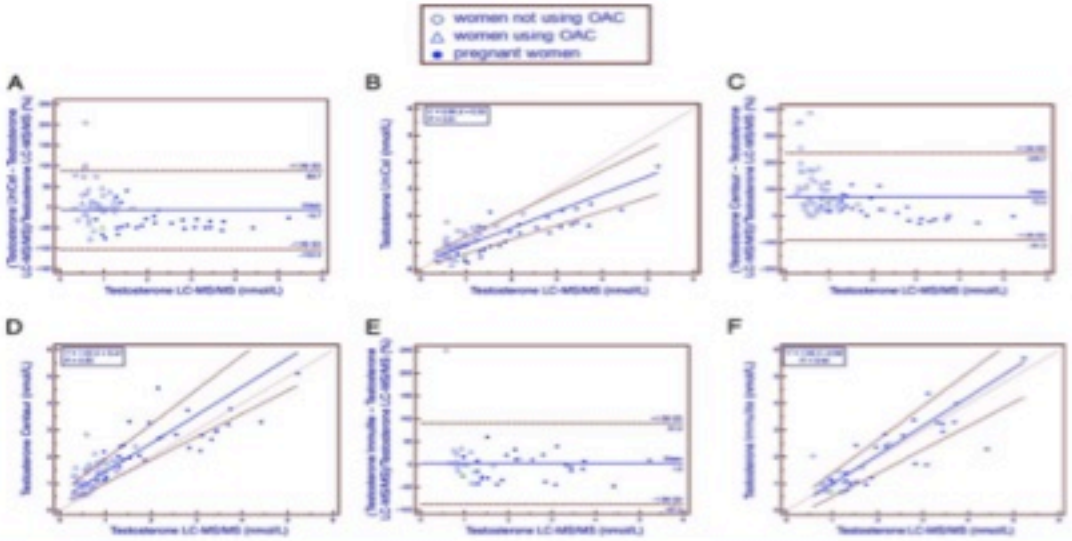
Trends Endocrinol Metab. 2012 Jan; 23(1): 32–40.

Testosterone: che metodi si usano ?

ARTICLES

Inaccurate First-Generation Testosterone Assays Are Influenced by Sex Hormone–Binding Globulin Concentrations

Annemieke C. Heijboer,[1]* Edo Savelkoul,[1] Adrian Kruit,[2] Erik Endert,[3] and Marinus A. Blankenstein[1]



Analisi regressione Passing–Bablok e grafici Bland–Altman per i 6 metodi automatici. *UniCel, Centaur, Cobas, e Liaison hanno* ***una significativa deviazione dalla linearità***.

In P–B: sull'asse x, [T] misurate con ID-LC/Tandem e sull'asse y, [T] con i rispettivi test automatici.

In B–A : sull'asse x, [T] misurate con ID-LC/Tandem e sull'asse y, la deviazione % dei rispettivi test automatici verso LC/Tandem.

(A - B), UniCel; (C - D), Centaur; (E - F), Immulite; (G - H), Liaison; (I - J), ARCHITECT; (K - L), Cobas.

Interferenza da SHBG

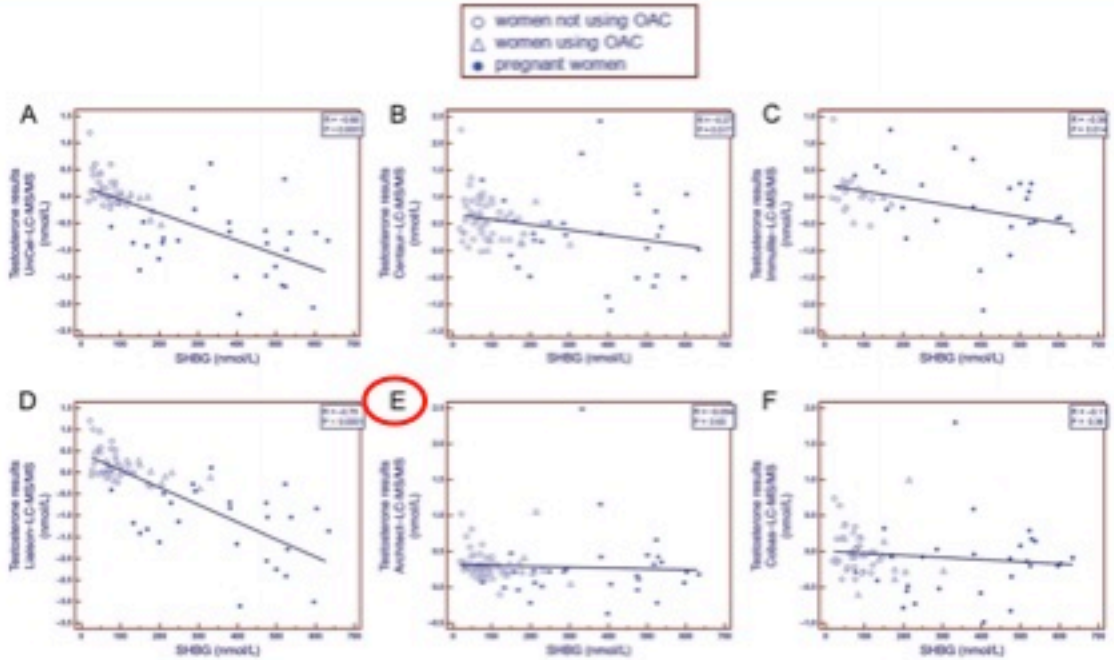


Fig. 3. Correlation between the SHBG concentration and the difference between the results of each of the 6 automated immunoassays and the ID-LC-MS/MS method.

(A), UniCel; (B), Centaur; (C), Immulite; (D), Liaison; (E), ARCHITECT; (F), Cobas. To convert testosterone concentrations to ng/mL, multiply by 0.3.

TSTII ottobre 2017

	Range of Samples TSTO Dose (nmol/L)	Average TSTII Dose (nmol/L)	Average TSTO Dose (nmol/L)	Bias (nmol/L)	Average % Bias
<3.47 nmol/L	0.75 – 2.97	0.90	1.63	-0.73	-44.6%
>3.47 nmol/L	5.05 – 43.14	17.65	16.49	1.16	+7.1%
All data	0.75 – 43.14	10.11	9.80	0.31	+3.2%

	Range of Samples ID-LC-MS/MS Dose (nmol/L)	Average TSTII Dose (nmol/L)	Average ID-LC-MS/MS Dose (nmol/L)	Bias (nmol/L)	Average % Bias
<3.47 nmol/L	0.30 – 3.05	1.28	1.30	-0.02	-1.3%
>3.47 nmol/L	5.62 – 48.37	21.74	22.18	-0.43	-1.9%
All data	0.30 – 48.37	15.83	16.14	-0.32	-2.0%

Le II generazioni

- **Risultati**: Il TSTII ha prodotto CV intra e interassay di 6.9% e 7.4% alla concentrazione di 0.3 nmol/L rispettivamente.
  - NESSUNA DIFFERENZA SIGNIFICATIVA TRA TSTII e LC/Tandem (TSTII = 0.973 × LC/Tandem – 0.02).
  - DIFFERENZE SIGNIFICATIVE TRA TSTO E LC/Tandem (TSTO = 0.753 ×LCMSMS + 0.692).
  - TSTO più alto a basse concentrazioni (<3 nmol/L) e più basso ad alte concentrazioni.
- **Discussione**: Il nuovo TSTII ha accuratezza e precisione accettabili e si confronta con i risultati LC/Tandem anche alle basse concentrazioni di donne e bambini.

Wijeratne N, K Weng Choy K, Montalto J et al Evaluation of the new Siemens ADVIA Centaur TESTOSTERONE II ASSAY. Pathology, 2017; 49: 102

RITORNIAMO ALLA NOSTRA LORENZA

Torniamo a Lorenza…

Iperandrogenismo clinico e biochimico, anovulazione cronica e aspetto micropolicistico delle ovaie. Si può fare diagnosi di PCOS?

- SI
- NO

Torniamo a Lorenza..

Iperandrogenismo clinico e biochimico, anovulazione cronica e aspetto micropolicistico delle ovaie, insulino-resistenza. Cambiano i criteri diagnostici di PCOS nell'adolescente?

- SI
- NO

The Diagnosis of Polycystic Ovary Syndrome during Adolescence

Selma F. Witchel[a] Sharon Oberfield[b] Robert L. Rosenfield[c] Ethel Codner[d]
Andrea Bonny[e] Lourdes Ibáñez[f] Alexia Pena[g] Reiko Horikawa[h]
Veronica Gomez-Lobo[i] Dipesalema Joel[j] Hala Tfayli[k] Silva Arslanian[l]
Preeti Dabadghao[m] Cecilia Garcia Rudaz[n] Peter A. Lee[o]

Horm Res Paediatr 2015;83:376–389

Criteri ESHRE/ASRM per la diagnosi di PCOS in adolescenza

- Consensus di Amsterdam 2010 -

La diagnosi richiede tutti i seguenti elementi

- Oligo-amenorrea (dopo almeno due anni dal menarca o a 16 anni se vi è amenorrea primaria)
- Iperandrogenismo (in particolare iperandrogenemia, in alternativa chiaro irsutismo progressivo)
- Ovaie micropolicistiche (volume ovarico > 10 mL)

dopo aver escluso altre cause

(Hum Reprod & Fertil Steril, Jan 2012)

Criteri per la diagnosi di PCOS

- Nell'adolescente: **Iperandrogenismo** (clinico* e/o biochimico)
  + oligomenorrea persistente**

* L'acne isolata non va considerata espressione di iperandrogenismo.

** In particolare quando l'oligo-amenorrea persiste due anni oltre il menarca. L'aspetto micropolicistico dell'ovaio e l'anovulazione non sono aspetti utili ai fini della diagnosi nell'adolescente.

(Legro et al, JCEM 2013)

Horm Res Paediatr 2015;83:376–389

TABLE 2 Diagnostic Criteria for PCOS in Adolescents

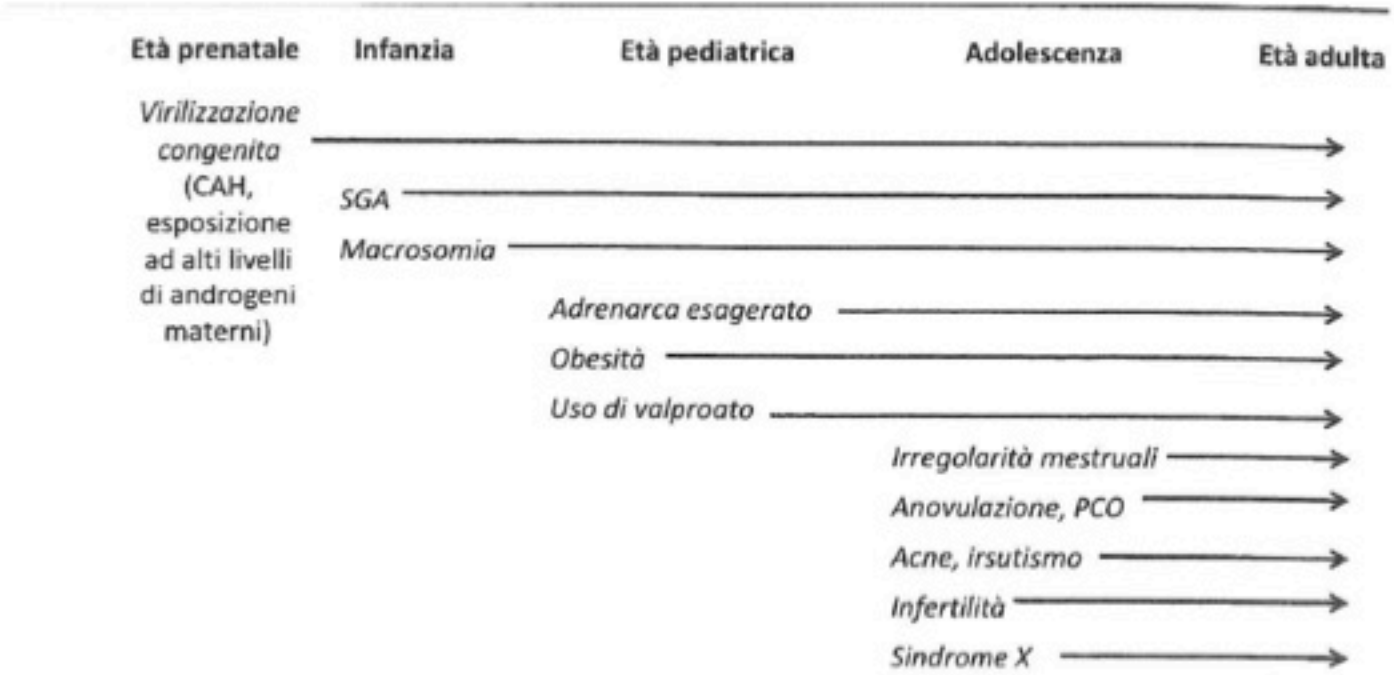
Otherwise unexplained combination of:

1. Abnormal uterine bleeding pattern
   a. Abnormal for age or gynecologic age
   b. Persistent symptoms for 1–2 y
2. Evidence of hyperandrogenism
   a. Persistent testosterone elevation above adult norms in a reliable reference laboratory is the best evidence
   b. Moderate-severe hirsutism is clinical evidence of hyperandrogenism
   c. Moderate-severe inflammatory acne vulgaris is an indication to test for hyperandrogenemia

The Diagnosis of Polycystic Ovary Syndrome during Adolescence

Selma F. Witchel[a] Sharon Oberfield[b] Robert L. Rosenfield[c] Ethel Codner[d] Andrea Bonny[e] Lourdes Ibáñez[f] Alexia Pena[g] Reiko Horikawa[h] Veronica Gomez-Lobo[i] Dipesalema Joel[j] Hala Tfayli[k] Silva Arslanian[l] Preeti Dabadghao[m] Cecilia Garcia Rudaz[n] Peter A. Lee[o]

Fattori di rischio in relazione all'età



L'Endocrinologo (2014) 15:1–8

Quali sono i criteri clinici di iperandrogenismo nell'adolescente?

Recommendations

(1) Isolated mild hirsutism should not be considered clinical evidence of hyperandrogenism in the early postmenarcheal years when it may be in a developmental phase (Level C).

(2) Moderate to severe hirsutism constitutes clinical evidence of hyperandrogenism (Level B).

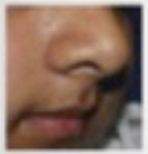
(3) Girls with acne that is persistent and poorly responsive to topical dermatologic therapy should be evaluated for the presence of hyperandrogenemia before initiation of any medical therapies (Level C).

Horm Res Paediatr 2015;83:376–389

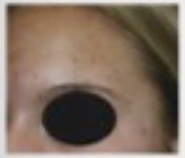
Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne

Mild Acne=Comedonal or Inflammatory/Mixed Lesions

Mild Comedonal Acne

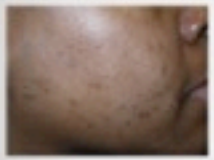


More Extensive Comedonal Acne



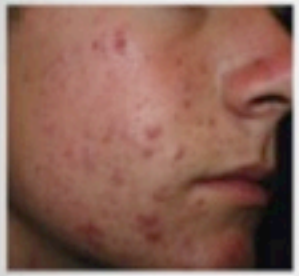
Mild Inflammatory Acne

(scattered superficial inflammatory papules/pustules + some comedones)

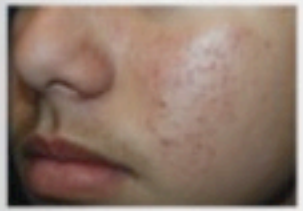


Moderate Acne=Comedonal or Inflammatory/Mixed Lesions

Note Marked Number of Inflammatory Lesions

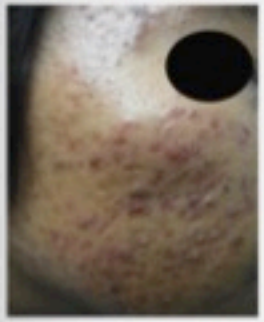


Some Comedones Present



Severe Acne=Inflammatory/ Mixed and/or Nodular Lesions

Extensive Inflammatory Lesion Involvement



Note Diffuse Scarring

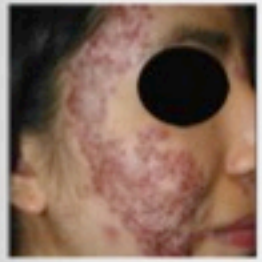


TABLE 4 An Acne Scoring System for Adolescents[a]

Severity	Comedonal Lesions[b]	Inflammatory Lesions[c]
Mild	1–10	1–10
Moderate	11–25	11–25
Severe	>25	>25

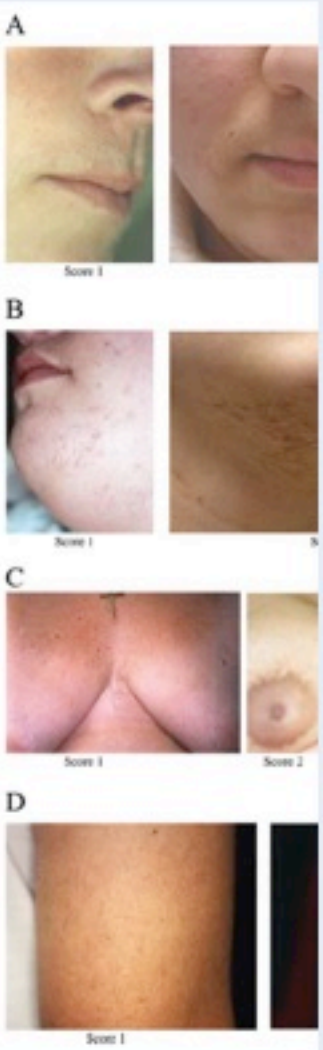
Roma, 9-12 novembre 2017

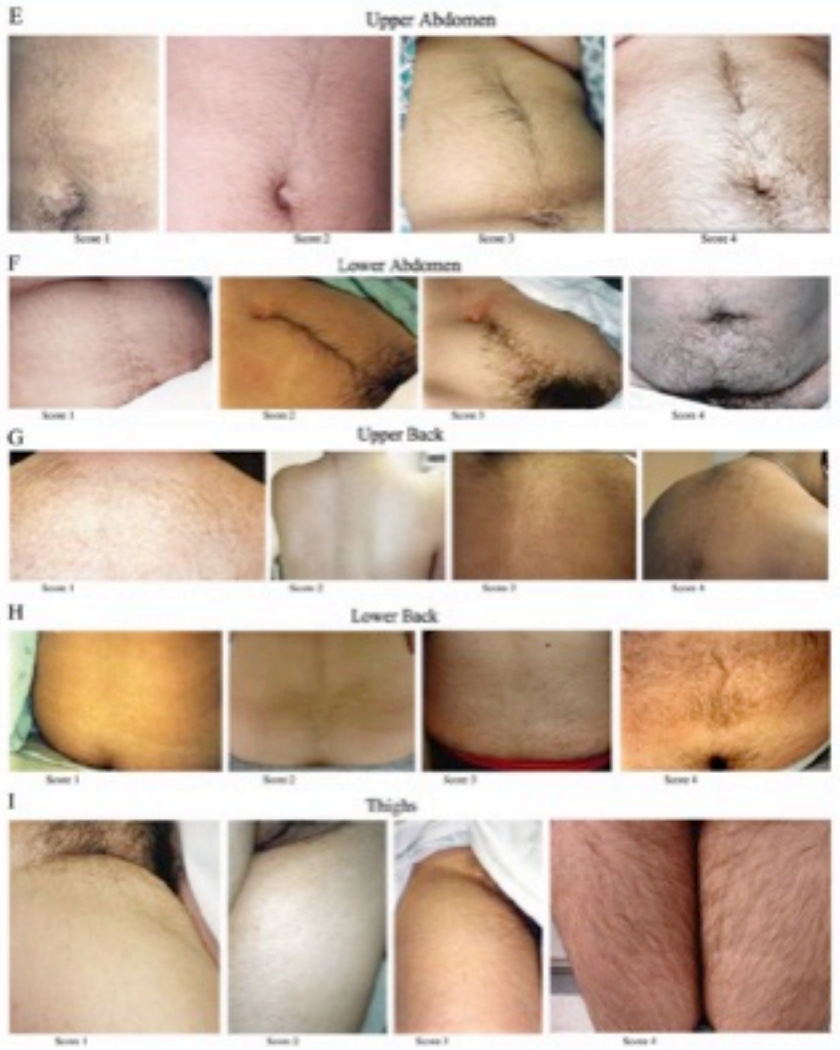
Visually scoring hirsutism

Bulent O. Yildiz[1], Sheila Bolour[2,3], Keslie Woods[4], A
and Ricardo Azziz[3,5,6,7]

La severità dell'irsutismo non correla bene con la concentrazione degli androgeni circolanti

Human Reproduction Update, Vol.16, No.1 pp. 51–64, 2





Quali sono i criteri biochimici di iperandrogenismo nell'adolescente?

Recommendations

(1) Hyperandrogenemia needs to be defined based on the detailed characteristics of the testosterone assay used (Level A).

(2) Biochemical evidence of hyperandrogenism, as indicated by persistent elevation of serum total and/or free testosterone levels and determined in a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS (Level B).

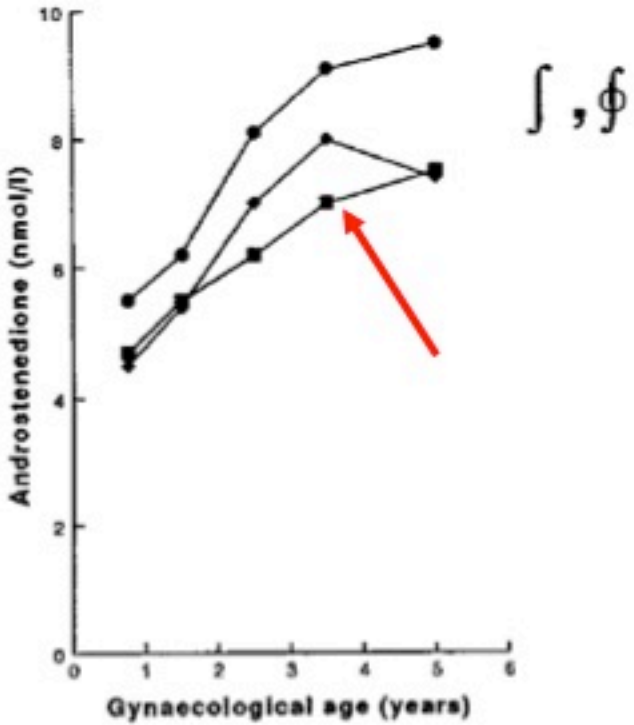
(3) A single androgen level >2 SD above the mean for the specific assay should not be considered to be evidence of hyperandrogenism in an otherwise asymptomatic adolescent girl (Level C).

Horm Res Paediatr 2015;83:376–389

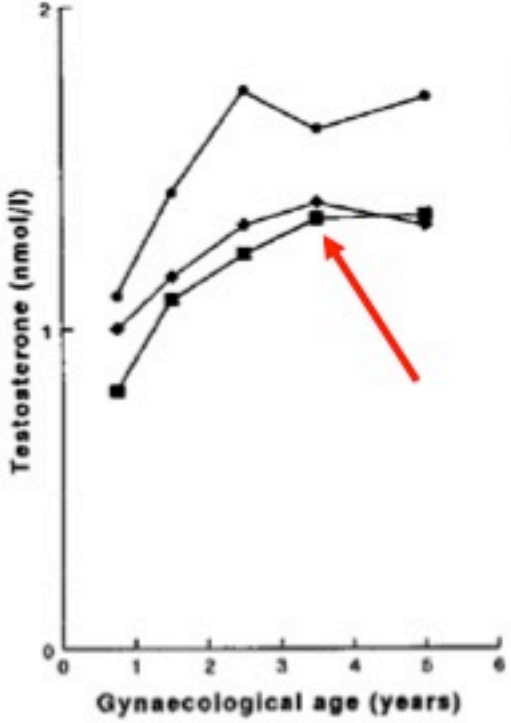
Insulin, Androgen, and Gonadotropin Concentrations, Body Mass Index, and Waist to Hip Ratio in the First Years after Menarche in Girls with Regular Menstrual Cycles, Irregular Menstrual Cycles, or Oligomenorrhea*

JCE & M • 2000
Vol 85 • No 4

RMC IMC Oligo



∫ , ϕ



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Quali sono i criteri per identificare l'oligo-anovulazione nell'adolescente?

Horm Res Paediatr 2015;83:376–389

Recommendations

(1) The majority of adolescents establish a menstrual interval of 20–45 days within the first 2 years after menarche. Menstrual intervals persistently shorter than 20 days or greater than 45 days in individuals 2 or more years after menarche are evidence of oligo-anovulation (Level B).

(2) A menstrual interval greater than 90 days is unusual even in the first year after menarche. As such, consecutive menstrual intervals greater than 90 days are rare and require further investigation regardless of years after menarche (Level B).

(3) Lack of onset of menses by age 15 years or by more than 2–3 years after thelarche regardless of chronologic age is statistically uncommon and warrants evaluation and consideration of diagnoses such as PCOS (Level B).

TABLE 3 Types of Abnormal Uterine Bleeding Found in Adolescent PCOS

Descriptor	Definition
Primary amenorrhea	Lack of menarche by 15 y of age or by 3 years after the onset of breast development[a]
Secondary amenorrhea	Over 90 d without a menstrual period after initially menstruating
Oligomenorrhea (infrequent AUB)	Postmenarcheal year 1: average cycle length >90 d (<4 periods/y) Postmenarcheal year 2: average cycle length >60 d (<6 periods/y) Postmenarcheal years 3–5: average cycle length >45 d (<8 periods/y) Postmenarcheal years ≥6: cycle length >38–40 d (≤9 periods/y)
Excessive anovulatory AUB†	Menstrual bleeding that occurs more frequently than every 21 d (19 d in yr 1) or is excessive (lasts >7 d or soaks >1 pad or tampon every 1–2 h)

Modified and reproduced with permission from Rosenfield RL. Clinical review: Adolescent anovulation: Maturational mechanisms and implications. *J Clin Endocrinol Metab.* 2013;98:3572–3583. AUB, abnormal uterine bleeding.

Cicli anovulatori nell'adolescente:

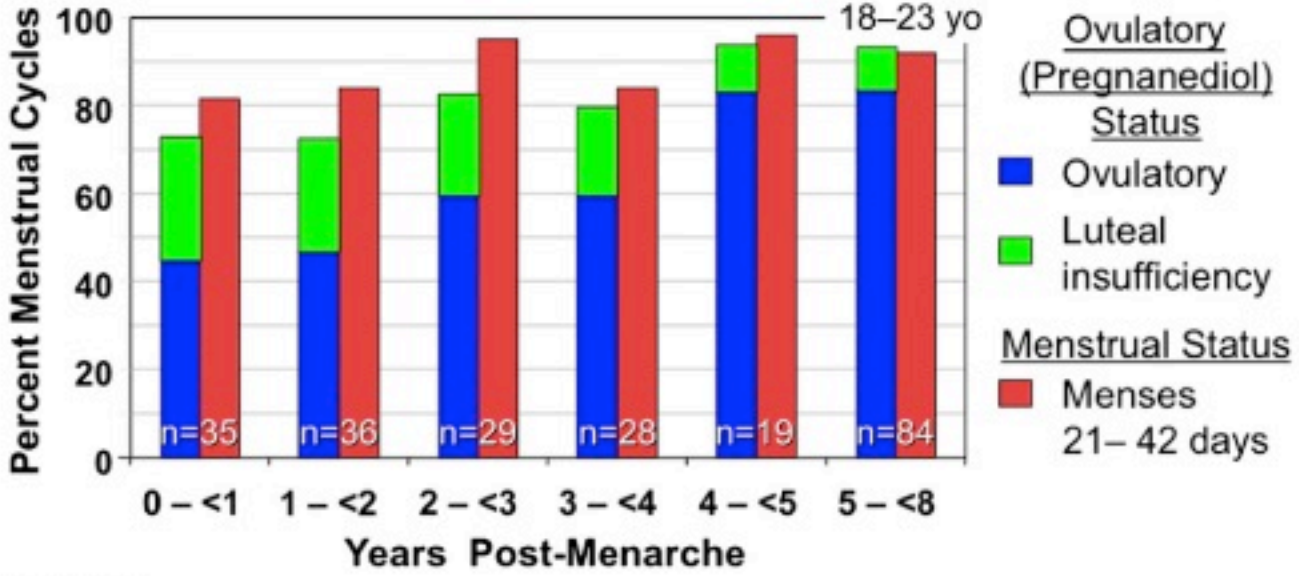


FIGURE 1

Comparison of the percent of menstrual cycles that are 21 to 45 days' duration (red) and percent of menstrual cycles that are ovulatory (blue) by postmenarcheal age through young adulthood. Ovu-

Prognosi dell'anovulazione sintomatica nell'adolescente

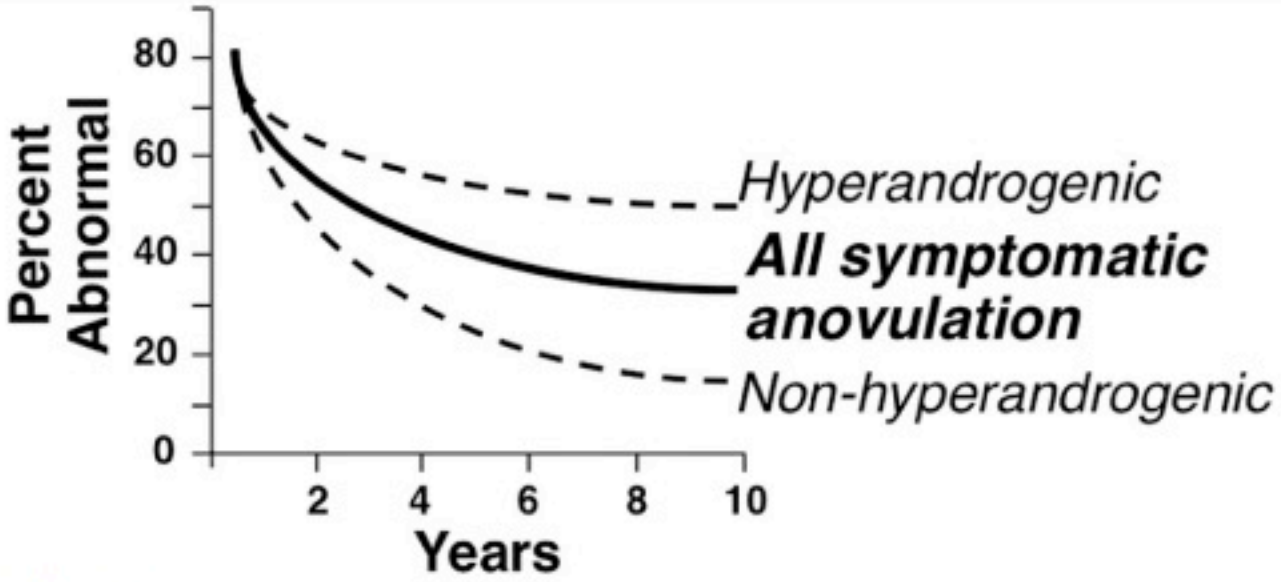


FIGURE 2

Probability that an adolescent with symptomatic anovulatory symptoms will have ongoing menstrual abnormality. "All symptomatic anovulation" curve represents the data of Southam et al.[26] "Hyper-

Southam AL Am J Obstet Gynecol 1966

Quali sono i criteri ecografici di PCOM nell'adolescente?

Recommendations

(1) No compelling criteria to define PCOM have been established for adolescents. Until further research establishes definitive criteria, an ovarian volume >12.0 cm^3 (by formula for a prolate ellipsoid) can be considered enlarged. Follicle counts should not be utilized to define PCOM in adolescents (Level B).

(2) Further, a multifollicular pattern, which is defined by the presence of large follicles distributed throughout the ovary, does not have a relationship with hyperandrogenism, is more common in adolescents, and should not be considered a pathological finding (Level C).

(3) Additionally, in healthy girls with regular menstrual cycles and without hyperandrogenism, PCOM does not indicate a diagnosis of PCOS (Level B).

(4) Abdominal ultrasound in adolescents, particularly obese girls, may yield inadequate information (Level C).

(5) AMH concentrations should not be used to characterize PCOM (Level B).

(6) Until better quality-consistent data are available, ovarian imaging can be deferred during the diagnostic evaluation for PCOS (Level C).

Horm Res Paediatr 2015;83:376–389

Circulating AMH Reflects Ovarian Morphology by Magnetic Resonance Imaging and 3D Ultrasound in 121 Healthy Girls

Casper P. Hagen, Annette Mouritsen, Mikkel G. Mieritz, Jeanette Tinggaard, Christine Wohlfahrt-Veje, Eva Fallentin, Vibeke Brocks, Karin Sundberg, Lisa Nesrup Jensen, Richard A. Anderson, Anders Juul, and Katharina M. Main

Table 1. Study Population Stratified by Breast Stage (Tanner's Classification)

	Breast Stage											
	B1			B2			B3			B4+5		
Characteristic	n	Median	Range	n	Median	Range	n	Median	Range	n	Median	Range
Age, y	15	10.9	(9.8–12.7)	31	11.8	(10.3–12.8)	34	12.4	(10.7–14.0)	38	12.6	(11.5–14.7)
Body mass index, kg/m^2	15	18	(13.1–21.4)	31	17	(13.8–21.2)	31	18.1	(14.2–22.4)	38	19.3	(16.3–33.9)
Ovarian volume, sum, Ellipsoid MRI, cm^3	10	2.3	(0.7–5.5)	19	4.6	(2.4–8.5)	23	6.7	(2.5–13.8)	30	8.4	(3.2–21.0)
Ovarian volume, max, Ellipsoid MRI, cm^3	11	1.6	(0.4–3.9)	25	2.6	(1.1–4.7)	25	4.1	(1.5–8.3)	32	4.9	(1.6–11.6)
Ovarian volume, sum, Ellipsoid TAUS, cm^3	13	5.5	(2.2–11.9)	30	8.8	(3.7–17.0)	29	12.7	(5.4–31.2)	28	11.7	(3.6–26.8)
Ovarian volume, max, Ellipsoid TAUS, cm^3	15	3.2	(1.1–6.9)	31	5.6	(1.9–13.4)	30	8	(3.1–20.1)	32	7.4	(2.4–14.6)
Ovarian volume, sum, 3D TAUS, cm^3	13	5.8	(2.4–13.5)	30	8.9	(3.7–18.9)	26	14.3	(4.5–20.2)	28	13.5	(4.6–29.3)
Ovarian volume, max, 3D TAUS, cm^3	15	3	(1.3–7.9)	31	5.9	(2.3–13.3)	29	8.3	(3.6–17.2)	32	7.4	(3.0–16.1)
Ovarian follicles, MRI, total	10	13	(3–21)	20	18	(9–33)	24	24	(10–63)	31	22	(6–62)
Small, 2–4 mm	10	8	(1–14)	20	10	(1–23)	24	12	(4–26)	31	8	(0–26)
Medium, 5–9 mm	10	5	(2–8)	20	8	(5–13)	24	12	(5–37)	31	11	(3–36)
Large, ≥10 mm	10	0	(0–0)	20	0	(0–2)	24	0	(0–5)	31	1	(0–4)
Ovarian follicles, 3D TAUS, total	11	40	(19–65)	30	40	(21–86)	24	41	(26–84)	26	43	(25–94)
Small, 1–4 mm	11	34	(15–53)	30	33	(13–70)	24	30	(18–75)	26	30	(13–63)
Medium, 5–9 mm	11	9	(3–16)	30	9	(1–22)	24	9	(5–30)	26	11	(2–29)
Large, ≥10 mm	11	0	(0–1)	30	1	(0–5)	24	2	(0–6)	26	2	(0–7)
AMH, pmol/L[a]	14	20	(8–45)	29	17	(5–55)	31	18	(2–37)	36	14	(4–63)
Inhibin B, pg/mL	14	24	(9–66)	29	43	(24–122)	31	64	(4–215)	36	70	(3–120)
Estradiol, pmol/L	14	32	(<18–45)	29	61	(<18–291)	31	88	(24–236)	36	150	(42–891)
T, nmol/L	14	<0.10	(<0.10–0.31)	29	<0.10	(<0.10–0.65)	31	0.53	(<0.10–2.03)	36	0.48	(<0.10–1.60)
Androstenedione, nmol/L	12	1.63	(<0.18–3.64)	29	2.1	(<0.18–6.09)	31	5.64	(<0.18–11.90)	34	4.08	(1.65 – 14.80)
FSH, IU/L	14	1.78	(0.09–3.69)	29	3.05	(0.64–6.84)	31	4.56	(1.31–6.53)	36	4.39	(0.64 – 7.39)
LH, IU/L	14	<0.05	(<0.05–0.38)	29	0.65	(<0.05–8.00)	31	2.34	(0.07–5.92)	36	3.34	(<0.05 – 8.72)
Menarche, Y/N/NA	15	0/15/0		31	3/28/2000		34	3/27/2004		38	20/17/1	
Gynecological age, y	0	NA		3	0.5	(0.27–0.90)	3	0.1	(0.03–0.28)	20	0.94	(0.08–2.30)
PCOM, MRI[b]	10	0 (0%)		20	6 (30%)		24	15 (63%)		31	17 (55%)	

Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Müllerian hormone

C. Villarroel[1], P.M. Merino[1,2], P. López[1,2], F.C. Eyzaguirre[1], A. Van Velzen[1], G. Iñiguez[1], and E. Codner[1,2]

Human Reproduction, Vol.26, No.10 pp. 2861–2868, 2011

Table I Clinical characteristics according to ovarian morphology.

	PCOM (−)	PCOM (+)
n (%)	49 (66.2)	25 (33.8)
Age (years)	16.2 ± 0.2	16.4 ± 0.4
Age of menarche (years)	12.2 ± 0.1	12.0 ± 0.2
Gynecological age (years)	3.6 + 0.3	4.0 + 0.5
BMI (kg/m^2)	22.7 ± 0.4	22.5 ± 0.5
BMI-SDS	0.5 ± 0.1	0.5 ± 0.1
Menstrual cycle (days)	30.0 ± 0.4	31.4 ± 0.8
Overweight (%)	15 (30.6)	4 (16.0)
Height (cm)	158.6 ± 0.8	160.3 ± 1.0
Waist-to-hip ratio	0.8 ± 0.01	0.8 ± 0.01
Ferriman–Gallwey	2.0 (0.0–6.0)	3.0 (0.0–7.7)

Data are shown as means ± SEM. FG scores are shown as medians (5th to 95th percentile). BMI, body mass index; BMI-SDS, body mass index-standard deviation score.

Table II Hormonal profiles and ultrasonographic characteristics according to ovarian morphology.

	PCOM (−)	PCOM (+)
n (%)	49	25
AMH (pmol/l)	33.4 ± 2.6**	72.5 ± 6.1**
Inhibin B (pg/ml)	57.4 ± 4.2	63.3 ± 6.5
LH (mIU/ml)	3.9 ± 0.3	4.2 ± 0.5
FSH (mIU/ml)	6.2 ± 0.2*	5.4 ± 0.3*
LH/FSH	0.6 ± 0.1	0.9 ± 0.1
Estradiol (pmol/l)	169.2 ± 12.5	167.3 ± 13.6
Testosterone (nmol/l)	1.6 ± 0.1	1.6 ± 0.1
SHBG (nmol/l)	53.3 ± 3.3	52.9 ± 3.4
free androgen index (%)	3.8 ± 0.4	3.4 ± 0.3
DHEAS (nmol/l)	4485 ± 254	4482 ± 362
Androstenedione (nmol/l)	5.6 ± 0.3	5.9 ± 0.3
17OH-Progesterone (nmol/l)	3.3 ± 0.3	4.5 ± 0.9
Glucose (mmol/l)	4.5 ± 0.1	4.3 ± 0.1
Insulin (mIU/ml)	6.5 ± 0.4	5.7 ± 0.5
HOMA-IR	1.3 ± 0.1	1.1 ± 0.1
Ovarian volume (ml)	6.3 ± 0.3**	9.9 ± 0.7**
Follicle number (n)	6.6 ± 0.4**	12.8 ± 0.8**
FN, follicle 2–5 mm (n)	5.2 ± 0.4**	11.2 ± 0.9**
FN, follicle 6–9 mm (n)	1.9 ± 0.3	2.4 ± 0.5

Results are reported as means ± SEM. The analysis was performed using Student's t-test P. Conversion to metric units: testosterone, nmol/l × 0.2882 = ng/ml; androstenedione, nmol/l × 0.2865 = ng/ml; DHEAS, nmol/l × 370.37 = ng/ml; estradiol, pmol/l × 0.2725 = pg/ml; 17OH progesterone, nmol/l × 0.3300 = ng/ml; SHBG, nmol/l/ 34.67 = μg/dl; AMH, pmol/l × 0.1400 = μg/l; glucose mmol/l/0.0555 = mg/dl.
*PCOM$^+$ versus PCOM$^-$: $P < 0.05$.
**PCOM$^+$ versus PCOM$^-$: $P < 0.0001$.

Escludere altre cause di iperandrogenismo

Recommendations

(1) A thorough medical history, physical examination, and appropriate laboratory assessment are essential to provide the information necessary to exclude other disorders associated with androgen excess (Level A).

Horm Res Paediatr 2015;83:376–389

Aspetti metabolici

Recommendations

(1) Although prevalent among adolescents at risk for PCOS, insulin resistance and hyperinsulinemia should not be utilized as diagnostic criteria (Level B).

(2) Insulin resistance and hyperinsulinemia can be considered as indications to investigate and treat potential comorbidities (Level B).

Horm Res Paediatr 2015;83:376–389

Raccomandazioni AE-PCOS sull'uso dell'OGTT (2010)

La donna con PCOS dovrebbe essere sottoposta a OGTT in presenza di fattori di rischio:

- BMI > 30 kg/m^2
- età > 40 anni
- storia personale di diabete gestazionale
- familiarità per diabete tipo 2

Se negativo, il test dovrebbe essere ripetuto almeno ogni due anni

Wild et al, JCE&M 2010

Raccomandazioni ESHRE/ASRM per lo screening con OGTT nelle donne con PCOS

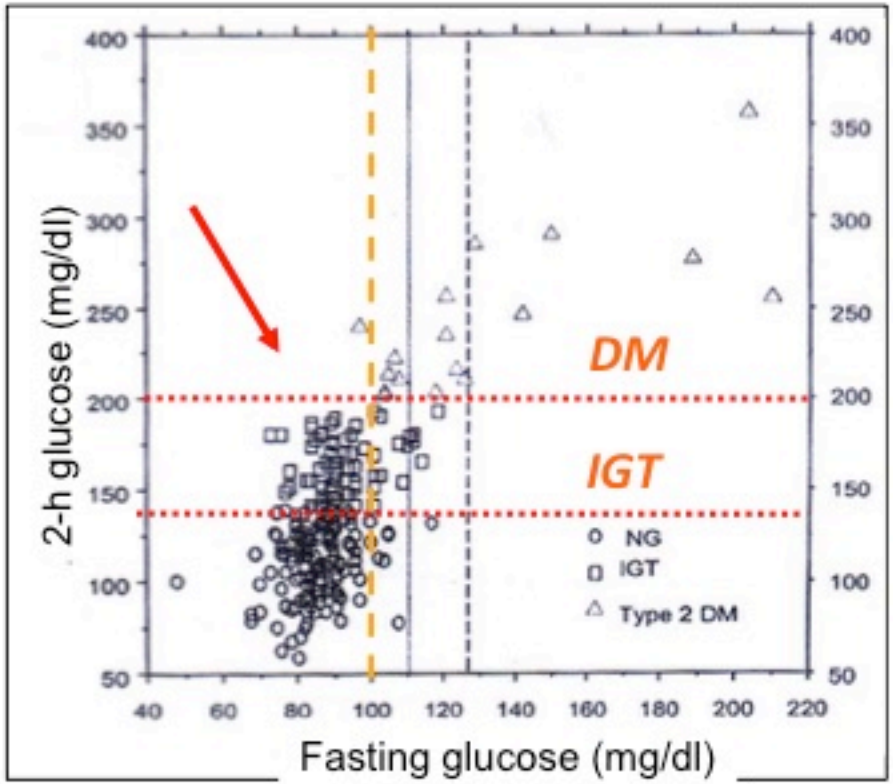
- Consensus di Amsterdam 2010 -

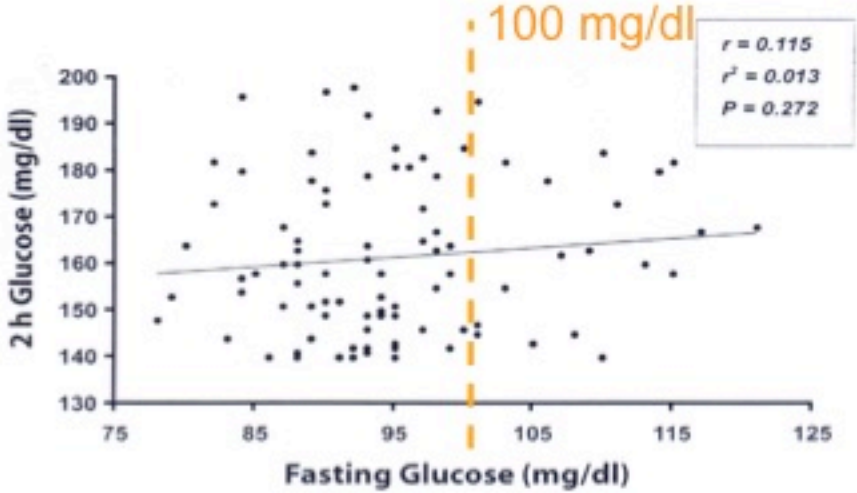
In presenza di fattori di rischio:

- **obesità** (o aumento circonferenza vita)
- **acanthosis nigricans**
- **storia familiare** di diabete tipo 2 o diabete gestazionale
- **forme tipiche** di PCOS

(Hum Reprod & Fertil Steril, Jan 2012)

Fasting glucose is a **poor predictor** of IGT in PCOS



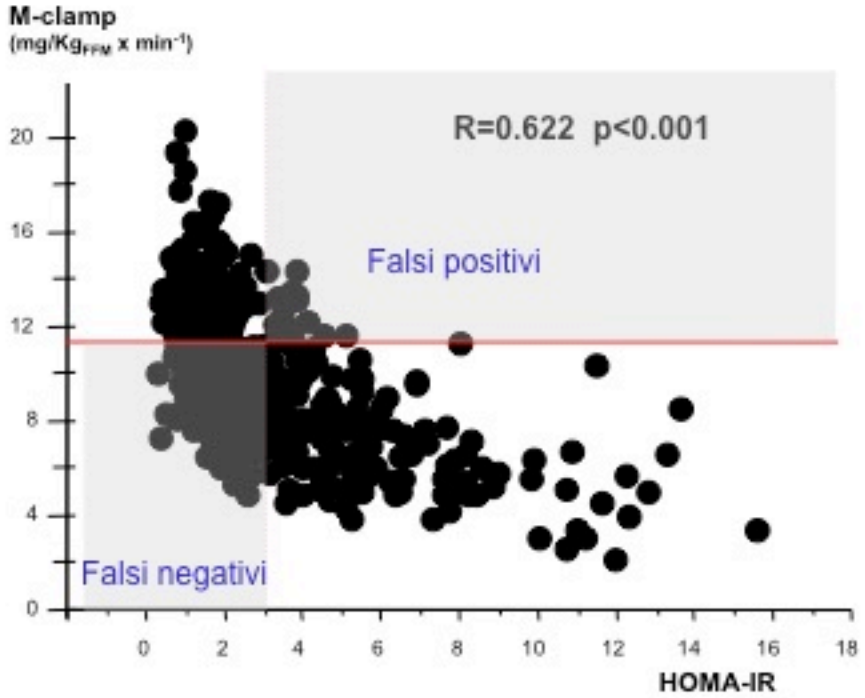


Ehrmann et al, JCEM 2004

Legro et al, JCEM 1999

- **HbA1c is normal in most women with PCOS and IGT (Golland, 1989)**

Indice HOMA nell'identificazione di soggetti insulinoresistenti, definiti da clamp, fra donne con PCOS (n = 375)

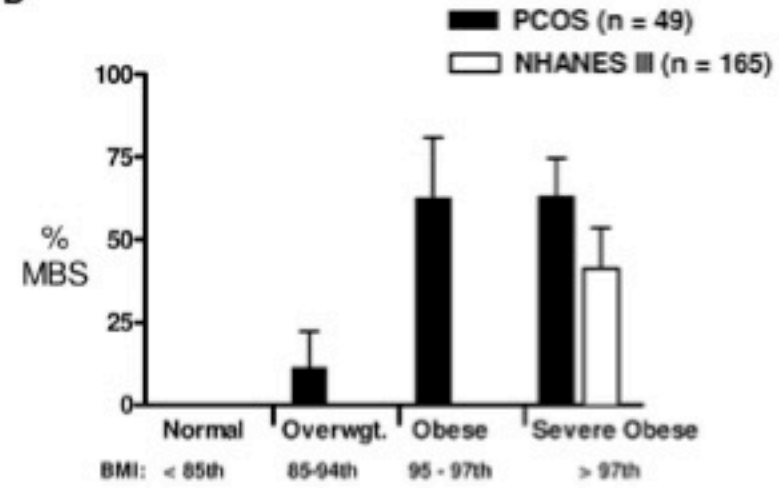


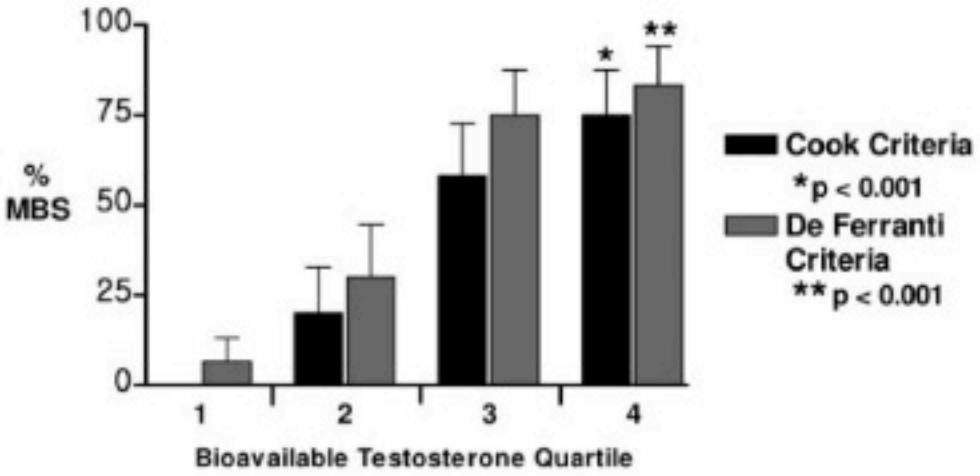
Tosi F et al, Hum Reprod 2017

Adolescent Girls with Polycystic Ovary Syndrome Have an Increased Risk of the Metabolic Syndrome Associated with Increasing Androgen Levels Independent of Obesity and Insulin Resistance

Andrea D. Coviello, Richard S. Legro, and Andrea Dunaif

B





J Clin Endocrinol Metab, February 2006, 91(2):492–497

Terapia?

Recommendations

(1) A timely diagnosis of PCOS in symptomatic adolescent girls is important for the initiation of appropriate screening and treatment (Level A).

(2) Validated diagnostic criteria supported by robust clinical and hormonal findings are needed to avoid overdiagnosis and unnecessary treatment in otherwise healthy normal girls without hyperandrogenism (Level C).

(3) Research evaluating long-term interventions using high-quality RCTs and lifelong follow-up of girls with PCOS diagnosed during adolescence would be ideal (Level C).

RITORNIAMO ALLA NOSTRA LORENZA

Caratteristiche di Lorenza…

- Amenorrea
- Irsutismo/acne
- Sovrappeso e iperinsulinemia

Fenotipo classico con oligo-anovulazione e iperandrogenismo

Lorenza, *che terapia?*

- Estro-progestinico.
- Estro-progestinico + metformina.
- Cambiamento stile di vita + metformina + estro-progestinico.
- Anti-androgeno + metformina.

Irsutismo: terapia farmacologica

I farmaci che hanno **indicazione ufficiale** nella terapia dell'irsutismo sono :

- Estro-progestinici (anche con Ciproterone acetato)
- Cortisonici (solo nel deficit della 21-idrossilasi surrenalica)
- Eflornitina

Gli altri farmaci che potremmo utilizzare (*Spironolattone, Finasteride, Flutamide*) sono **off-label**

Fattori condizionanti la scelta terapeutica

Grado manifestazioni cutanee

Alterazioni mestruali e aspettative di gravidanza

Obesità/IGT/Diabete mellito

Aspetti psicologici

Età, altre patologie e fattori di rischio CV associati

Controindicazioni alla terapia EP

Preferenze, sicurezza e costi

Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

Kathryn A. Martin, R. Jeffrey Chang, David A. Ehrmann, Lourdes Ibanez, Rogerio A. Lobo, Robert L. Rosenfield, Jerry Shapiro, Victor M. Montori, and Brian A. Swiglo

- "For women with patient-important hirsutism despite cosmetic measures, we suggest either pharmacological therapy or direct hair removal methods."

J Clin Endocrinol Metab 2008, 93: 1105–20

Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

Kathryn A. Martin, R. Jeffrey Chang, David A. Ehrmann, Lourdes Ibanez, Rogerio A. Lobo, Robert L. Rosenfield, Jerry Shapiro, Victor M. Montori, and Brian A. Swiglo

- Recommendations: **Oral contraceptive (Ocs) as first line** and against antiandrogen monotherapy because of its potential teratogenic effect, unless adequate contraception (the choice depends on the willing of conceiving).

J Clin Endocrinol Metab 2008, 93: 1105–20

Suggestions against the use of:

- topical antiandrogens
- flutamide
- Insuling-lowering drugs (e.i metformin)
- Glucocorticoid therapy in women without 21OH hyroxylase deficit; conversely it should be used in women with 21-OH hydroxylase deficiency when there is the OCs failure o they cannot tolerate them
- GnRH agonist (with the exception of women with ovarian hyperthecosis)

J Clin Endocrinol Metab 2008 93: 1105–20

- Per ogni tipo di terapia farmacologica per l'irsutismo, viene consigliato un trial di **almeno 6 mesi** prima di eseguire cambiamenti di dosaggio, di farmaci o passare alla terapia combinata.
- Nessun particolare EP rispetto ad un altro viene suggerito nella terapia dell'irsutismo.
- Opportuno non utilizzare composti con dosi elevate di Etinilestradiolo (> 30–35 μg) e contenenti progestinici ad azione androgena (es. levonorgestrel).

J Clin Endocrinol Metab 2008 93: 1105–20

- Orientare la scelta su preparati con progestinici neutri o ad azione anti-androgena (ciproterone acetato, drospirenone, clormadinone).

- Non è raccomandato un particolare farmaco anti-androgeno rispetto ad un altro (tranne la flutamide che non va utilizzata).

J Clin Endocrinol Metab 2008 93: 1105–20

Farmaci anti-androgeni

- **Spironolattone**: antagonista del recettore degli androgeni, debole effetto progestinico; dose 50-200 mg/die. *Effetti collaterali:* iperkaliemia, alterazioni mestruali, tensione mammaria, cefalea, poliuria.

- **Ciproterone acetato**: progestinico con effetto anti-androgeno, dose 25-100 mg/die per 10 gg/mese (es. sequenziale inversa 50 mg dal 1° al 10° con EE 10-30 μg), o 2 mg + EE 35 μg. *Effetti collaterali*: epatotossicità, cefalea, tensione mammaria, edema, alterazione dell'umore.

Farmaci anti-androgeni

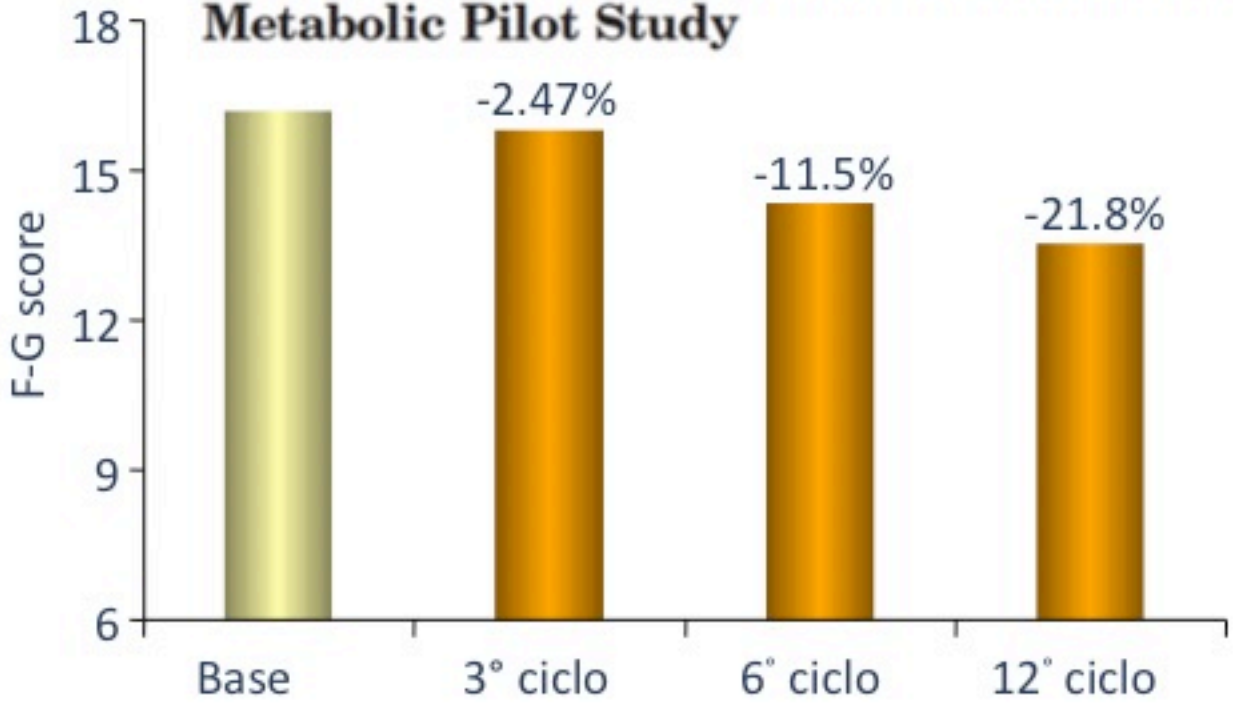
- **Flutamide**: anti-androgeno non-steroideo, dose 62.5-250 mg/die. *Effetti collaterali*: epatotossicità.

- **Finasteride:** inibitore della 5α-reduttasi tipo II, che inibisce la conversione del T in DHT; dose 2.5-5 mg/die. *Effetti collaterali*: disturbi gastrointestinali, profilo di sicurezza ancora poco noto nella donna.

Consenso informato!

EP E IRSUTISMO

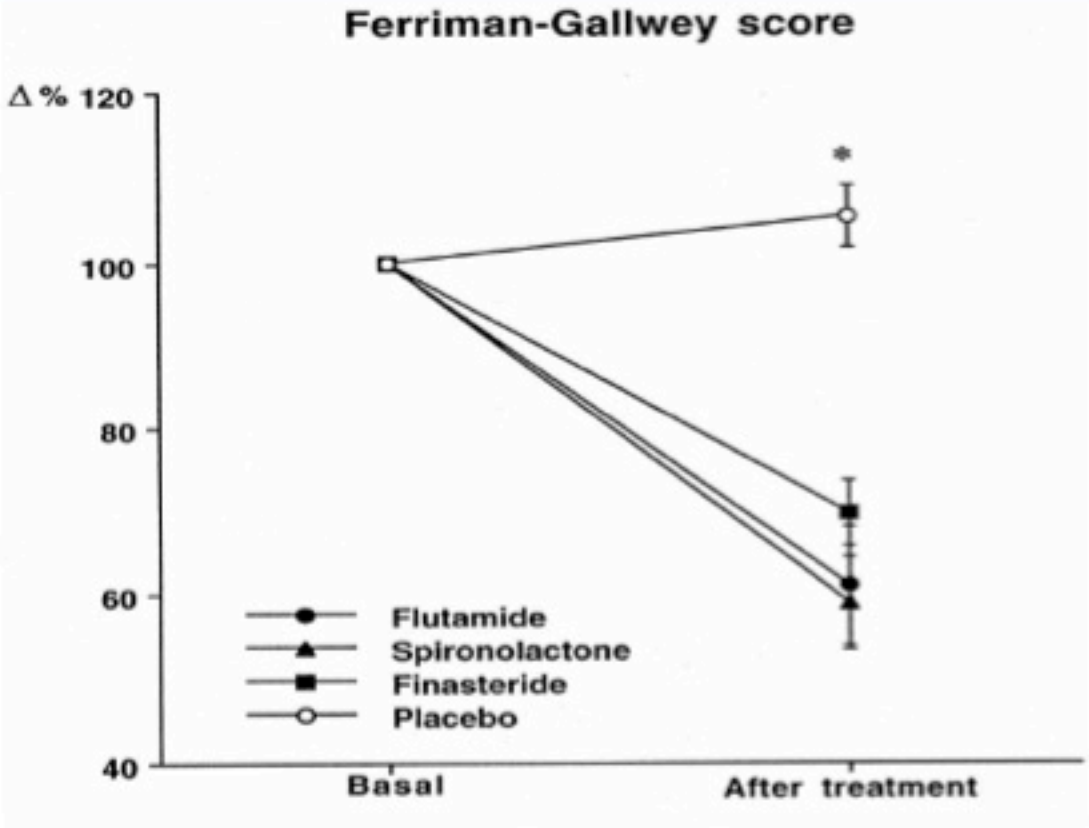
Drospirenone for the Treatment of Hirsute Women with Polycystic Ovary Syndrome: A Clinical, Endocrinological, Metabolic Pilot Study



30 µg EE + 3 mg DRSP
for 12 cycles

JCEM 2004;89:2817-23

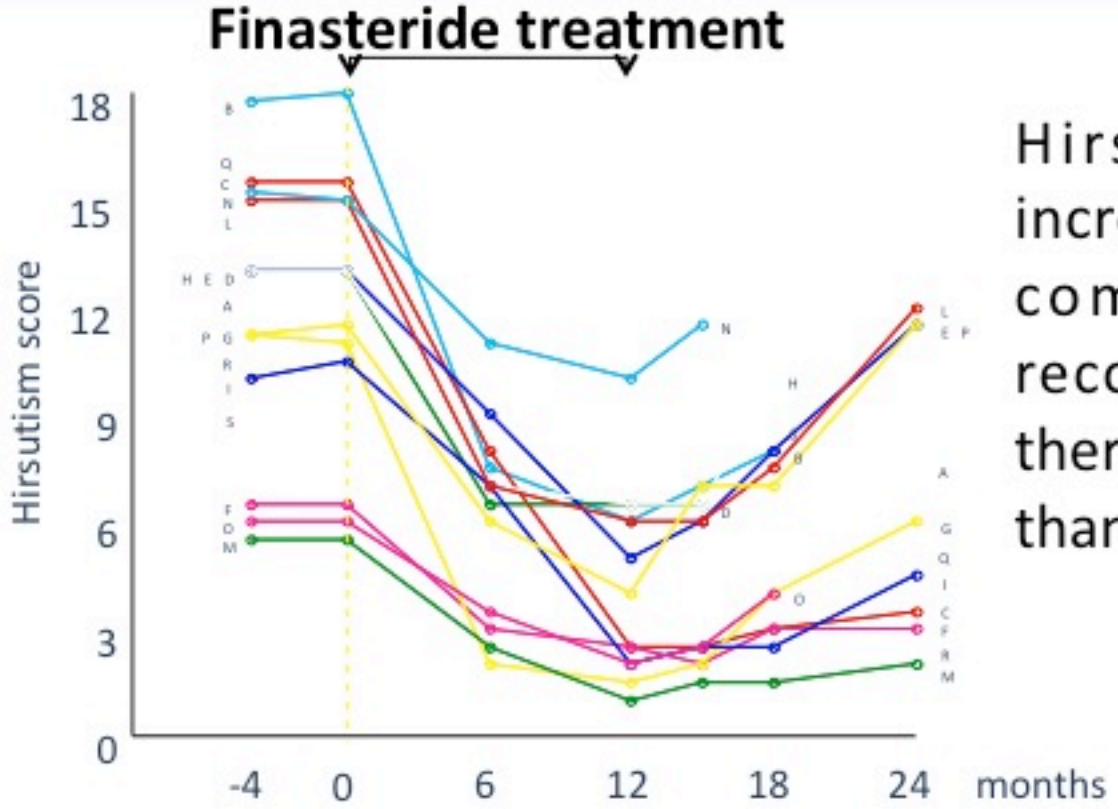
Comparison of Spironolactone, Flutamide and Finasteride Efficacy in the treatment of Hirsutism: a randomized, double blind, placebo-controlled trial



After a 6-month course therapy, the clinical efficacies of these drugs are similar.

Moghetti et Al. JCEM Vol.85, Issue 1, 1 January 2000

Anti-androgeni: dopo la sospensione?



Hirsutism scores were increased substantially as compared with values recorded at the end of therapy, but still were lower than baseline values.

Fertility and Sterility, 1996: 734-40

Iperandrogenismo di origine surrenalica

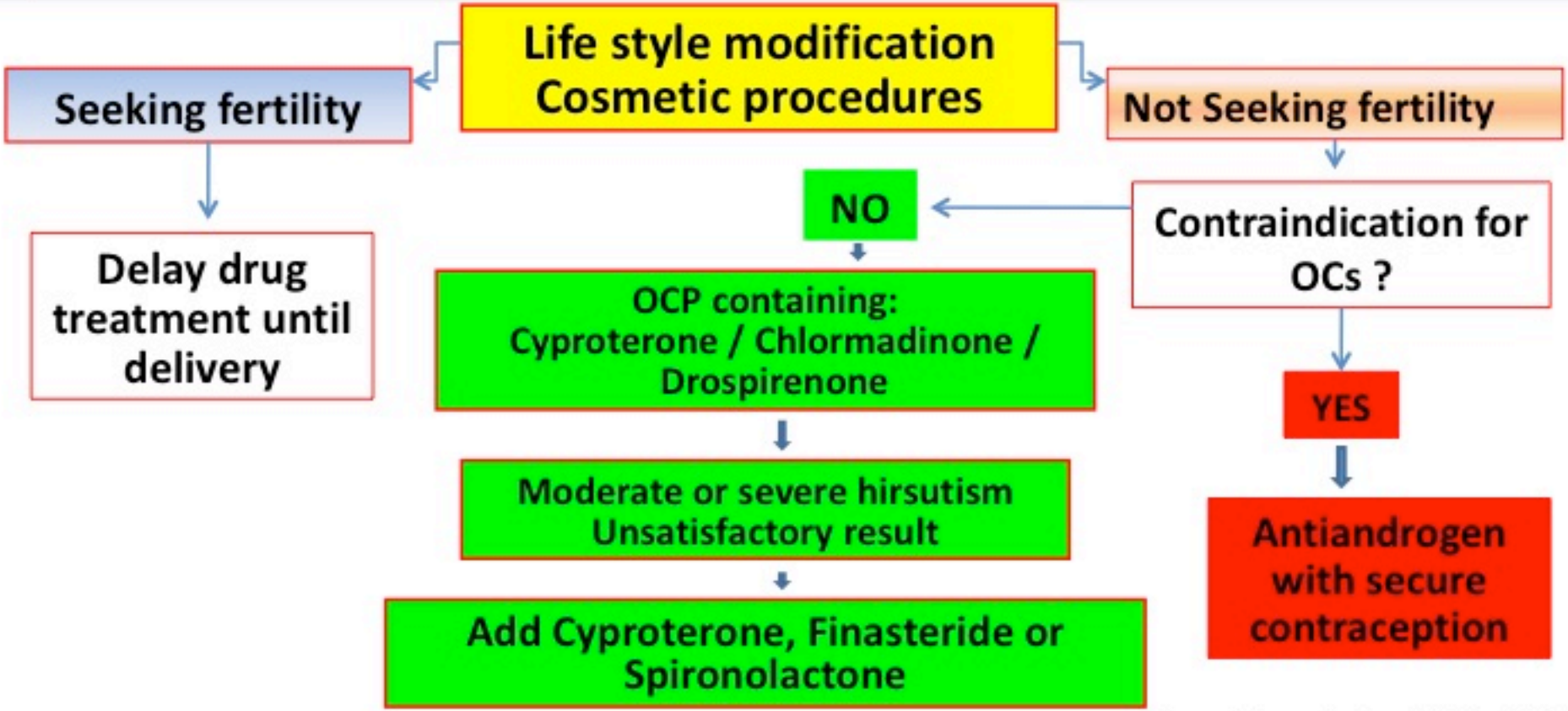
I cortisonici vanno utilizzati nella donne con irsutismo da NCCAH con risposta non ottimale all'estroprogestinico e/o ai farmaci anti-androgeni, non tolleranti tali terapie o per induzione dell'ovulazione.

- Idrocortisone (10-20 mg/m^2 di superficie corporea/die, in tre dosi)
- Prednisone (5 e 7.5 mg/die, in due dosi)
- Desametasone (0.25 e 0.5 mg/die, in una o due dosi).

… e dopo le linee guida Endocrine Society per il trattamento dell'irsutismo pubblicate nel 2008, **ci sono state novità negli ultimi anni ?**

Algorithm for management of hirsutism

(Consensus Statement by the Androgen Excess and PCOS Society)



Human Reproduction Update, 2012

Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

Richard S. Legro, Silva A. Arslanian, David A. Ehrmann, Kathleen M. Hoeger, M. Hassan Murad, Renato Pasquali, Corrine K. Welt

- "We recommend **HCs as first-line management for the menstrual abnormalities and hirsutism/acne of PCOS"** *(refer to hirsutism guidelines 2008).*

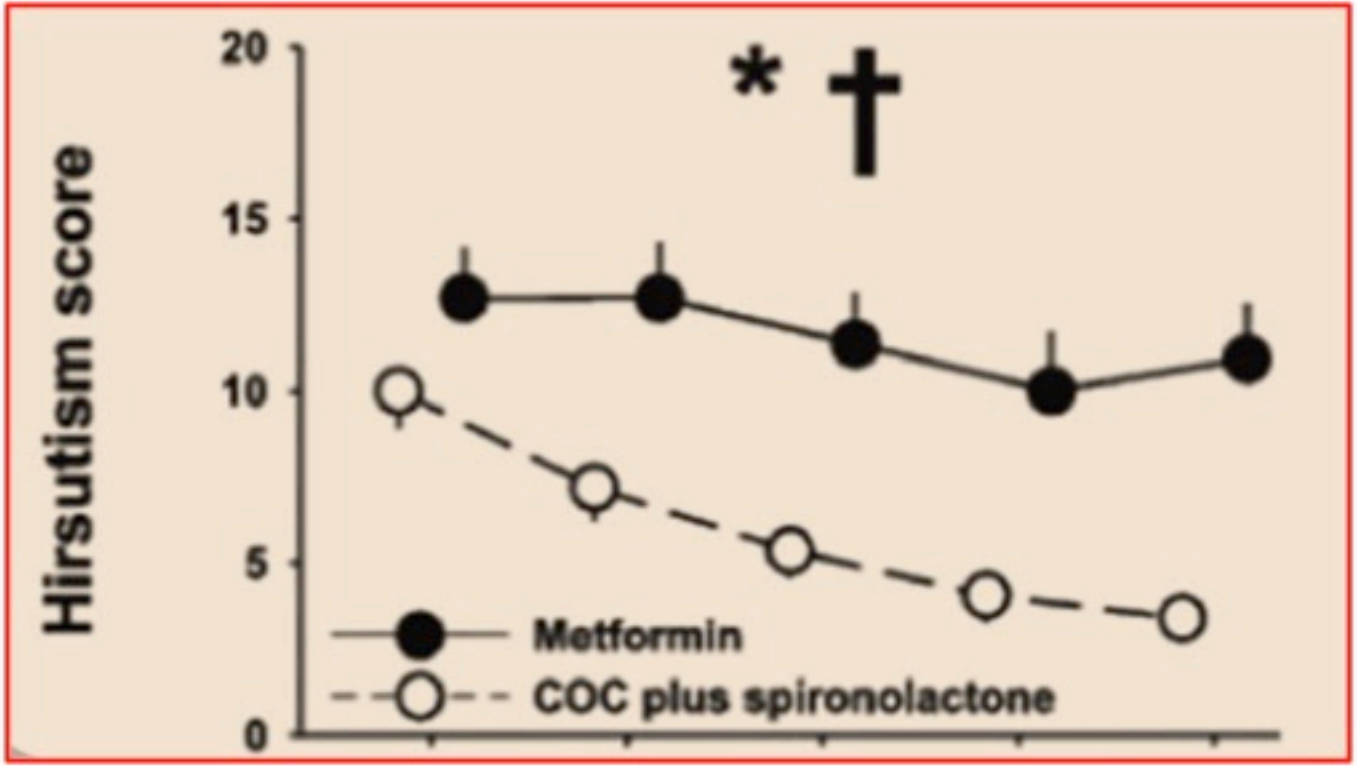
JCEM Vol. 98, Issue 12, 1 December 2013, Pages 4565–4592

Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

Richard S. Legro, Silva A. Arslanian, David A. Ehrmann, Kathleen M. Hoeger, M. Hassan Murad, Renato Pasquali, Corrine K. Welt

- **We suggest against the use of metformin as a first-line treatment of cutaneous manifestations**, for prevention of pregnancy complications, or for the treatment of obesity.
- *We recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification*.

Oral contraceptives + spironolactone vs metformin in obese women with PCOS



Alpanes M, et al. Eur J Endocrinol. 2017 Nov;177(5):399-408

The polycystic ovary syndrome: a position statement from the European Society of Endocrinology

EJE (2014) 171, P1–P29

AACE/ACE Disease State Clinical Review

ENDOCRINE PRACTICE Vol 21 N 11 Nov 2015

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME – PART 1

Neil F. Goodman, MD, FACE[1]; Rhoda H. Cobin, MD, MACE[2]; Walter Futterweit, MD, FACP, FACE[3]; Jennifer S. Glueck, MD[4]; Richard S. Legro, MD, FACOG[5]; Enrico Carmina, MD[6]

EP restano i farmaci di prima scelta per le manifestazioni di iperandrogenismo, eccetto se controindicati

Terapia topica con EFLORNITINA

- Inibitore dell'enzima ornitina-decarbossilasi a livello dei follicoli piliferi.
- Ha indicazione nel trattamento dell'irsutismo facciale.
- La crema (11.5%) si applica due volte al giorno.
- Una riduzione della crescita pilifera si può osservare dopo le prime 6-8 settimane di trattamento.
- Scarso assorbimento sistemico (< 1%).
- Ripresa crescita pilifera dopo sospensione (8 settimane).

Esistono terapie particolari per le adolescenti?

- Non ci sono studi randomizzati, controllati verso placebo, di durata adeguata
- Per la terapia ci si basa sulle linee guida e gli studi eseguiti in donne adulte
- La prima linea di trattamento è l'intervento sullo stile di vita, seguito dalla terapia EP
- Non è definita la durata ottimale della terapia EP

JCEM Vol. 98, Issue 12, 1 December 2013, Pages 4565–4592

RITORNIAMO ALLA NOSTRA LORENZA

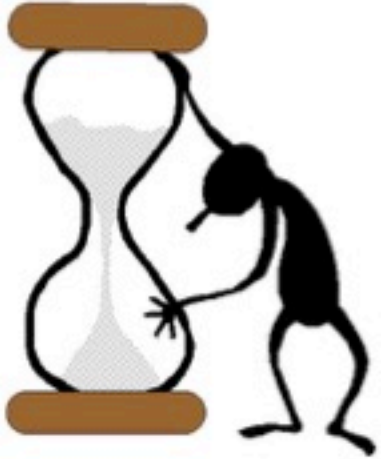
Terapia

Veniva prescritta dieta ipocalorica ed attività fisica aerobica (camminata 45’ 4 volte a settimana)

Metformina 500 mg, 1 cp ai tre pasti

Estroprogestinico contenente Drospirenone

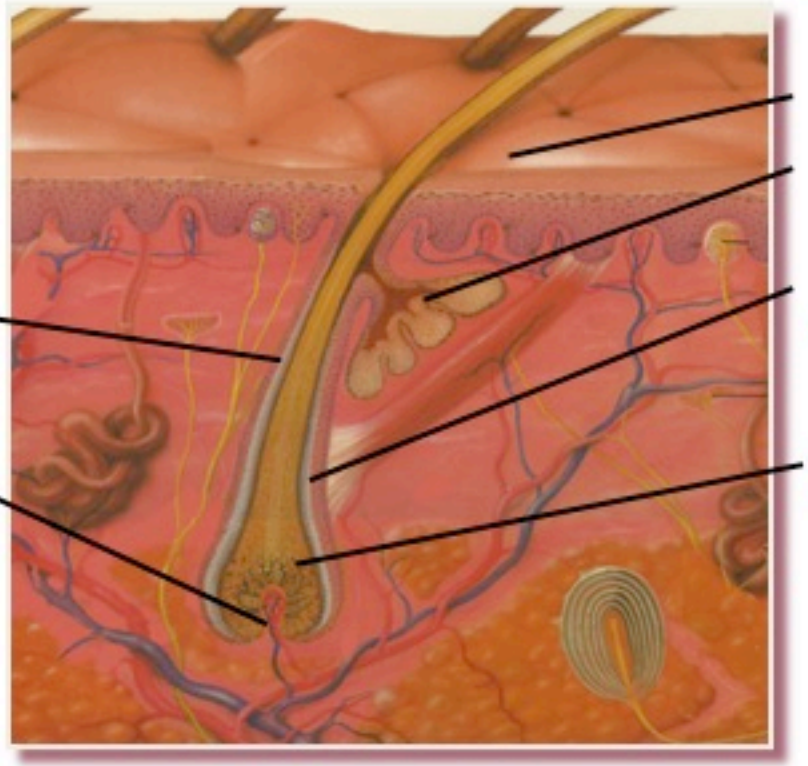
- ✓ Rivalutata a distanza di 2 mesi (fine Settembre):
  - ✓ Riduzione del peso di circa 5 kg: BMI 27,8 kg/m^2
  - ✓ Segue le indicazioni dietetiche e l'attività fisica



- ✓ Le è stato consigliato inoltre di eseguire trattamento cosmetico: epilazione laser

- ✓ Successiva rivalutazione clinica dopo 6 mesi di terapia

Hair Anatomy

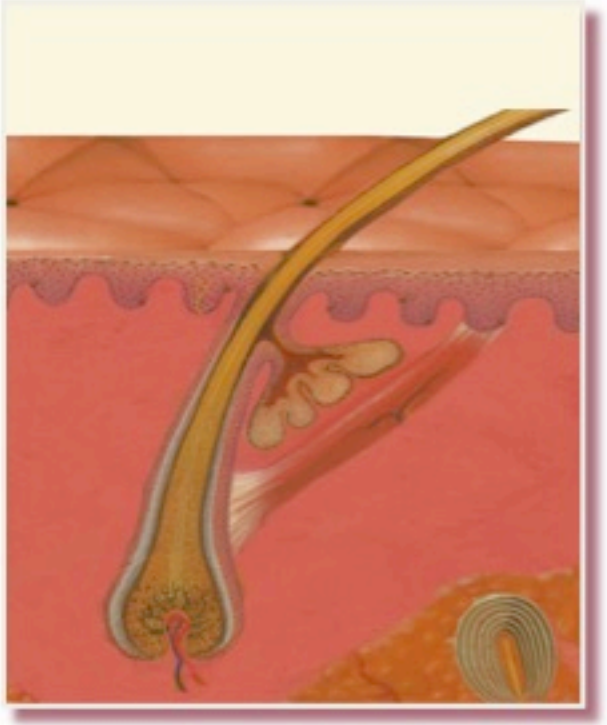


- Bulb / bulge are critical structures responsible for hair regrowth

Biologia del capello

- I follicoli sono più vulnerabili nella fase precoce dell'anagen (early anagen)
- I follicoli nella fase catagen possono sopravvivere
- Per area saranno necessari trattamenti multipli

Anagen



Sistemi depilatori

- Shaving
- Epilazione:
  - meccanica (cera, pinzetta)
  - chimica
- Farmacologica: terapia ormonale sistemica, terapia topica (eflornithine)
- Electrolysis

- Laser-assisted hair removal

Indicazioni

- Irsutismo
  - Patologie endocrine/farmaci
- Ipertricosi
  - genetica/etnica
  - normale/anormale distribuzione
- Post Surgery
  - Lembi di avanzamento e trasposizione
  - Cambio di sesso
- Cosmetica/Estetica

LASER/IPL EPILATION
Selective Photothermolysis

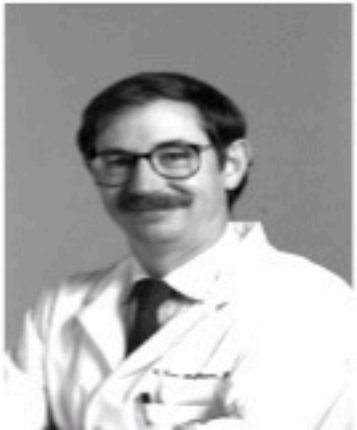
- Laser assisted hair removal is obtained by a process of selective heating of hair follicle irradiated through the epidermis
- The Laser effect is based on the principle of Selective Photothermolysis that, using specifics wavelengths, allows to destroy / damage selectively a target with minimal or any side effects on the surrounding tissues
- The target is the eumelanin of Hair Follicles concentrated at the level of the bulge and bulb

- Dark hair responds to Laser-Treatment much better than light hair

Marchell NL, Alster TS. Evaluation of hair removal methods. Aesthetic Dermatology and Cosmetic Surgery 1999; 1: 3-12.

Fototermolisi selettiva

"The matching of a specific wavelength and pulse duration to obtain optimal effect on a targeted tissue with minimal effect to surrounding tissue."

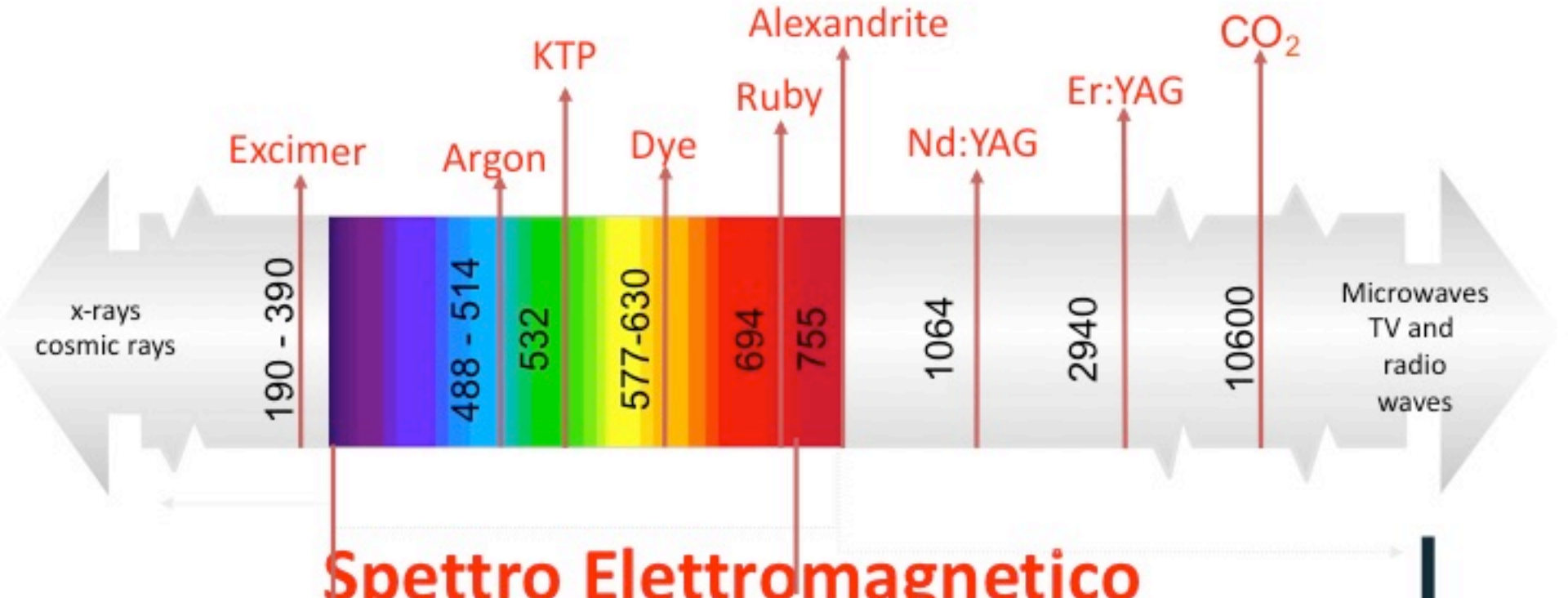


Anderson & Parrish, Science, 1983

DESCRIVE UN DANNO TISSUTALE TERMICO DI TARGET MICROSCOPICI
"PRINCIPALMENTE PIGMENTARI "
OTTENUTO TRAMITE IMPULSI ASSORBITI IN MODO SELETTIVO DAI CROMOFORI CORRISPONDENTI

RAPPRESENTA L'IMPIEGO PIU' SELETTIVO DELL' ENERGIA RAGGIUNTO FINORA NELL' INTERAZIONE LUCE TESSUTO

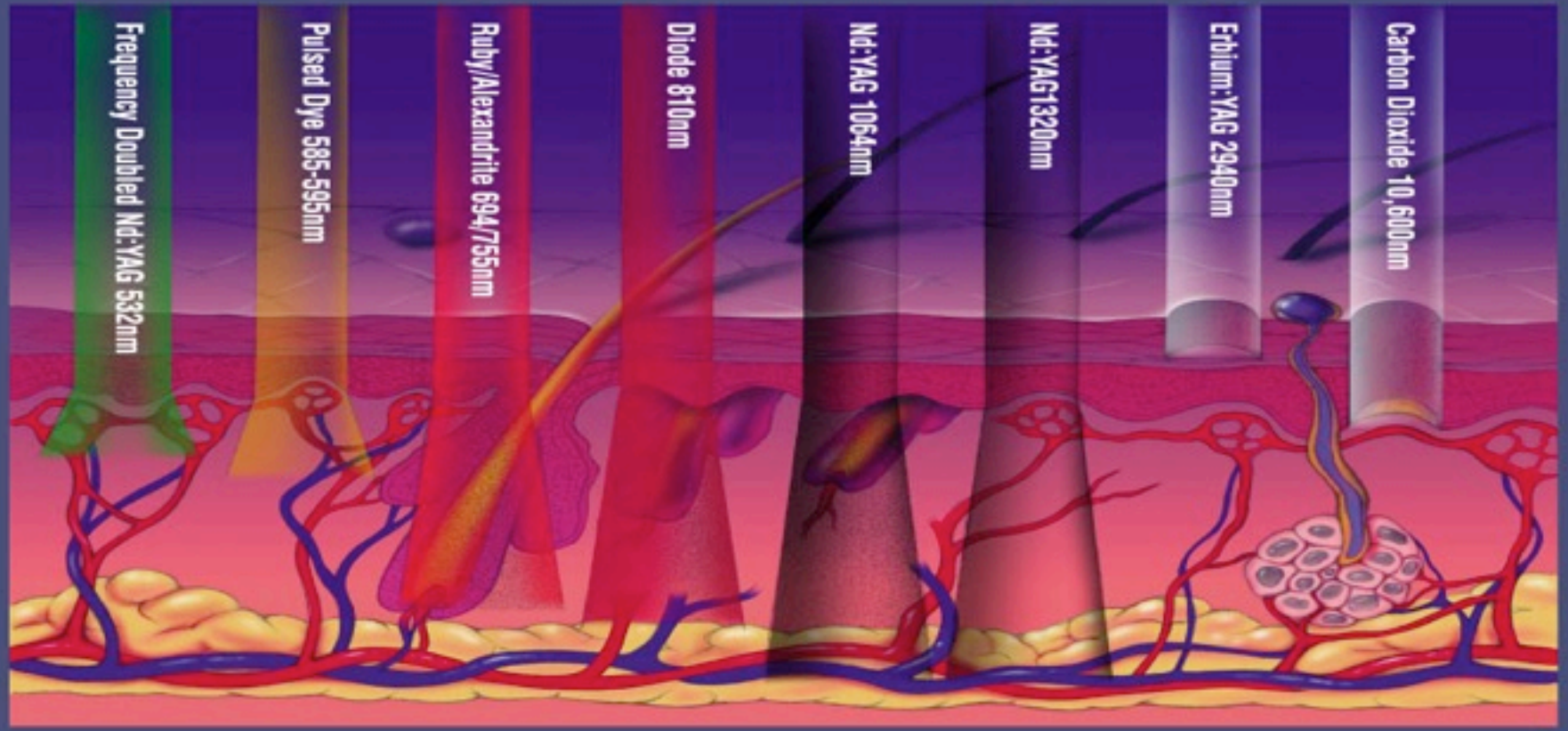
LA LUCE DEPOSITA L'ENERGIA **SOLO** NEI LUOGHI DI ASSORBIMENTO
IL CALORE VIENE SVILUPPATO DA LUNGHEZZE D'ONDA CHE
SELETTIVAMENTE
VENGONO ASSORBITE DA STRUTTURE CHE CONTENGONO
PIGMENTO MELANICO ED EMOGLOBINA O OSSIEMOGLOBINA
IL CALORE INIZIA A DISPERDERSI A CAUSA DELLA CONDUZIONE E DEL TRASFERIMENTO TERMICO
PER CUI IL GRADO DI SURRISCALDAMENTO E' DATO DALLA COMPETIZIONE FRA
RISCALDAMENTO ATTIVO E RAFFREDDAMENTO PASSIVO



Spettro Elettromagnetico

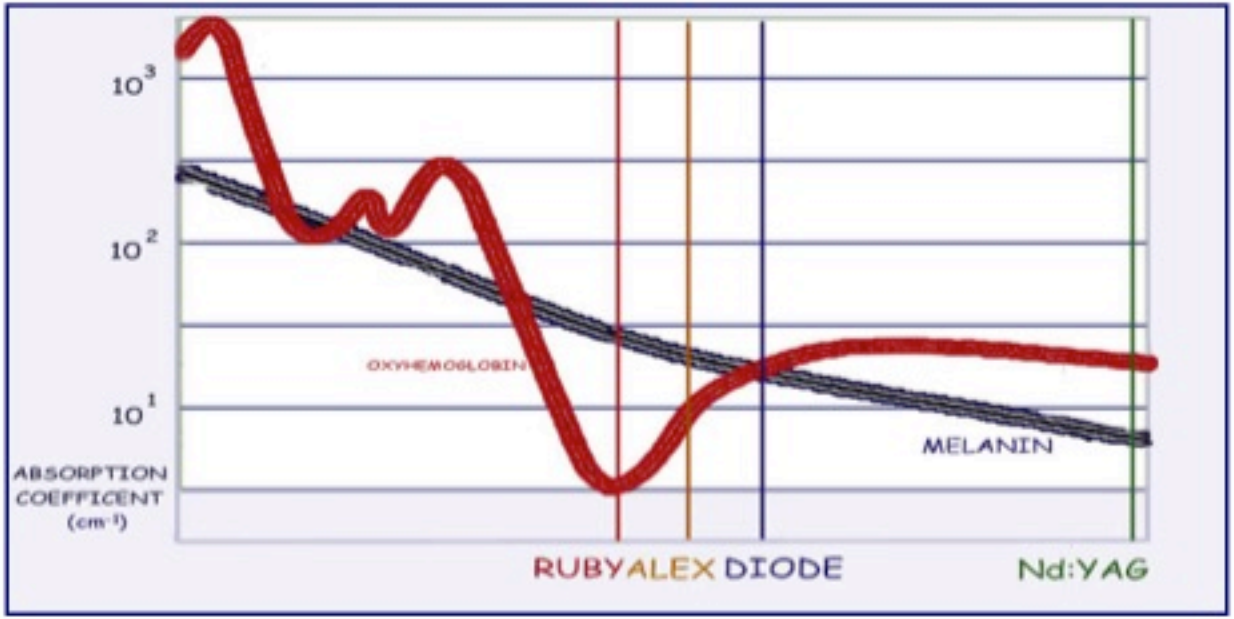
in nanometri

Energy Penetration and Clinical Effect of Commonly-Used Cutaneous Lasers



Laser Parameters: Wavelength

Melanin and oxyhemoglobin absorption coefficient



The figure shows the (indicative) pattern of the absorption coefficient of melanin and haemoglobin depending on the wavelength; in particular the picture highlights the differences in the behaviour of the four most commonly marketed lasers used for epilation:

- Ruby
- Alexandrite
- Diode
- Nd:YAG

FOTOTERMOLISI SELETTIVA
PARAMETRI LEGATI ALLO STRUMENTO

LUNGHEZZA D'ONDA

DURATA E CARATTERISTICHE DELL'IMPULSO

CARATTERISTICHE DELLO SPOT

POTENZA DELLO STRUMENTO

SISTEMI DI RAFFREDDAMENTO

Table of Hair Growth Cycle

Site	%		Duration	Depth	
	TELOGEN	ANAGEN	TELOGEN	ANAGEN	(ANAGEN)
CHEEK	30-50	50-70	10 weeks	1 year	2-4 mm
CHIN	20	70	10 weeks	1 year	2-4 mm
UPPER LIP	35	65	6 weeks	10 weeks	1-2.5 mm
PUBIS	70	30	3 months	4 months	3.5-5 mm
ARM	80	20	18 weeks	13 weeks	2-4.5 mm
LEG	80	20	24 weeks	16 weeks	2.5-4 mm

Laser Epilation

- RUBY Laser
- ALEXANDRITE Laser
- DIODE Laser
- Nd:YAG Laser
- I. P. L.

RUBY LASER:

- Wavelength of 694 nm
- First Laser used
- It does **not** reach the same depth of other Lasers
- Good absorption by Melanin
  (perhaps too much !!!!!)
- Not useful in dark phototypes
- Good results, but it is necessary to pay a lot of attention and caution in dark phototypes and tanned patients

Alexandrite Laser:

Wavelength

- 755 nm (high depth of penetration)
- strongly absorbed by melanin within the hair follicle

Pulse duration

- 3 msec – 40 msec
- localized heating of follicle
- not to exceed TRT limit

Spot Size

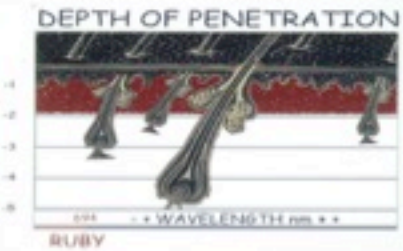
- Up to 18 mm and repetition rate up to 2 Hz
  (Tx are fast: very useful for treating large areas)

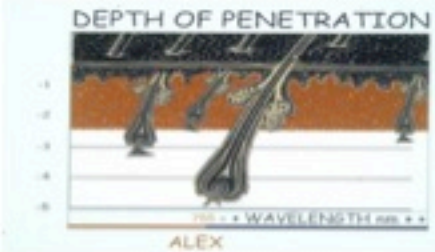
Diode Laser:

- Wavelength of 800 nm
- Similar performances to Alexandrite Laser……

Nd:YAG LASER:

- Wavelength of 1064 nm
- Less absorption by the MELANIN
- Useful for treating dark phototypes and tanned patients
- Poor photoselectivity, than used with higher fluorescences than other systems (Cooling Devices associated are very important)
- This wavelength reaches the biggest depth.

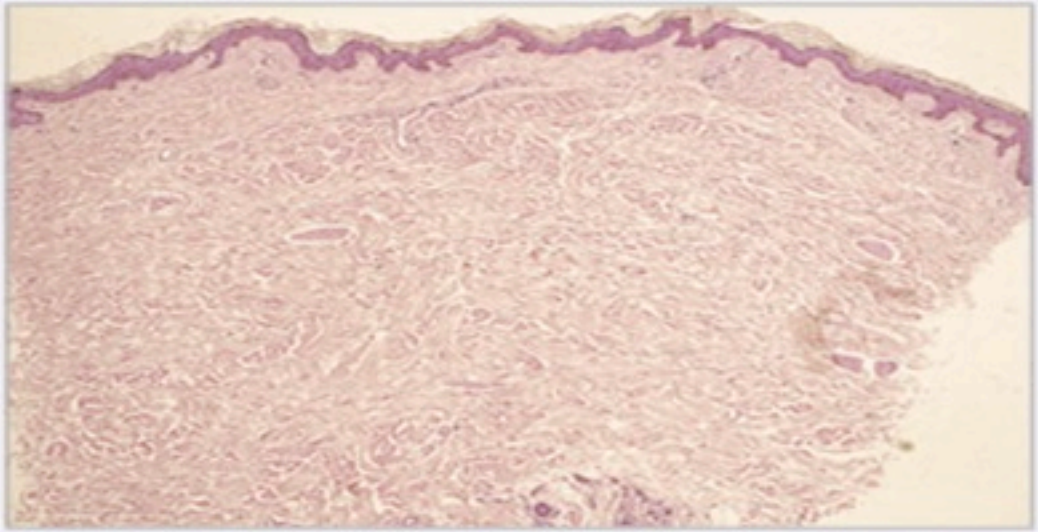




Nuove tecnologie

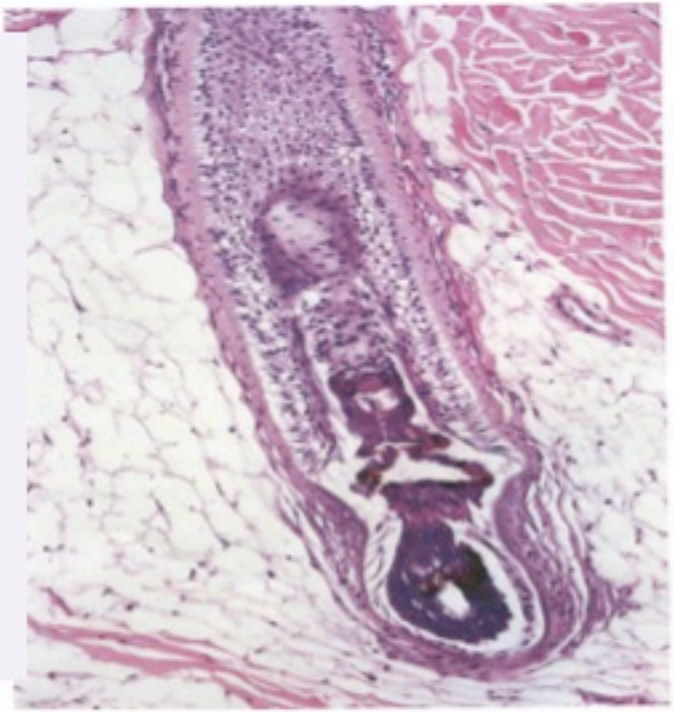
Strumentazioni a flusso misto che consentono una performance maggiore, con minori effetti collaterali ed un numero minore di sedute

Bencini PL, Luci A, Galimberti M, et al. Long-term epilation with long-pulsed neodimium:YAG laser. Dermatol Surg 1999; 25(3):175-78.



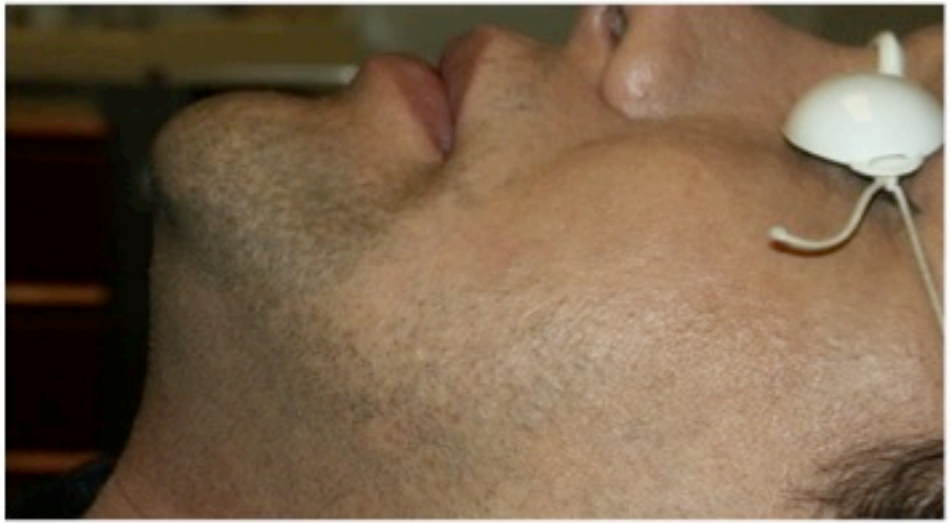
3 months afterTx:

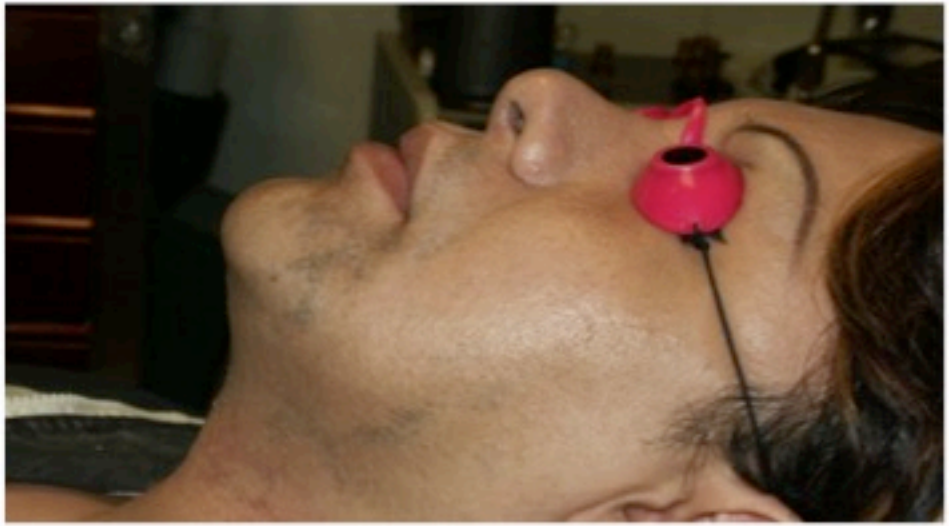
fibrosis replaces hair follicles



immediately after Tx:

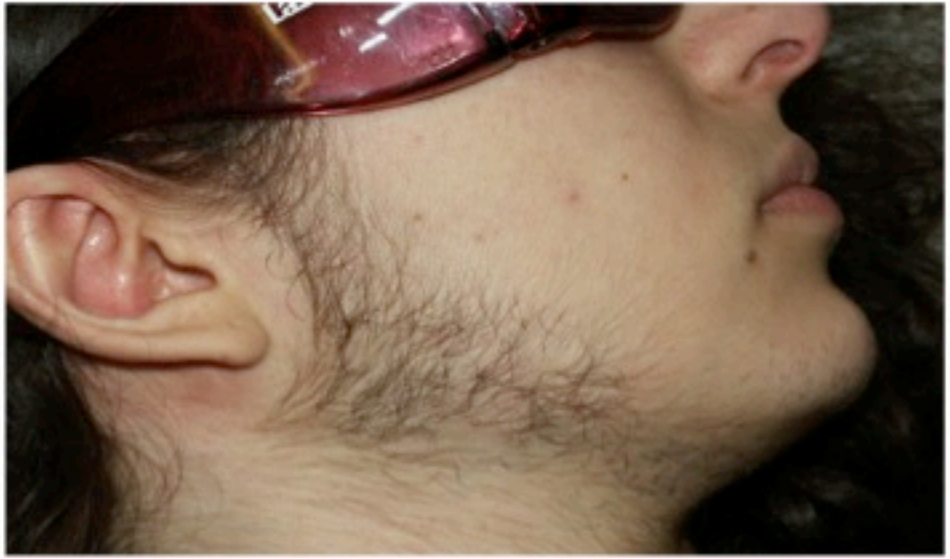
necrosis of hair follicle

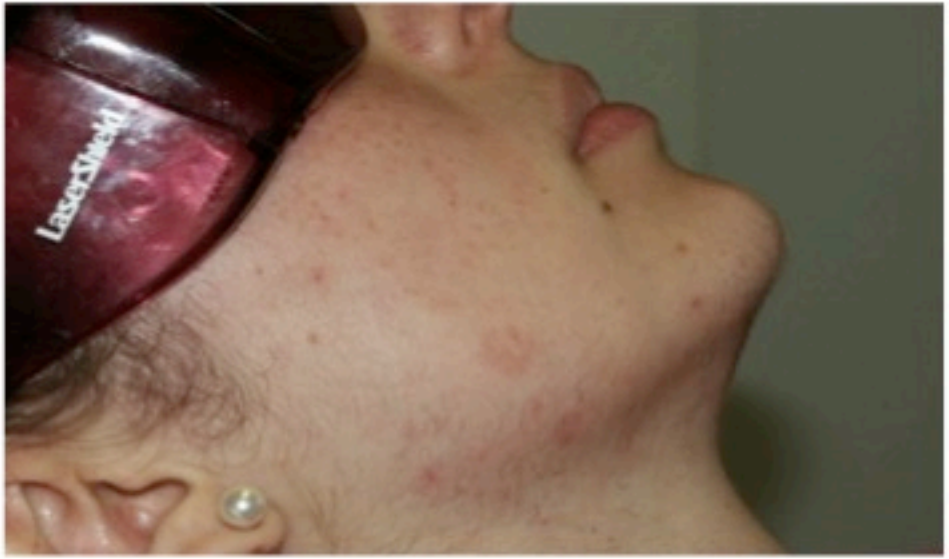




6 weeks after 1° Tx using
Nd:YAG Laser 1064 nm:
24 j, 3 msec, Diam 15,Hz 1, DCD 50/20, P.C. 135

2 years after 5° tx





Laser + Eflornithine 11.5%: Smith SR et al.

Eflornithine Cream combined with Laser Therapy in the management of unwanted facial hair growth in women: a randomized trial

Dermatol Surg 2006, 32: 1237 - 1243

34-weeks, randomized, placebo-controlled Double blind study

RESULTS:

- 42 women completed the trial. From week 6 to week 22, eflornithine treated sides showed significant reduction in hair growth

CONCLUSION:

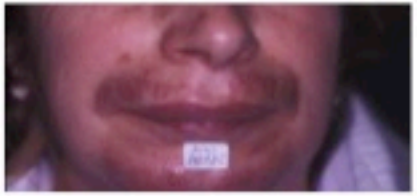
- Eflornithine was well tollerated in conjunction with Laser (safety profile for combination therapy was similar to E. alone) and…..
- Promotes more rapid hair removal when combined with Laser
- Patients demonstrate a clear preference for treatment with Laser and eflornithine

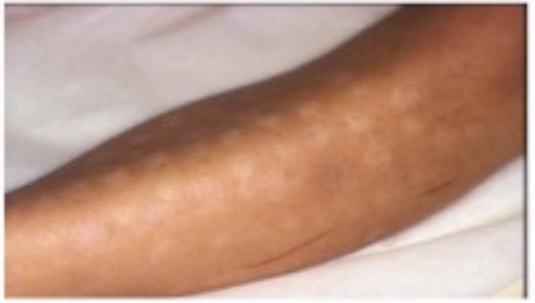
effetti immediati e complicanze

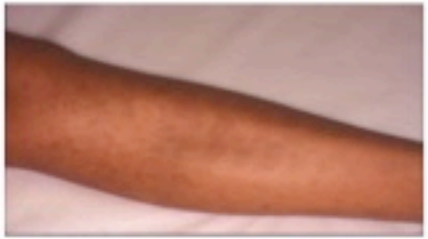
Importante reazione infiammatoria
in zone ad alta densità follicolare e/o
con bulbi grossi
(> upper lip and chin)

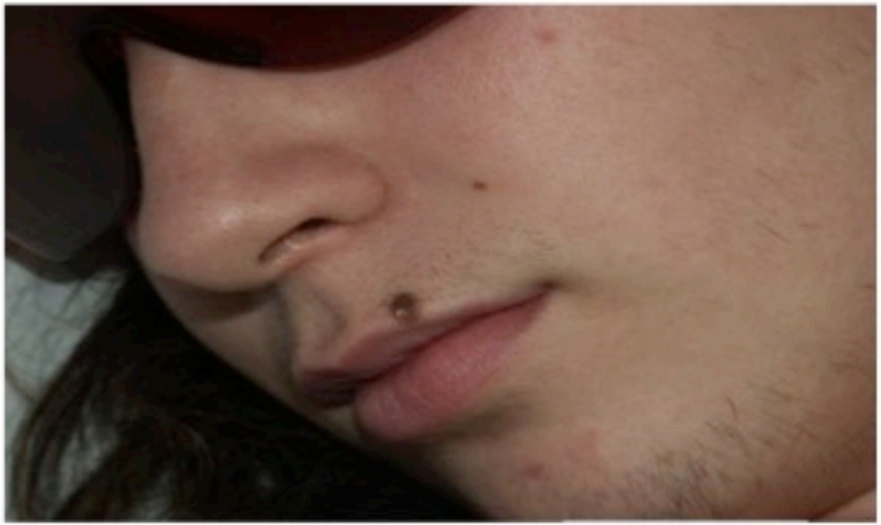
Follicoliti da Pseudomonas

IPOPIGMENTAZIONE
IPERPIGMENTAZIONE

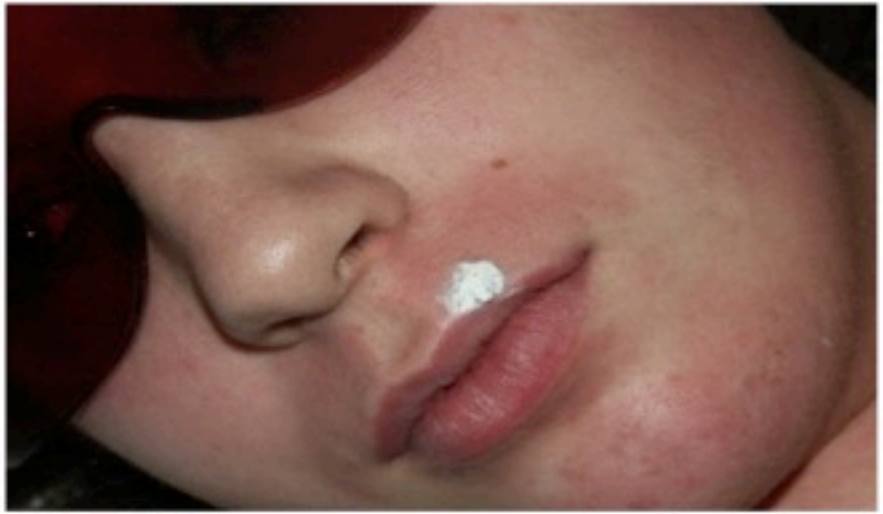


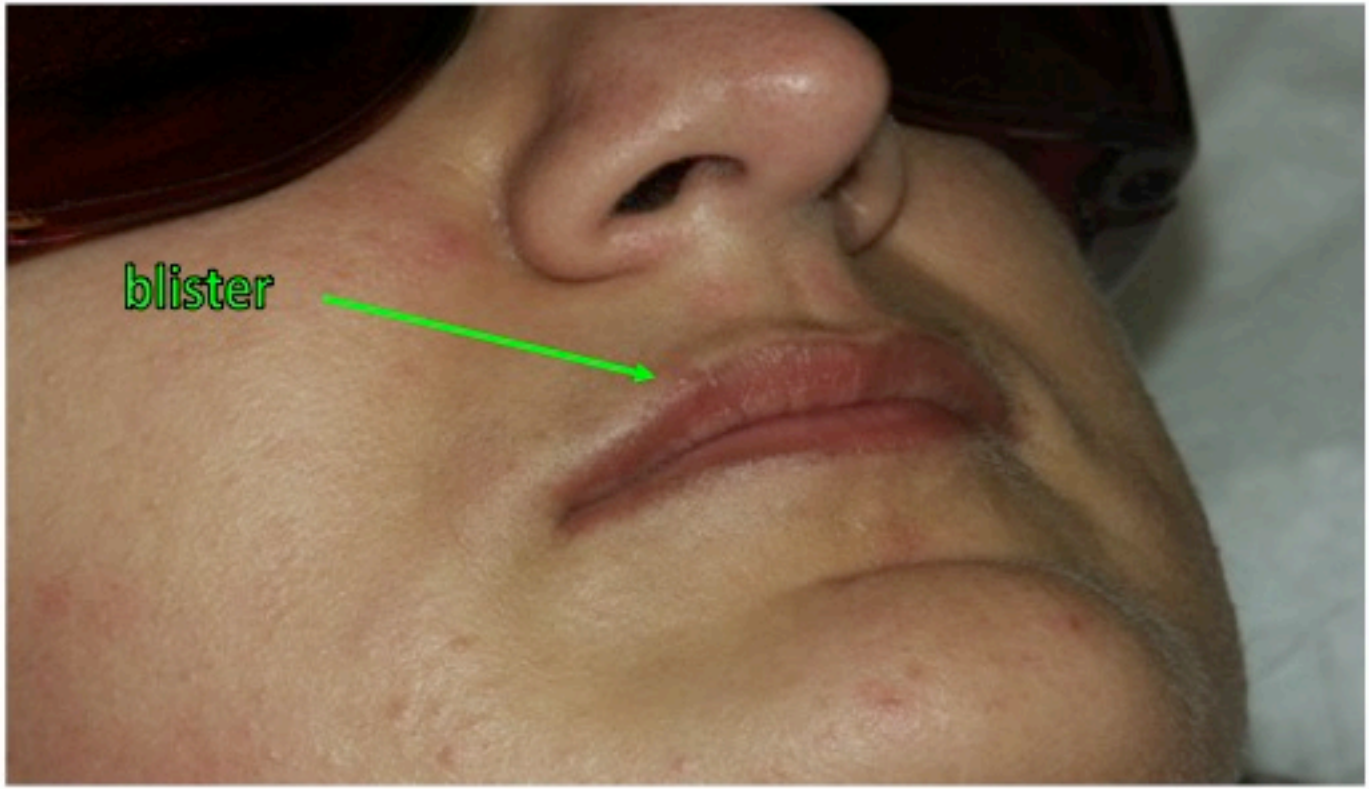


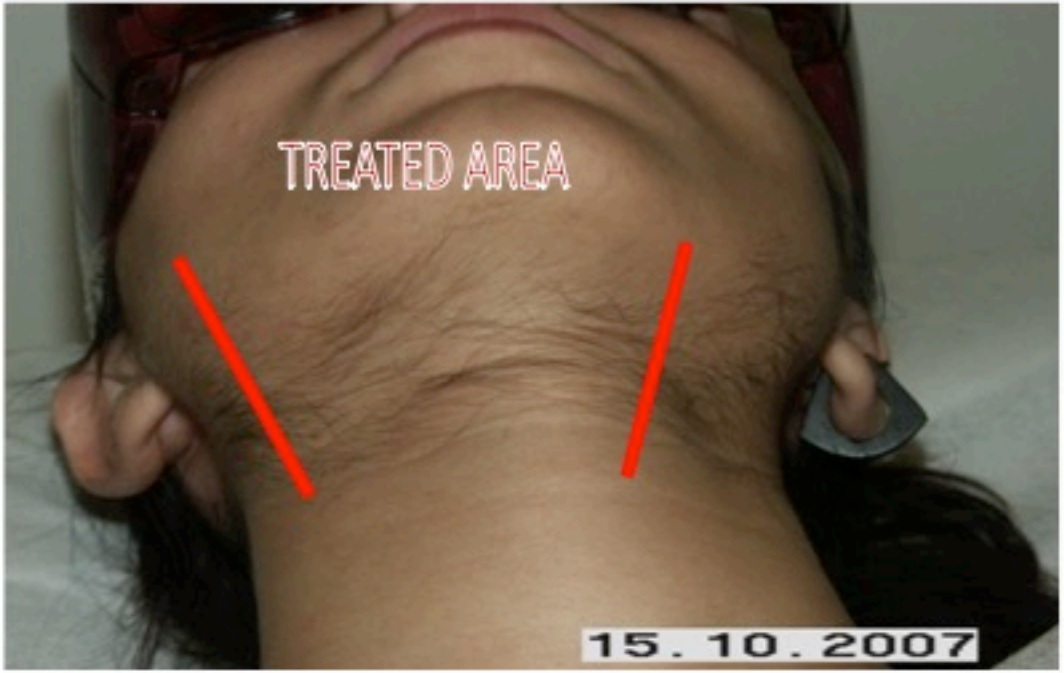




immediately after Laser Tx – Alex L.P.




blister



PARADOXICAL INCREASED HAIR GROWTH

" Laser-induced " thermic stimulation of thin hair or near treated sites

I found eflornithine very helpful to impede this SIDE EFFECT

Randomised Controlled Trial of Laser Tx in Women with PCOS

Clayton W, Lipton M, Elford J et Al.

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

Br J Dermatol 2005; 152: 986–92

- Objective: to evaluate the impact of Laser Tx on the severity of facial hirsutism and on psychological morbidity
- 88 women with hirsutism due to PCOS
- Found that Laser Tx reduced:
  - self-reported severity of facial hair
  - mean depression scores
  - mean anxiety rating
- Significantly greater amount in the treatment group vs controls over the 6-month study period.

Take home message

- Essere molto chiari ed esaustivi nelle spiegazioni al paziente, specificando il numero medio di sedute da effettuare;
- Sottoporre un consenso informato con le precauzioni da prendere prima del trattamento;
- Fare un test con basse fluenze;
- Essere cauti nel trattamento dei fototipi scuri e di pelli abbronzate peraltro oggi possibili con i laser a flusso misto;

- Chiedere sempre, laddove necessario, una consulenza **Endocrinologica**