



**VALDAGNO, 11/04/2014**  
**PALAZZO FESTARI**

**OSTETRICIA e GINECOLOGIA**  
**2014**

ULSS5 OVEST VICENTINO  
U.O.C. **OSTETRICIA** E **GINECOLOGIA** VALDAGNO

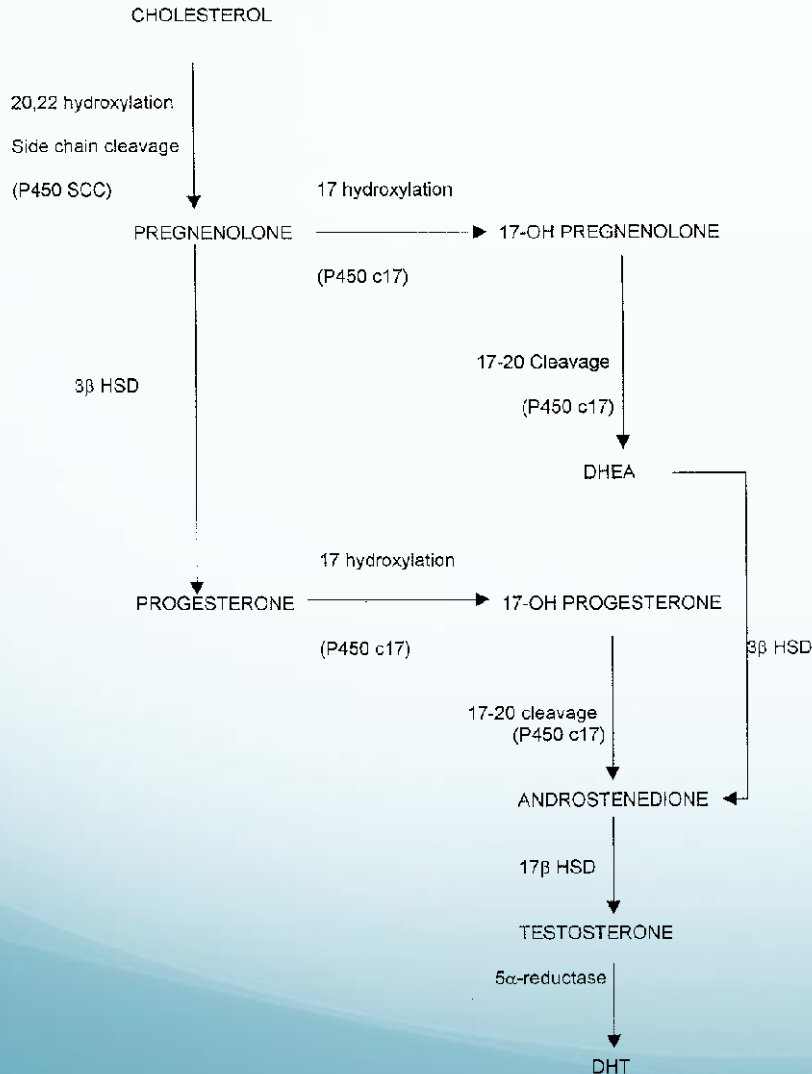
***Approccio***

***contraccettivo***

***nell'iperandrogenismo***



# Iperandrogenismo



**Influenzano il comportamento e l'umore**

[Weiner CL. Psychosom Med 2004;66:356–62.](#)

**Modificano la composizione corporea**

[Rebuffe-Scrive. Horm Metab Res 1989;21: 391–7.](#)

[Lindstedt G. Diabetes 1991;40:123–8.](#)

**Alterano il metabolismo glicidico**

[DeFronzo RA. Diabetes Care 1991;14:173–94.](#)

# **Iperandrogenismo**

**Irregolarità mestruali**

**Acne**

**Irsutismo**

**Seborrea**

**Adiposità androgenica**

# Irsutismo

A livello dell'unità pilo-sebacea è presente l'enzima 5- $\alpha$ -reduttasi di tipo 1 e 2 che converte DHEA e testosterone in forme attive come DHT

L'eccesso di DHT agisce attivando fattori come IGF-1 che hanno un effetto mitogeno sui follicoli piliferi e prolunga la fase anagen

Randall VA. Lippincott-Raven Publishers, 1997

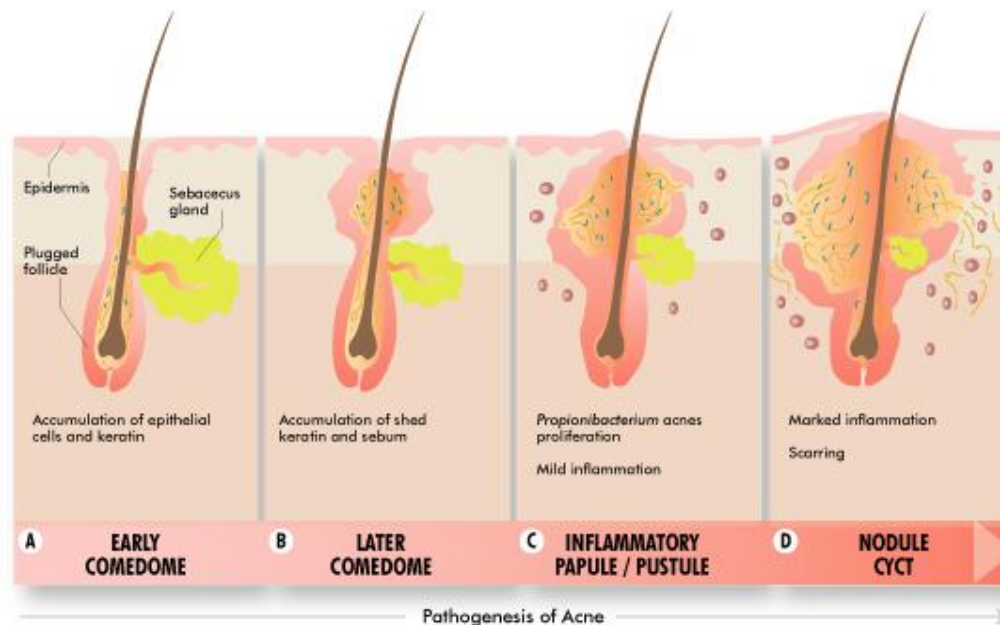
**Table 2.** Distribution of terminal hair under endocrine conditions.

Endocrine condition	Type of terminal hair					
	Eyelash	Scalp	Axial	Pubic	Abdominal/ chest	Facial
Normal child	+	+	-	-	-	-
Adult female androgens	+	+	+	+	-	-
Excess female androgens	+	+	+	+	±	±
Adult male androgens	+	+	+	+	+	+
5 $\alpha$ -Reductase II deficiency	+	+	+	+	-	-
Androgen receptor deficiency	+	+	-	-	-	-

# Acne - Seborrea

L'eccesso di DHT stimola la produzione di sebo a livello dell'unità pilosebacea

Si forma il comedone chiuso che colonizzato dai batteri permette la formazione di lesioni infiammatorie



# Alopecia

## Scala di Ludwig

Sistema di Classificazione della Calvizie Femminile

I-1



I-2



I-3



I-4



II-1



II-2



III



Advanced



Frontal



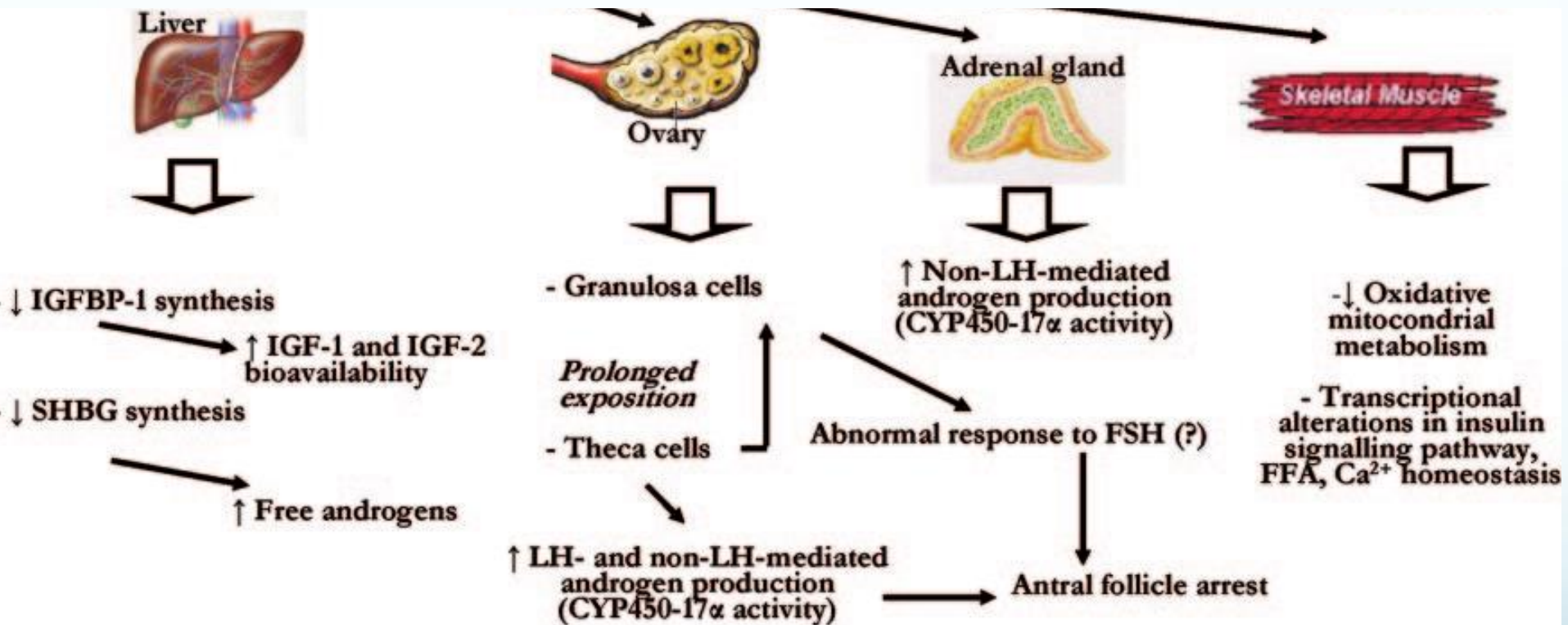
**La fase anagen è più breve e la fase telogen più lunga**

**Continuo e diffuso assottigliamento dei capelli a partire dalla loro punta**

**Elevati livelli di 3-alfa-androstenedione solfato e androsterone solfato**

**Alterato meccanismo di solfatazione degli androgeni nelle iperandrogeniche con alopecia**

# Irregolarità mestruali



# Quale terapia?

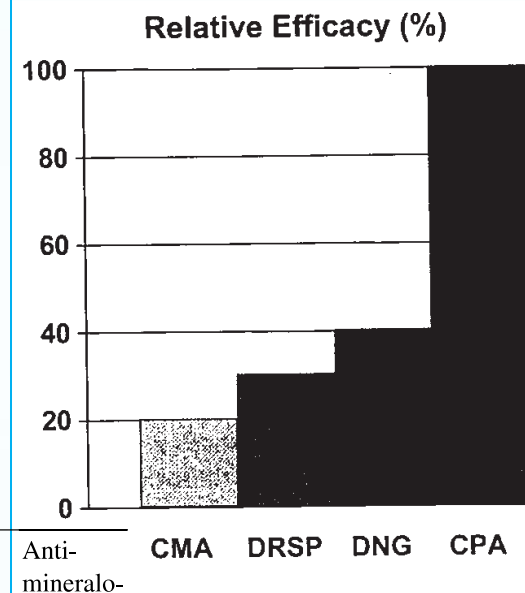
**Desiderio di gravidanza?**



# Quale contraccettivo?



# Quale progestinico?



Biological activities of natural progesterone and synthetic progestins

Progestin	Progesterogenic	Anti-gonadotropic	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone	+	+	+	-	-	±	+	+
Dydrogesterone	+	-	+	-	-	±	-	±
Medrogestone	+	+	+	-	-	±	-	-
17α-Hydroxy-derivatives								
Chlormadinone acetate	+	+	+	-	-	+	+	-
Cyproterone acetate	+	+	+	-	-	+++	+	-
Megestrol acetate	+	+	+	-	±	+	+	-
Medroxy-progesterone-acetate	+	+	+	-	±	-	+	-
19-Nor-progesterone-derivatives								
Nomegestrol acetate	+	+	+	-	-	±	-	-
Promegetstone	+	+	+	-	-	-	-	-
Trimegestone	+	+	+	-	-	±	-	±
Spirolactone-derivatives								
Drospirenone	+	+	+	-	-	+	-	+
19-Nortestosterone derivatives								
Norethisterone	+	+	+	+	+	-	-	-
Lynestrenol	+	+	+	+	+	-	-	-
Norethinodrel	±	+	±	+	±	-	-	-
Levonorgestrel	+	+	+	-	+	-	-	-
Norgestimate	+	+	+	-	+	-	-	-
3-Keto-desogestrel	+	+	+	-	+	-	-	-
Gestoden	+	+	+	-	+	-	+	+
Dienogest	+	+	±	±	-	+	-	-

# Combined oral contraceptive pills for treatment of acne (Review)

Arowojolu AO, Gallo MF, Lopez LM, Grimes DA



**THE COCHRANE  
COLLABORATION®**

# COC vs placebo

**Di 10 trial analizzati, ben 9 erano concordi nell'affermare un miglioramento delle lesioni cutanee nelle pz in tp ep.**

**Combined oral contraceptive pills for treatment of acne  
(Review)**

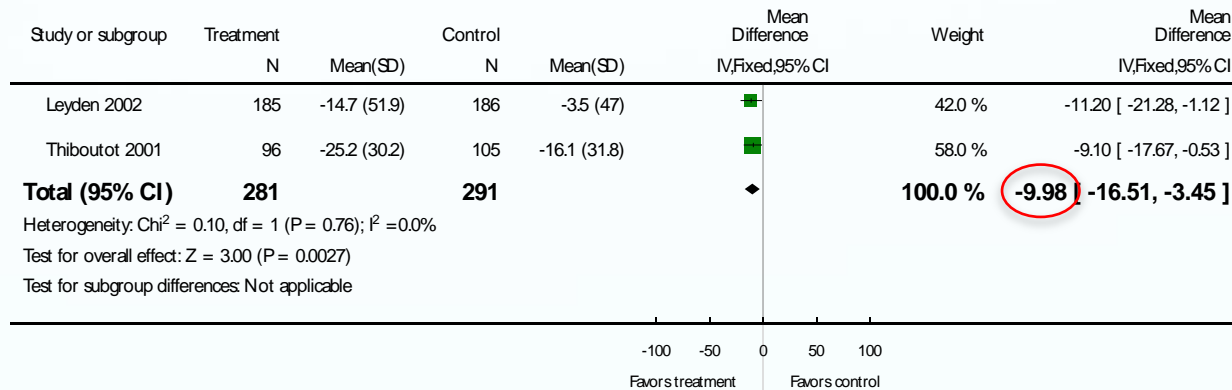
Arowojolu AO, Gallo MF, Lopez LM, Grimes DA



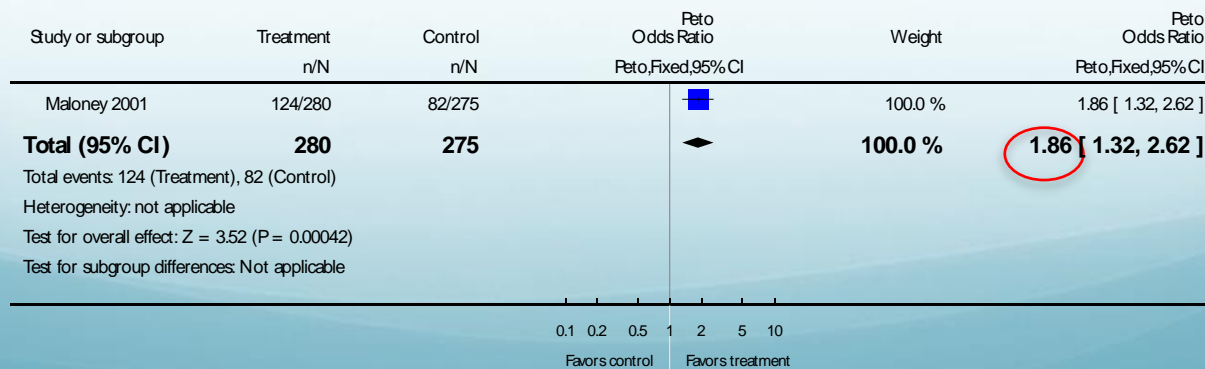
**THE COCHRANE  
COLLABORATION®**

# COC vs placebo

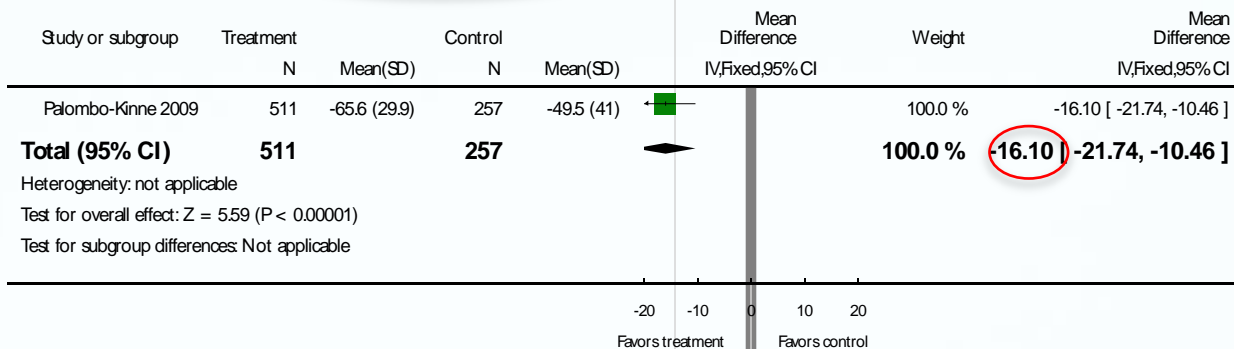
## Comparison 1 LNG 100 µg / EE 20 µg versus placebo, Outcome 1 Mean change in total lesion count.



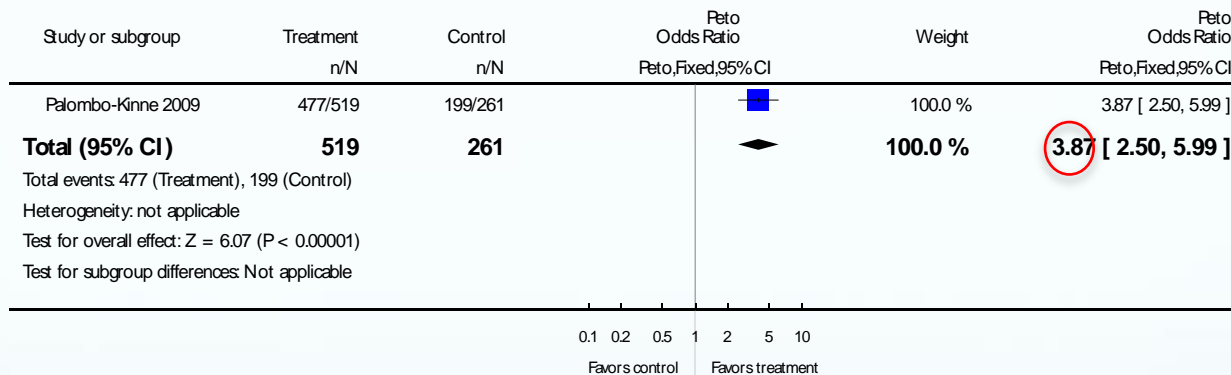
## Comparison 2 NA 1 mg / EE 20-30-35 µg versus placebo, Outcome 1 Clinician assessment of no, minimal or mild acne at cycle 6.



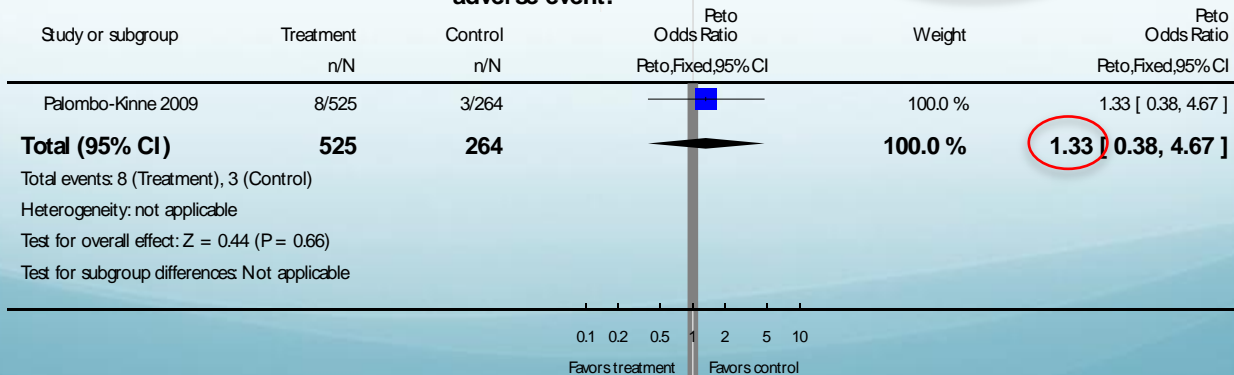
**Comparison 4 Dienogest 2 mg / EE 30 µg versus placebo, Outcome 1 Mean percentage change in inflammatory lesion count after cycle 6.**



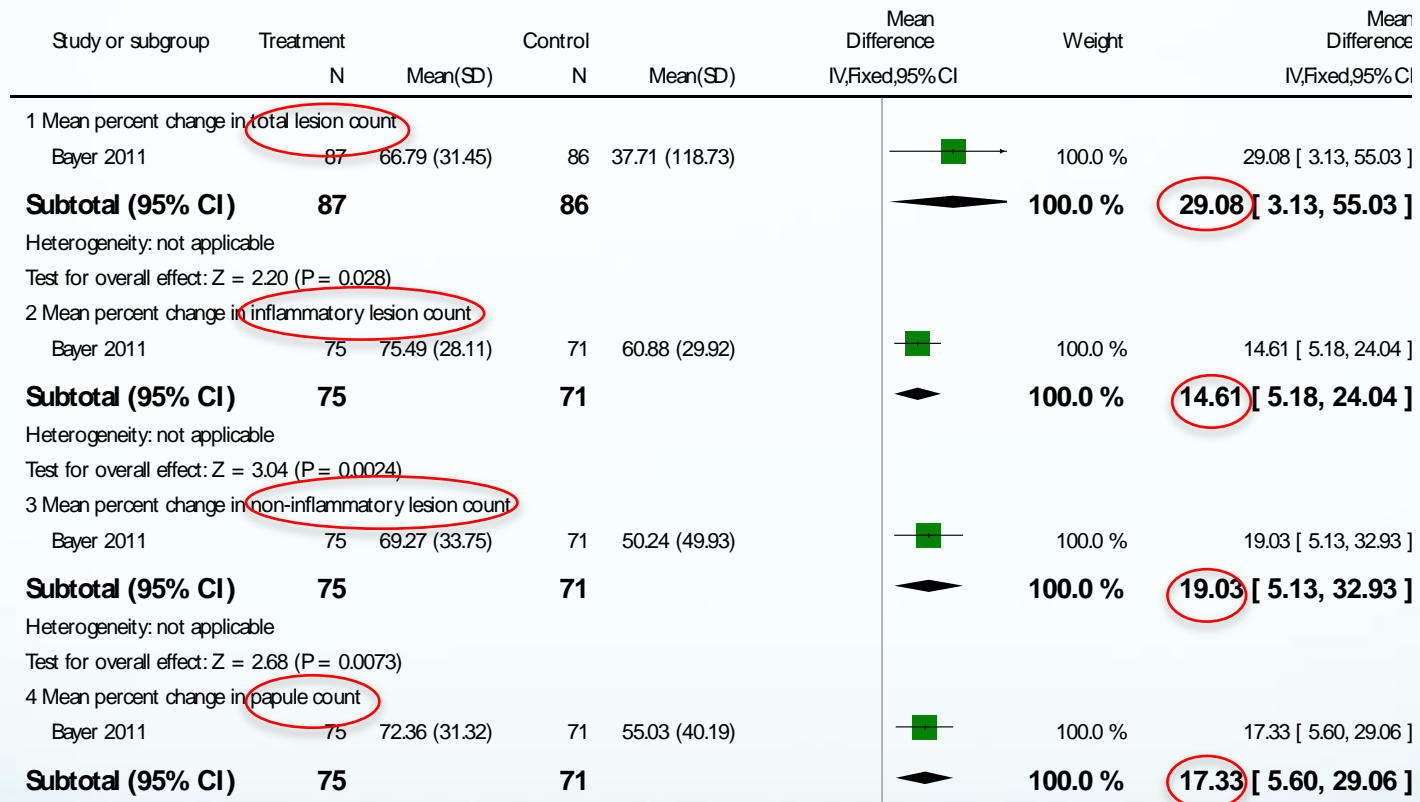
**Comparison 4 Dienogest 2 mg / EE 30 µg versus placebo, Outcome 3 Improvement of facial acne (clinical assessment).**



**Comparison 4 Dienogest 2 mg / EE 30 µg versus placebo, Outcome 4 Discontinuation due to adverse event.**



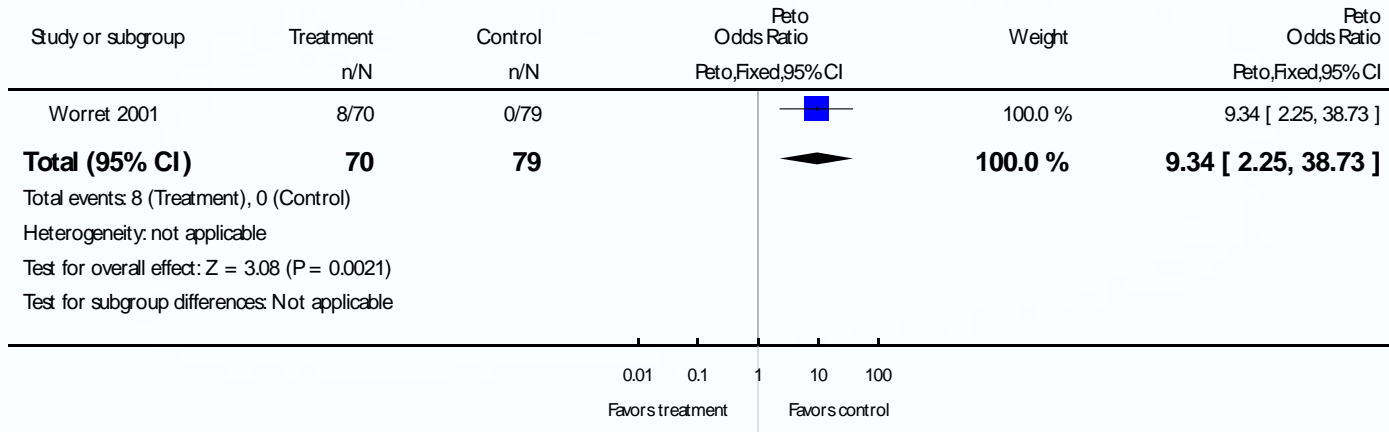
Comparison 5 DRSP 3 mg / EE 20 µg versus placebo, Outcome 1 Mean percent change in lesion counts at cycle 6.



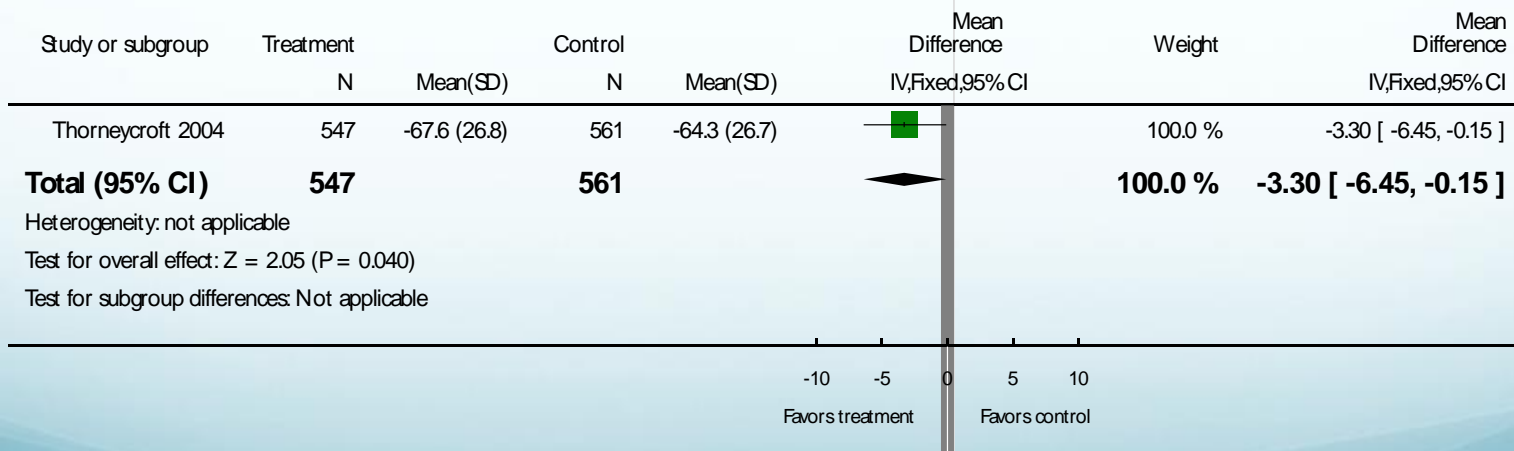
**COC vs COC**



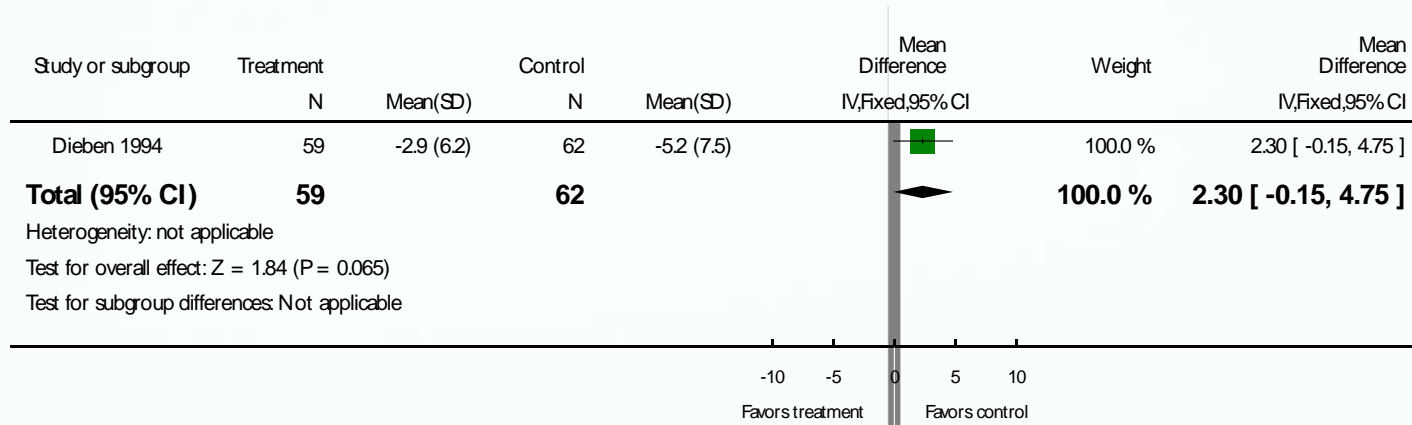
**Comparison 16 LNG 150 µg / EE 30 µg versus CMA 2 mg / EE 30 µg, Outcome 3 Women with increased pustules or papules lesion count at cycle 12.**



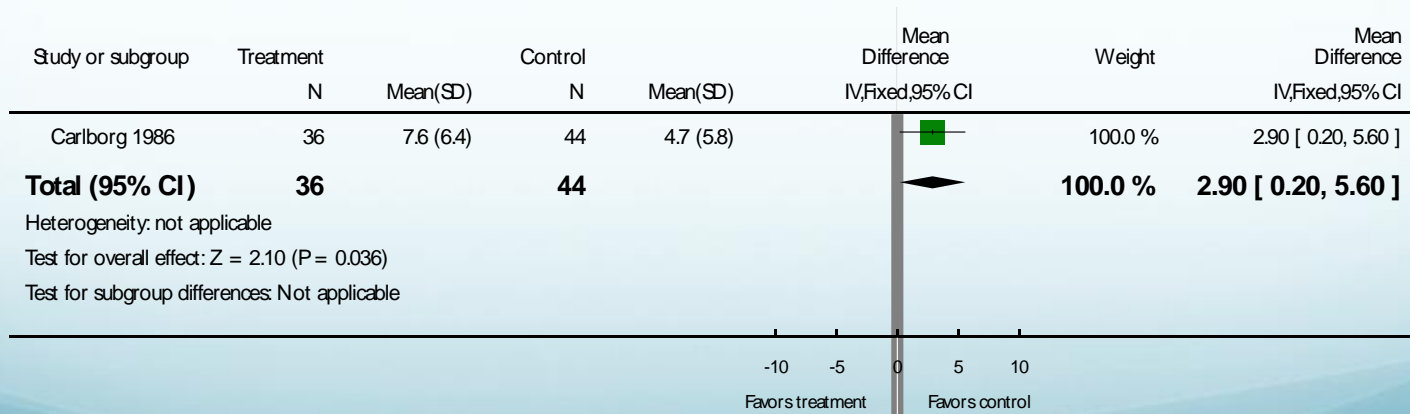
**Comparison 9 DRSP 3 mg / EE 30 µg versus NGM 180-215-250 µg / EE 35 µg, Outcome 2 Mean percentage change in total lesion count after cycle 6.**



**Comparison 11 DSG 25-125 µg / EE 40-30 µg versus CPA 2 mg / EE 35 µg, Outcome 5 Mean change in pustule count at cycle 4.**

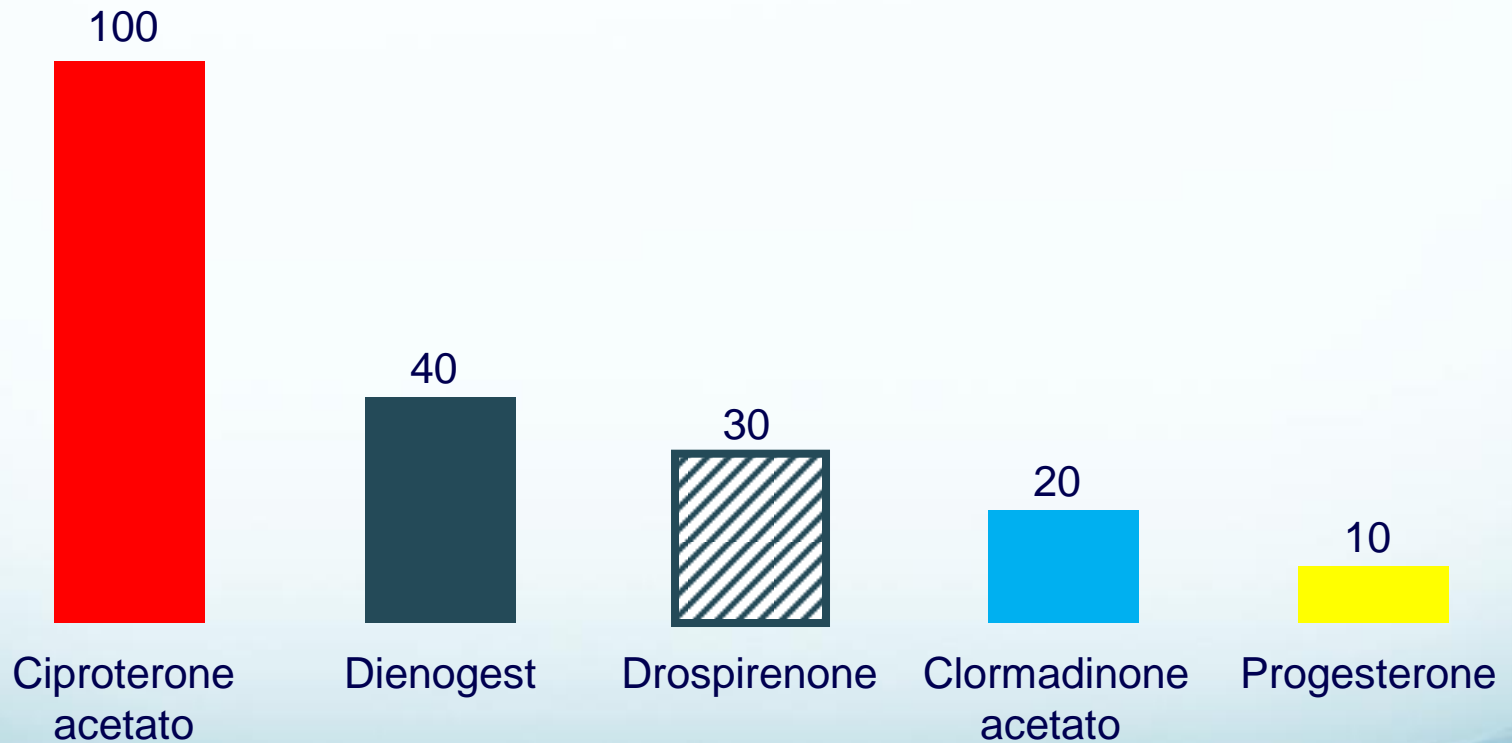


**Comparison 17 LNG 150 µg / EE 30 µg versus CPA 2 mg / EE 35 µg, Outcome 3 Mean papule count at cycle 6.**



# Cosa scegliere?

Attività antiandrogenica relativa di diversi progestinici



*Valutata col test di Hershberger (rodent seminal vesicle hypertrophy test)*

# CPA vs DRSP

Multicentrico doppio cieco

*Pz con acne lieve-moderata*

*82 pz DRPS*

*43 pz CPA*

9 cicli di tp

**Outcomes: *numero di lesioni cutanee, dosaggio testosterone, androstenedione, DHEAS, SHBG***

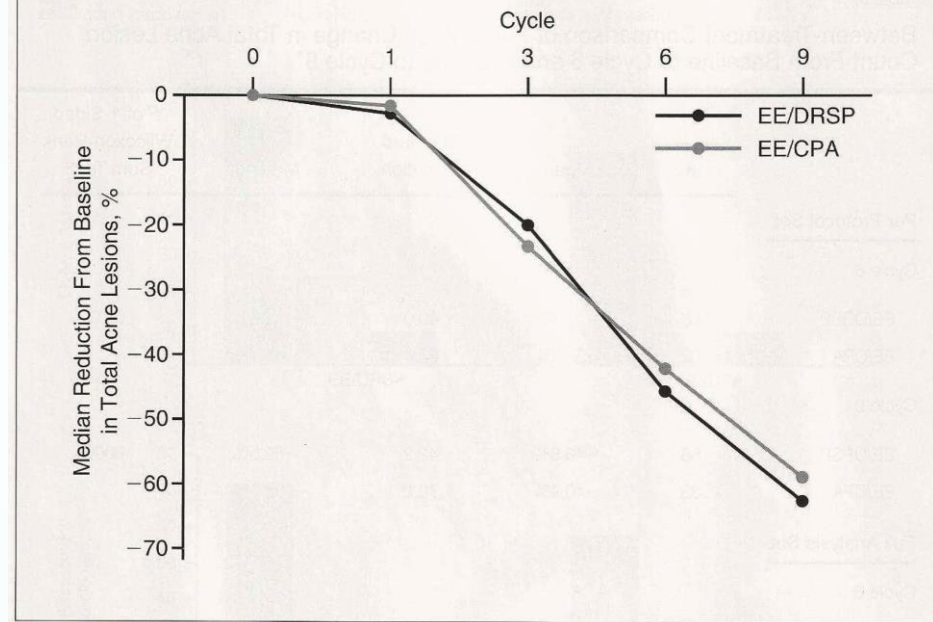
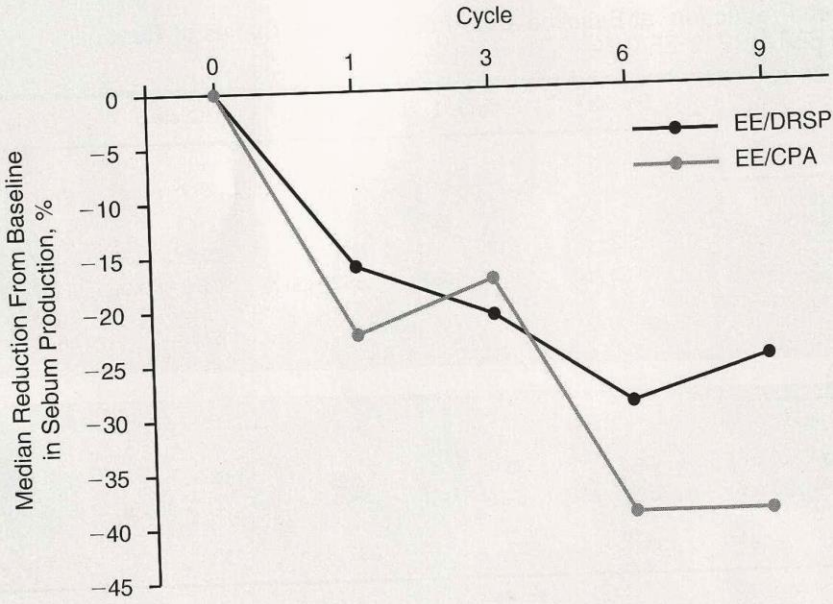


Figure 1. Median percentage reduction from baseline in total acne lesions (per protocol set). EE/DRSP indicates 30 µg ethinyl estradiol/3 mg drospirenone; EE/CPA, 35 µg ethinyl estradiol/2 mg cyproterone acetate.

Median (25th–75th Quartile) Acne Lesion Count for the Per Protocol Set at Baseline and Cycles 1, 3, 6, and 9 of Treatment With EE/DRSP (n=58) or EE/CPA (n=33)\*

	Cycle 0		Cycle 1		Cycle 3		Cycle 6		Cycle 9	
	EE/DRSP	EE/CPA	EE/DRSP	EE/CPA	EE/DRSP	EE/CPA	EE/DRSP	EE/CPA	EE/DRSP	EE/CPA
All lesions	50 (23–68)	43 (30–76)	48 (27–74)	49 (27–74)	35 (23–46)	46 (19–61)	24 (15–38)	22 (13–44)	17.5 (10–29)	18 (8–31)
Noninflammatory lesions	23 (8–52)	21 (6–53)	25 (10–50)	20 (10–47)	20 (8–28)	20 (8–37)	12.5 (5–25)	12 (5–30)	9 (5–20)	6 (4–20)
Inflammatory lesions	16 (11–29)	20 (13–25)	19 (11–28)	19 (12–28)	13 (8–21)	13 (9–29)	8 (5–12)	7 (4–14)	4 (3–8)	5 (2–10)
Open comedos	6.5 (0–20)	11 (0–25)	6 (0–20)	11 (3–20)	7 (0–12)	10 (0–20)	6 (0–10)	5 (0–12)	3.5 (0–10)	3 (0–8)
Closed comedos	10.5 (4–22)	11 (0–30)	12 (6–26)	9 (5–25)	9 (5–18)	10 (3–20)	5 (3–12)	7 (0–18)	4 (2–13)	4 (0–10)
Papules	10.5 (8–18)	15 (10–23)	12 (7–21)	13 (9–22)	9 (5–14)	10 (6–18)	6 (4–10)	7 (3–11)	3.5 (2–6)	5 (2–7)
Pustules	5 (2–10)	3 (2–8)	5 (1–10)	4 (2–7)	2 (0–7)	2 (0–7)	1 (0–3)	0 (0–1)	0 (0–2)	0 (0–1)
Nodules	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

\*EE/DRSP indicates 30 µg ethinyl estradiol/3 mg drospirenone; EE/CPA, 35 µg ethinyl estradiol/2 mg cyproterone acetate.



Sebum Production\* at Baseline and After 3, 6, and 9 Cycles of Treatment With EE/DRSP or EE/CPA<sup>†</sup>

	Baseline	Cycle 1	Cycle 3	Cycle 6	Cycle 9
<b>EE/DRSP</b>					
Median Sebum					
Production, $\mu\text{g}/\text{cm}^2$ (25th–75th Quartile)	126.2 (94.7–165)	112.7 (62.7–146.3)	91.2 (65.3–130.7)	79.0 (55.3–121.0)	84.0 (54.0–132.3)
n	58	57	58	57	58
<b>EE/CPA</b>					
Median Sebum					
Production, $\mu\text{g}/\text{cm}^2$ (25th–75th Quartile)	120.7 (87.3–165.7)	78.0 (66.3–115.3)	79.3 (57.3–140.0)	62.3 (41.7–108.0)	72.7 (51.0–105.0)
n	33	33	33	33	33

\*Per protocol set.

<sup>†</sup>EE/DRSP indicates 30  $\mu\text{g}$  ethinyl estradiol/3 mg drospirenone; EE/CPA, 35  $\mu\text{g}$  ethinyl estradiol/2 mg cyproterone acetate.

### Hormone Levels\* Before and After 9 Cycles of Treatment With EE/DRSP or EE/CPA<sup>†</sup>

	EE/DRSP		EE/CPA	
	Baseline	Cycle 9	Baseline	Cycle 9
LH, U/L (mean±SD)	6.23±8.10	1.38±2.19	4.99±3.85	1.09±1.62
Total testosterone, nmol/L (mean±SD)	1.31±0.66	0.94±0.50	1.24±0.66	1.05±0.61
Free testosterone, nmol/L (mean±SD)	0.0065±0.0055	0.0023±0.0027	0.0074±0.0062	0.0028±0.0036
DHEAS, nmol/L (mean±SD)	6390±2840	4320±2110	6943±4011	4166±2028
Androstenedione, nmol/L (mean±SD)	8.85±3.18	6.68±3.15	8.88±3.26	6.59±2.65
SHBG, nmol/L (mean±SD)	55.5±35.0	184.2±48.5	58.9±35.1	190.3±53.9

# CPA vs DRSP

Studio prospettico randomizzato

91 pz con diagnosi di irsutismo

DRSP CPA per 12 mesi

**Outcomes: free T2, androstenedione,  
DHEAS, SHBG, miglioramento dei  
sintomi (Ferriman-Gallwey)**

Percentuale di riduzione irsutismo :

**0.70 (0-0.58) vs. 0.57 (0.10-1.00) (*p = 0.028*) a 6 mesi**

**0.80 (0-0.42) vs. 0.81 (0-0.75) (*p = 0.6*) a 12 mesi**



DNG

DIAG

VS

CPA??

*The European Journal of Contraception and Reproductive Health Care 1999; 4: 155–164*

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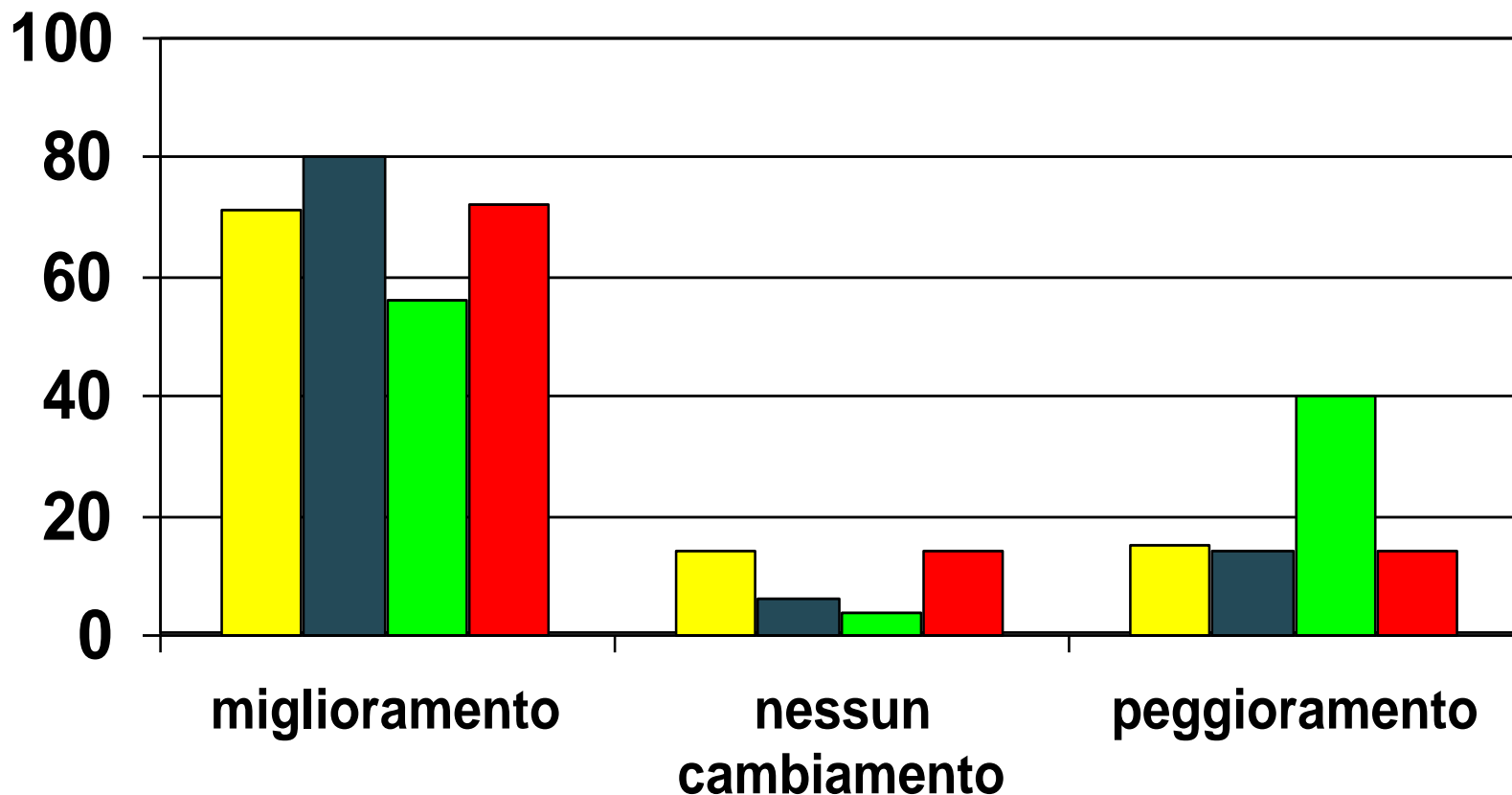
# The efficacy and tolerability of Valette<sup>®</sup>: a postmarketing surveillance study

T. Zimmermann, H. Dietrich, K.-H. Wisser and H. Hoffmann\*

Department of Medical Affairs and \*Drug Safety Unit, Jenapharm GmbH & Co. KG, Jena, Germany

per cento su 1110 donne

acne pelle grassa capelli irsutismo



effetto al sesto ciclo di trattamento con EE30+DNG2 vs basale

Zimmermann T et al, 1999

## **Clinical Findings with the Oral Contraceptive Combination Ethinylestradiol/Dienogest in Poland**

*S. Golbs, R. Domhardt, S. Radowicky<sup>1</sup>, Z. Kałuzny<sup>2</sup>, K.H. Wisser and T. Zimmermann*

Department of Medical Affairs, Jenapharm GmbH & Co. KG, Jena, Germany; <sup>1</sup>Medical Academy Warsaw; <sup>2</sup>Schering Office, Warsaw, Poland

# Inestetismi cutanei

**Multicentrico**  
**N = 431 pz per 12 mesi di tp**

**TABLE 4. Shifts in the severity of skin blemishes during the use of EE/DNG.**

Status	Cycle 3		Cycle 6		Cycle 12	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Improved	75	18.8	101	27.1	75	26.7
Unchanged	321	80.7	271	72.7	206	73.3
Worsened	2	0.5	1	0.3	0	0
All	398	100	373	100	281	100

# Acne vulgaris

**TABLE 6. Shifts in severity of acne in the patients with acne vulgaris during the use of EE/DNG.**

	Cycle 6		Cycle 12	
	<i>n</i>	%	<i>n</i>	%
Healed	1	2.0	13	37.1
Improved	40	80.0	19	54.3
Unchanged	8	16.0	3	8.6
Worsened	1	2.0	0	0
Total	50	100	35	100

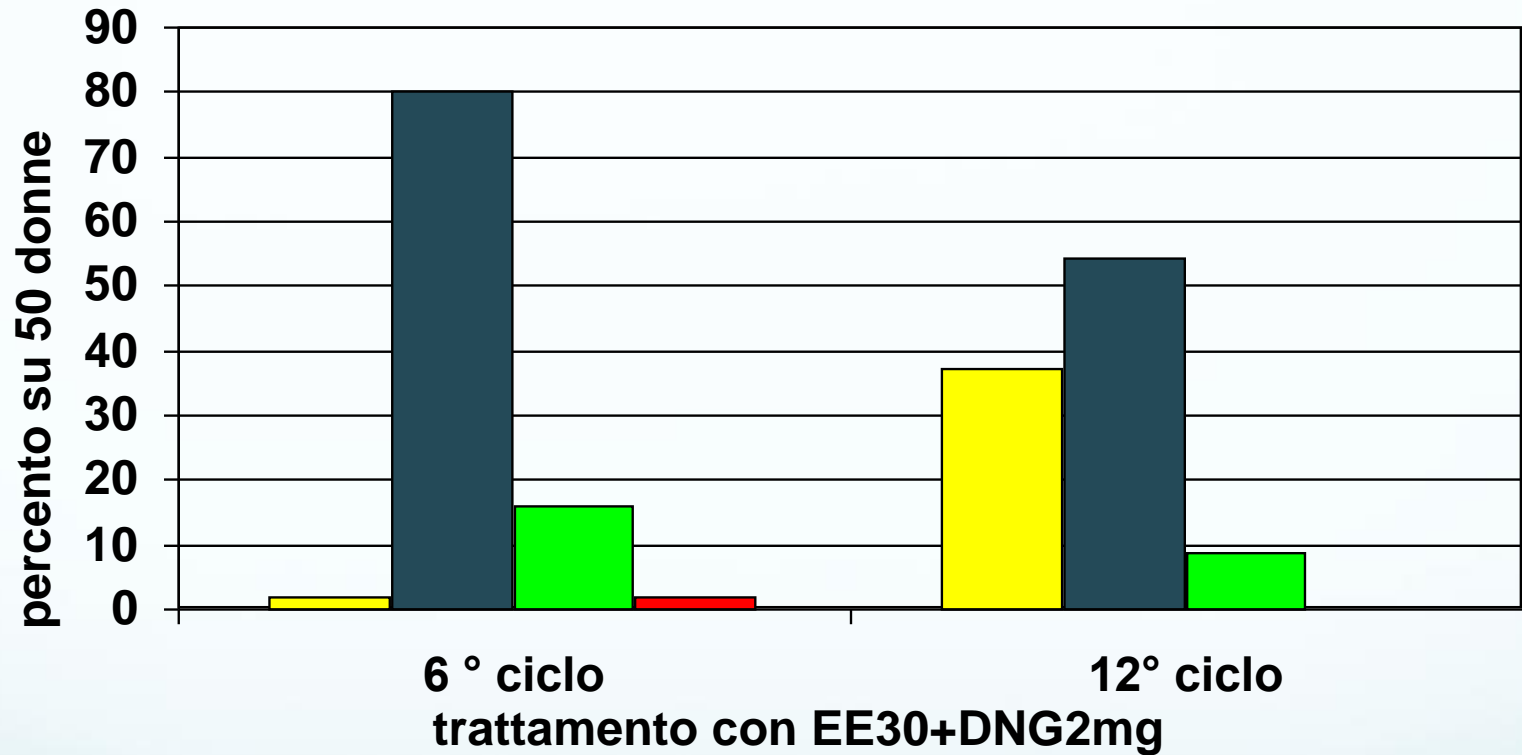
# Seborrea

**Multicentrico**  
**N = 431 pz per 12 mesi di tp**

**TABLE 5. Shifts in the severity of the hair greasiness during the use of EE/DNG.**

Status	Cycle 3		Cycle 6		Cycle 12	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Improved	131	32.6	187	49.3	159	53.9
Unchanged	270	67.2	191	50.4	136	46.1
Worsened	1	0.2	1	0.3	0	0
All	402	100	379	100	295	100

■ guarita ■ migliorata ■ immodificata ■ peggiorata



*Golbs S et al, 2002;24:585-92*



ELSEVIER

Contraception 79 (2009) 282–289

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Contraception

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Original research article

Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate<sup>☆</sup>

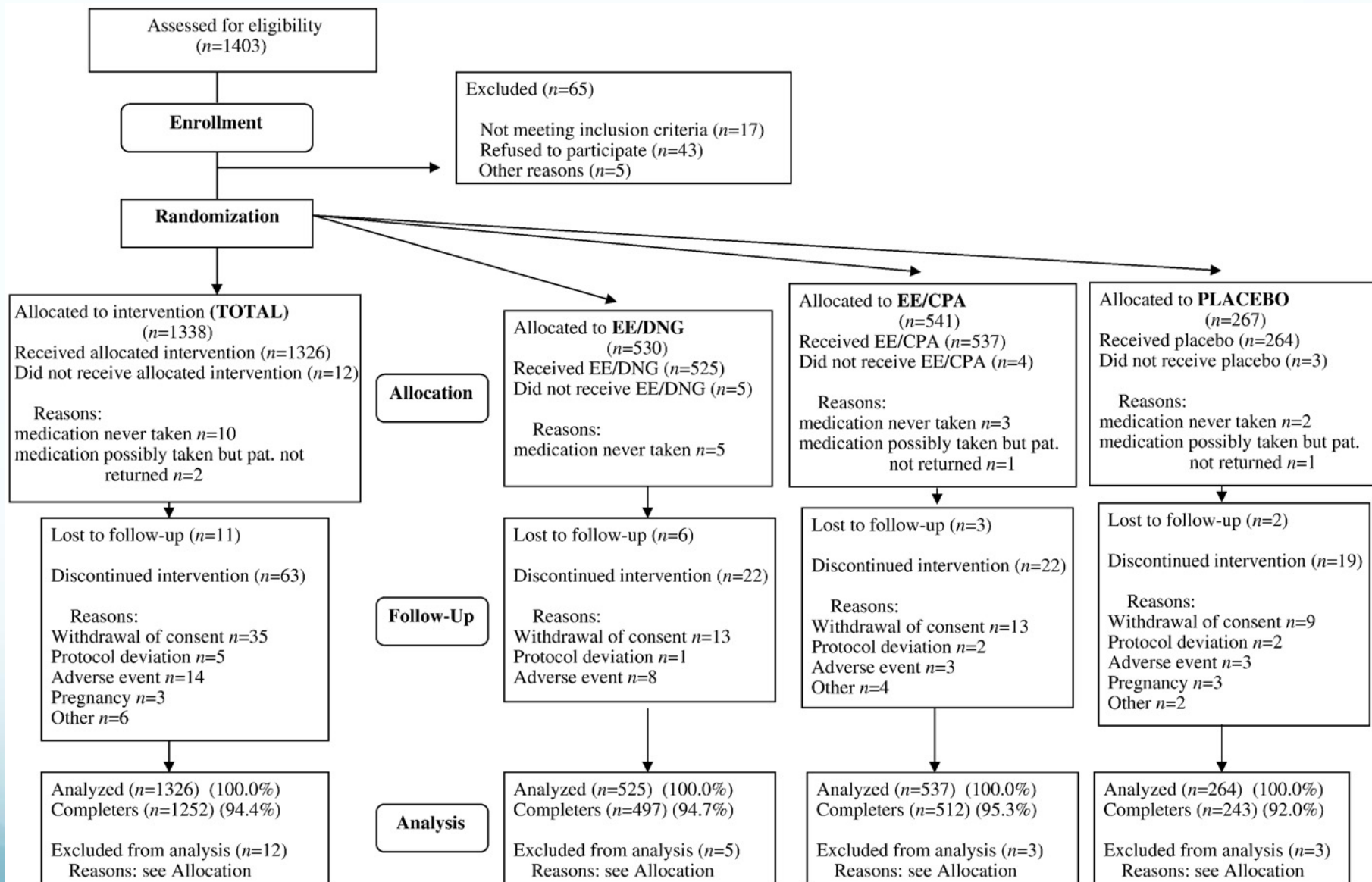
Ernesta Palombo-Kinne<sup>a,\*</sup>, Ilka Schellschmidt<sup>b</sup>, Ulrike Schumacher<sup>a</sup>, Thomas Gräser<sup>a</sup>

<sup>a</sup>*Jenapharm GmbH & Co. KG, 07745 Jena, Germany*

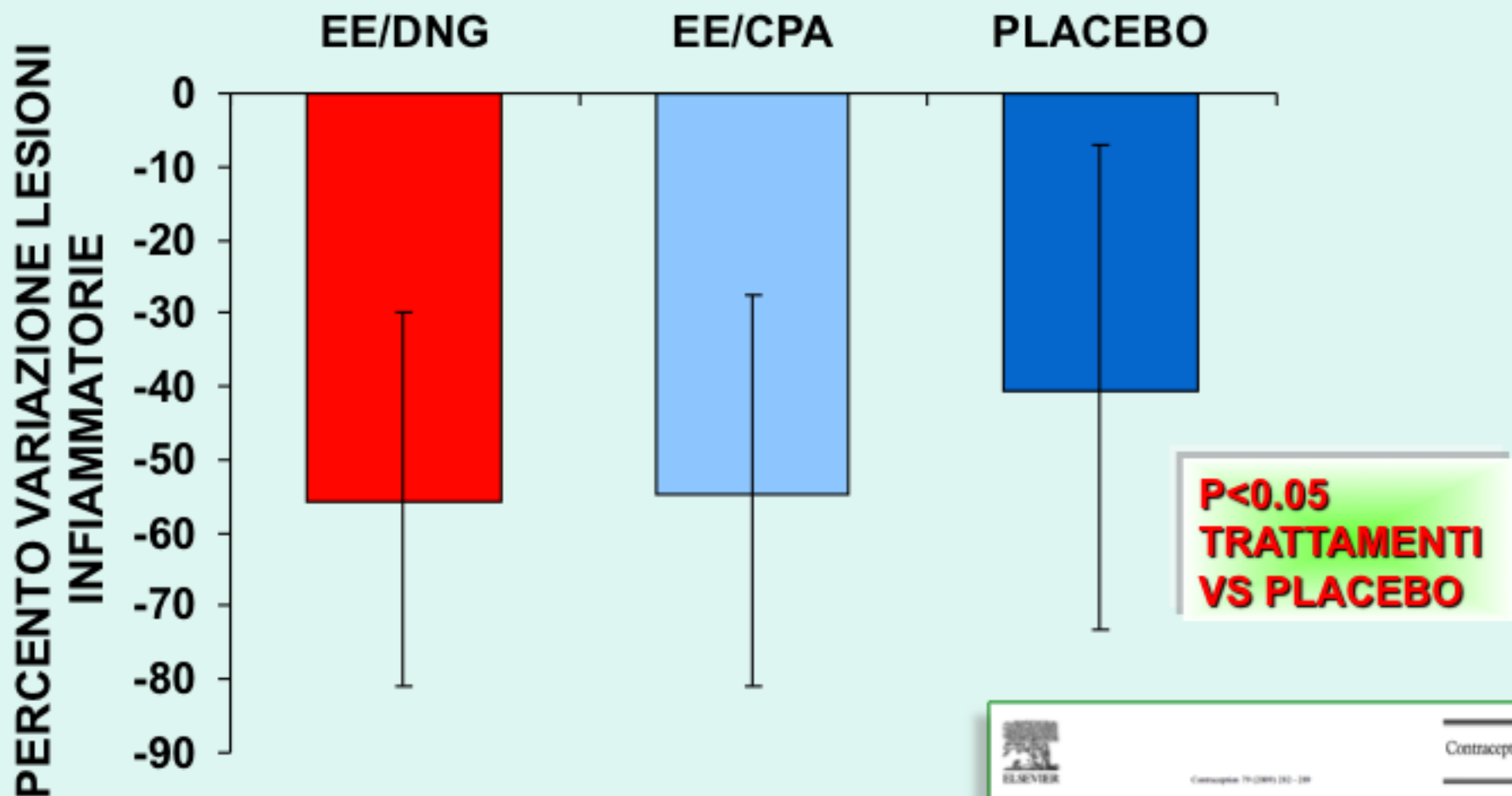
<sup>b</sup>*Bayer Schering Pharma AG, 13353 Berlin, Germany*

Received 30 April 2008; revised 20 October 2008; accepted 20 October 2008

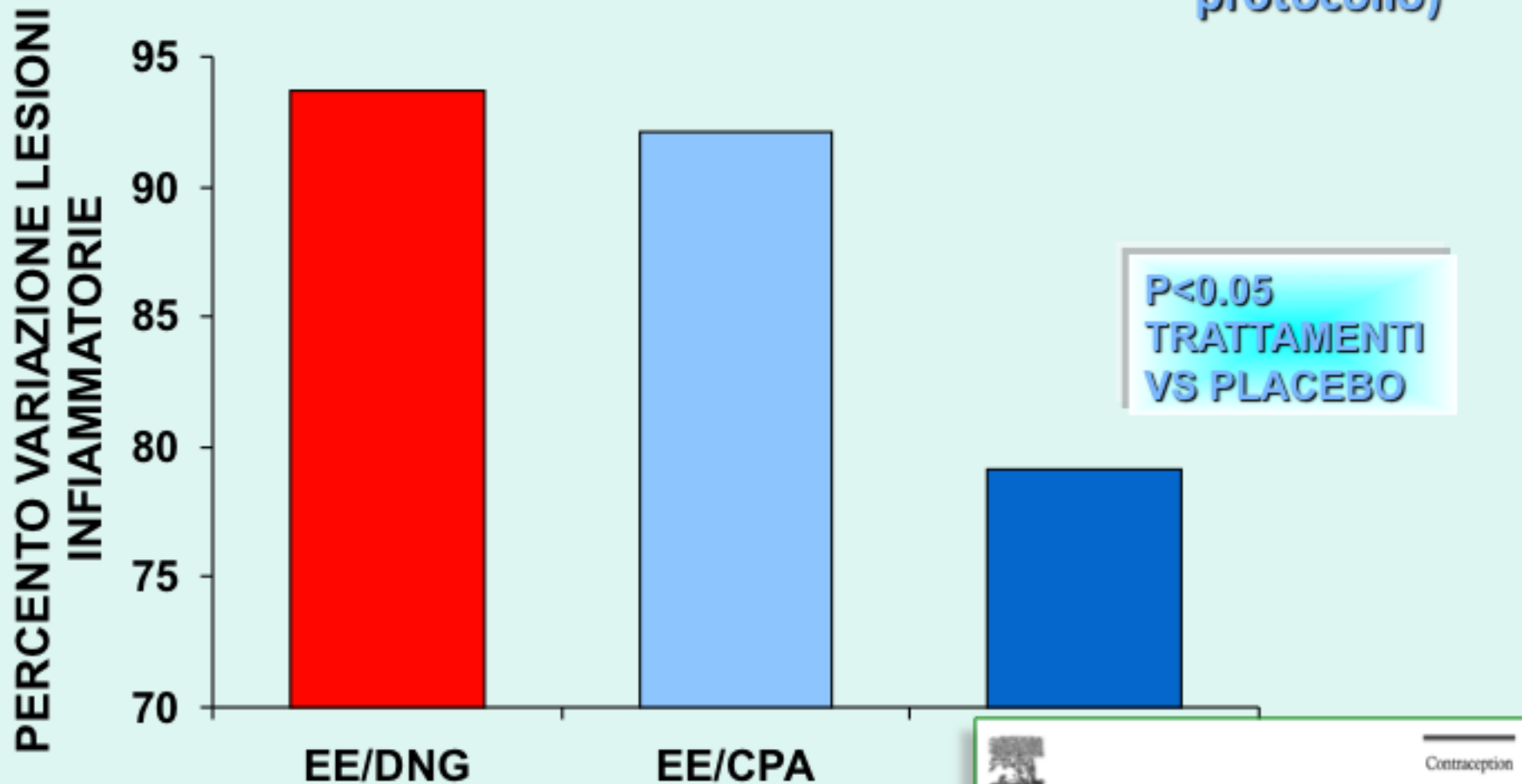




**Primary efficacy . Percento di variazione delle lesioni TOTALI al 6° ciclo vs basale (FAS intent-to-treat Per protocol set (escluso pazienti con grosse variazioni da protocollo))**



Primary efficacy . Percento di PAZIENTI CON MIGLIORAMENTO al 6° ciclo vs basale (FAS intent-to-treat Per protocol set (escluso pazienti con grosse variazioni da protocollo))



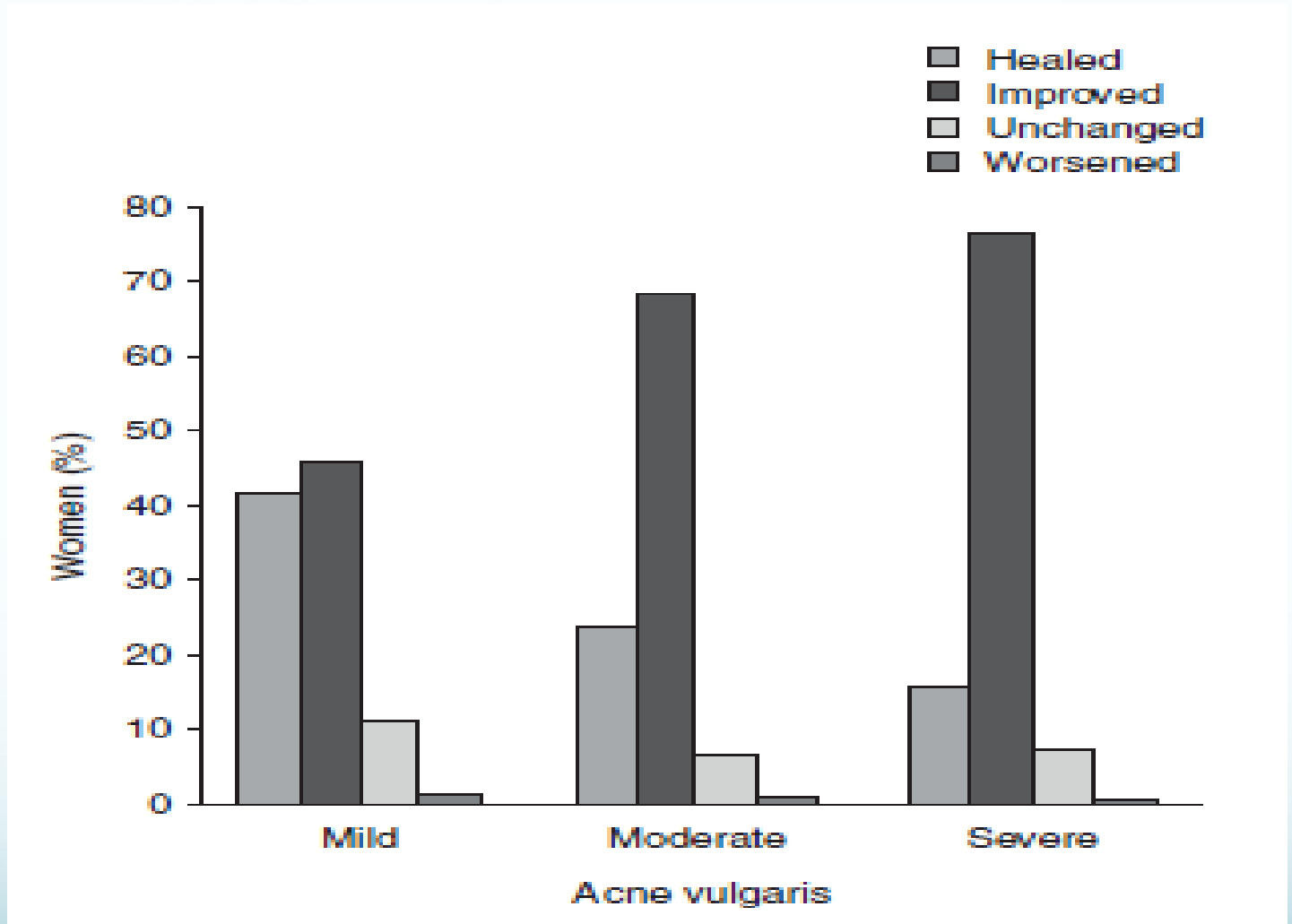
Contraception 75 (2005) 282–289

Original research article

Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate<sup>©</sup>

Ernesta Palombo-Kinne<sup>a,\*</sup>, Ilka Schellischmidt<sup>b</sup>, Ulrike Schumacher<sup>c</sup>, Thomas Geisler<sup>d</sup>

Contraception

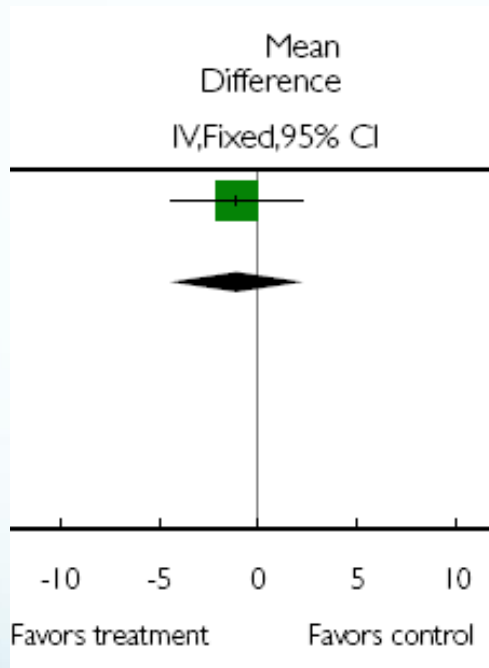


Most frequent adverse events (related and unrelated; number and percentage of affected patients)

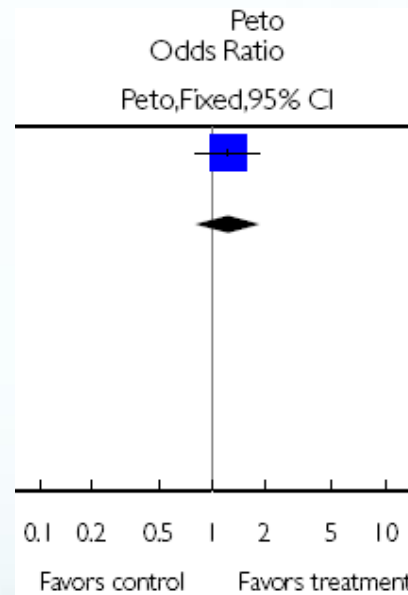
	EE/DNG (n=525)	EE/CPA (n=537)	Placebo (n=264)
Total adverse events	170 (32.4%)	188 (35.0%)	86 (32.6%)
Most common adverse events			
Headache	28 (5.3%)	28 (5.2%)	14 (5.3%)
Nausea	22 (4.2%)	34 (6.3%)	7 (2.7%)
Vomiting	16 (3.0%)	21 (3.9%)	5 (1.9%)
Breast pain	11 (2.1%)	9 (1.7%)	–
Influenza	11 (2.1%)	14 (2.6%)	3 (1.1%)
Metrorrhagia	11 (2.1%)	<1.0%	–
Nasopharyngitis	9 (1.7%)	14 (2.6%)	8 (3.0%)
Breast tenderness	8 (1.5%)	15 (2.8%)	<1.0%
Respiratory tract infection	8 (1.5%)	<1.0%	–
Diarrhea	7 (1.3%)	11 (2.0%)	6 (2.3%)
Breast edema	<1.0%	11 (2.0%)	<1.0%
Weight increase	<1.0%	7 (1.3%)	<1.0%

# DNG vs CPA

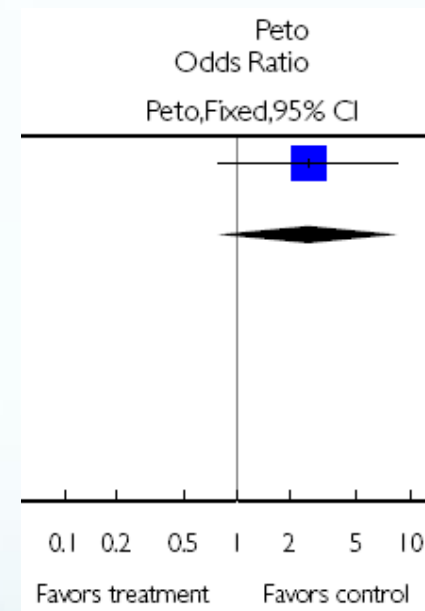
% riduzione del numero di lesioni dopo 6 mesi  
P = 0.51



Miglioramento clinico dell'acne vulgaris  
P = 0.34



Sospensione tp per effetti collaterali  
P = 0.12



➤ DNG/EE non è inferiore al „gold standard” CPA/EE

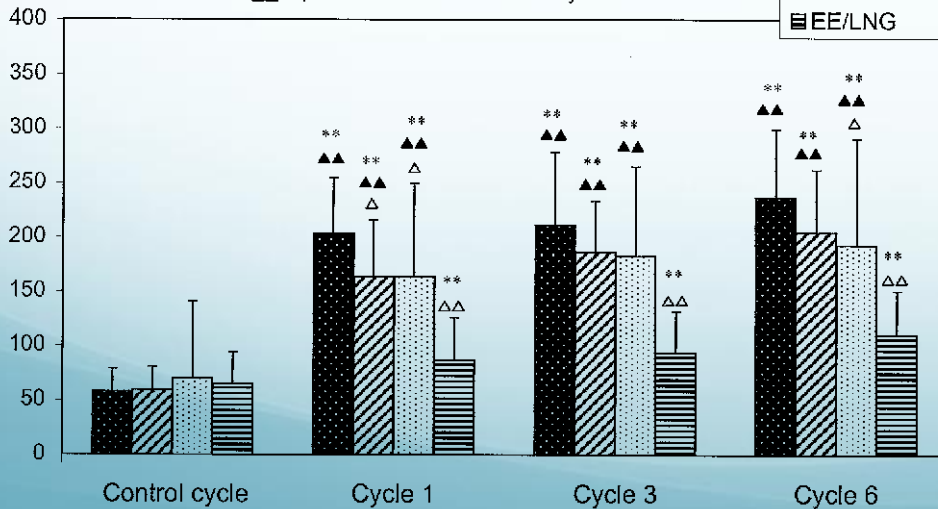
# Quale estrogeno?

Serum concentration of free testosterone (pg/mL), DHEAS ( $\mu\text{g/mL}$ ), and prolactin ( $\mu\text{IU/mL}$ ) in the control cycle and in the first, third and sixth cycle of treatment with 30EE/DNG, 20EE/DNG, EE/EV/DNG or EE/LNG

Formulation	Control cycle	Cycle 1	Cycle 3	Cycle 6
Free testosterone				
30EE/DNG	1.40 $\pm$ 0.87	0.45 $\pm$ 0.35**	0.38 $\pm$ 0.29**	0.56 $\pm$ 0.52**
20EE/DNG	1.83 $\pm$ 1.20	0.68 $\pm$ 0.45**	0.52 $\pm$ 0.32**	0.59 $\pm$ 0.45**
EE/EV/DNG	1.90 $\pm$ 1.80	0.89 $\pm$ 0.64**	0.74 $\pm$ 0.50**	0.86 $\pm$ 0.66**
EE/LNG	1.56 $\pm$ 0.79	0.82 $\pm$ 0.60**	0.59 $\pm$ 0.42**	0.63 $\pm$ 0.47**
DHEAS				
30EE/DNG	1.69 $\pm$ 1.06	1.25 $\pm$ 0.59**	1.19 $\pm$ 0.69**	1.06 $\pm$ 0.51**
20EE/DNG	2.22 $\pm$ 1.10	1.75 $\pm$ 0.99**	1.63 $\pm$ 0.83**	1.57 $\pm$ 0.76**
EE/EV/DNG	2.03 $\pm$ 0.99	1.78 $\pm$ 1.00**	1.70 $\pm$ 1.04**	1.52 $\pm$ 0.96**
EE/LNG	2.01 $\pm$ 0.92	1.81 $\pm$ 0.85**	1.76 $\pm$ 0.85**	1.53 $\pm$ 0.86**
Prolactin				
30EE/DNG	275 $\pm$ 149	316 $\pm$ 189	328 $\pm$ 207	339 $\pm$ 169
20EE/DNG	331 $\pm$ 257	274 $\pm$ 135	315 $\pm$ 159	311 $\pm$ 137
EE/EV/DNG	310 $\pm$ 177	369 $\pm$ 264	361 $\pm$ 192*	438 $\pm$ 276**
EE/LNG	363 $\pm$ 261	392 $\pm$ 245	356 $\pm$ 209	380 $\pm$ 252

## SHBG

nmol/L



# Take at home....

**Valutare la gravità delle lesioni dermatologiche**

**Acne moderata-grave ed irsutismo rappresentano un'indicazione assoluta per un CO con progestinico ad azione anti-androgenica**

**Eventuali sintomi associati (ad es. menorragia, endometriosi)**



# Take at home...

**Valutare fattori di rischio associati e l'impatto metabolico considerando anche i diversi regimi di terapia (per l'acne miglioramenti evidenti già dopo 3 mesi di trattamento)**

**Table 1: Estimates of risk of nonfatal venous thromboembolism**

Group*	Estimated 1-year risk of nonfatal venous thromboembolism
Baseline (women not using OC) <sup>6,13</sup>	1 in 20 000 to 1 in 9090
Women using OC containing levonorgestrel <sup>13,14</sup>	1 in 6666 to 1 in 6211
Women using OC containing desogestrel <sup>†13</sup>	1 in 3333
Women using any low-dose OC <sup>6,13</sup>	1 in 3333
Women not using OC but who have factor V Leiden mutation <sup>6</sup>	1 in 1754
Women using OC containing cyproterone <sup>‡</sup>	1 in 1666
Pregnant women and those post partum <sup>13,15</sup>	1 in 1666 to 1 in 1500
Women using OC and who have factor V Leiden mutation <sup>6</sup>	1 in 350

# Take at home....

**La superiorità *in vitro* del CPA non è tale *in vivo***

**DRSP è un'ottima alternativa.....tuttavia i numeri che supportano l'uso del DNG sono talmente "importanti" da farlo considerare come prima scelta**

***Grazie per  
l'attenzione!!!!***