Sovrappeso. Obesità e la pillola contraccettiva: profilo di tollerabilità e di sicurezza

Centro Salute Donna
Azienda USL Ferrara

OSTETRICIA e GINECOLOGIA 2017

"RICONOSCERE I RISCHI ASSOCIATI ALL'OBESITA"

Ferrara 19 maggio 2017
SALA IMBARCADERO
CASTELLO ESTENSE
Crediti E.C.M. per Medici ed Ostetriche

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

THE EUROPEAN SOCIETY OF CONTRACEPTION AND REPRODUCTIVE HEALTH

S.I.C.
Società Italiana della Contraccezione

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

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Editor of the European Journal of Contraception and Reproductive HealthCare

Obesità
Linee guida 2015-2016

OBESITY	COC	World Health Organization	CDC
≥ 30 kg/m² BMI	2		

	CHC	POP	DMPA/ NET-EN	IMP	Cu-IUD	LNG-IUD
OBESITY						
a) ≥30-34 kg/m² body mass index	2	1	1	1	1	1
b) ≥35 kg/m² body mass index	3	1	1	1	1	1

Evidence: The risk of VTE rises as BMI increases over 30 and rises further with BMI over 35. Use of CHC raises this inherent increased risk further.[28,34,38–41] Limited evidence suggests that obese women who use COC do not have a higher risk of acute MI or stroke than obese non-users.[34,42–44]

Chirurgia bariatrica
Linee guida 2016

History of bariatric surgery	
a) With BMI <30 kg/m²	1
b) With BMI ≥30–34 kg/m²	2
c) With BMI ≥35 kg/m²	3

Evidence: Limited evidence demonstrates no substantial decrease in effectiveness of oral contraception among women who undergo laparoscopic placement of an adjustable gastric band or biliopancreatic diversion.[45,46] However, evidence from pharmacokinetic studies report conflicting results of oral contraception effectiveness among women who undergo a jejunoileal bypass.[47,48]

Obesità e farmacocinetica

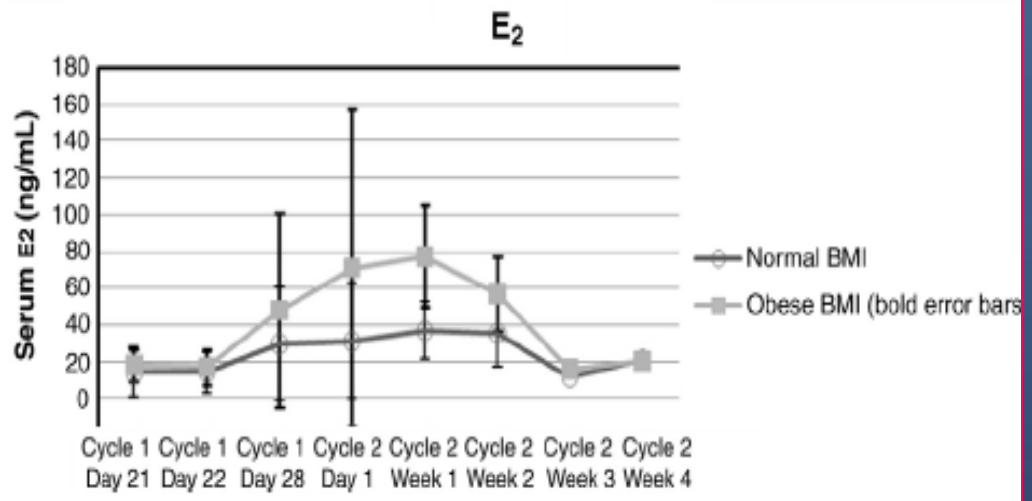


Fig. 5. Mean LH, FSH and E_2 levels.

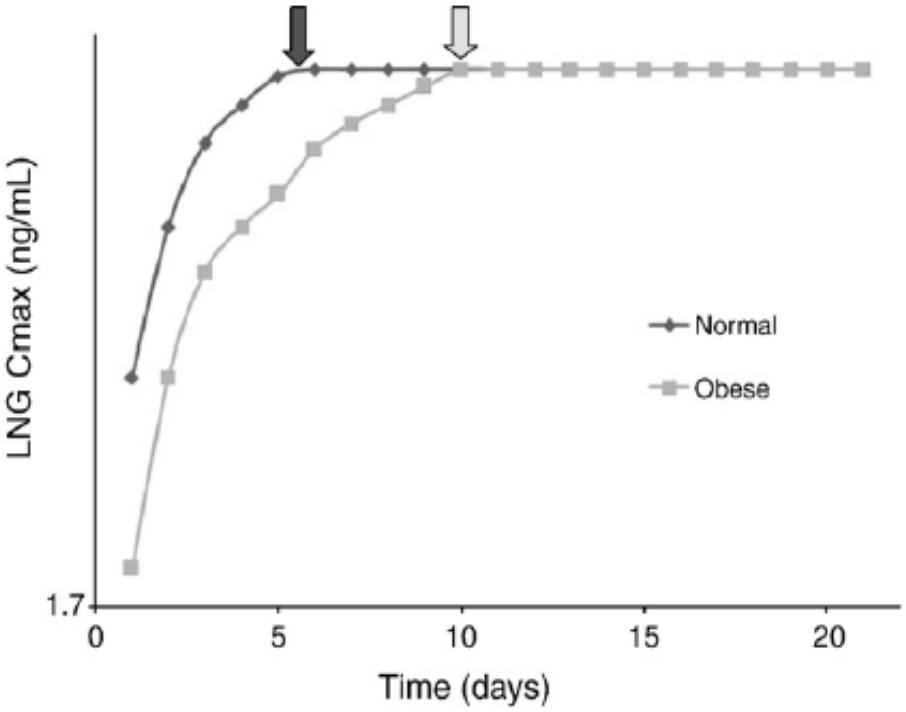


Fig. 6. Calculated time to reach LNG steady-state (steady state=$t_{1/2}\times5$) concentrations based on the serum sample series from Cycle 2, Day 1 (the first day of restarting active OC pills after a 7-day hormone-free interval).

Compared to normal weight women, obese women have a different pill pharmacokinetics associated to a greater activity of the hypotalamic-pituitary-ovarian axis.

Edelman AB et al. Contraception 2009;80:119-27

Contraception
an international reproductive health journal

Obesità ed efficacia

Table 1
Studies examining the effect on weight/BI

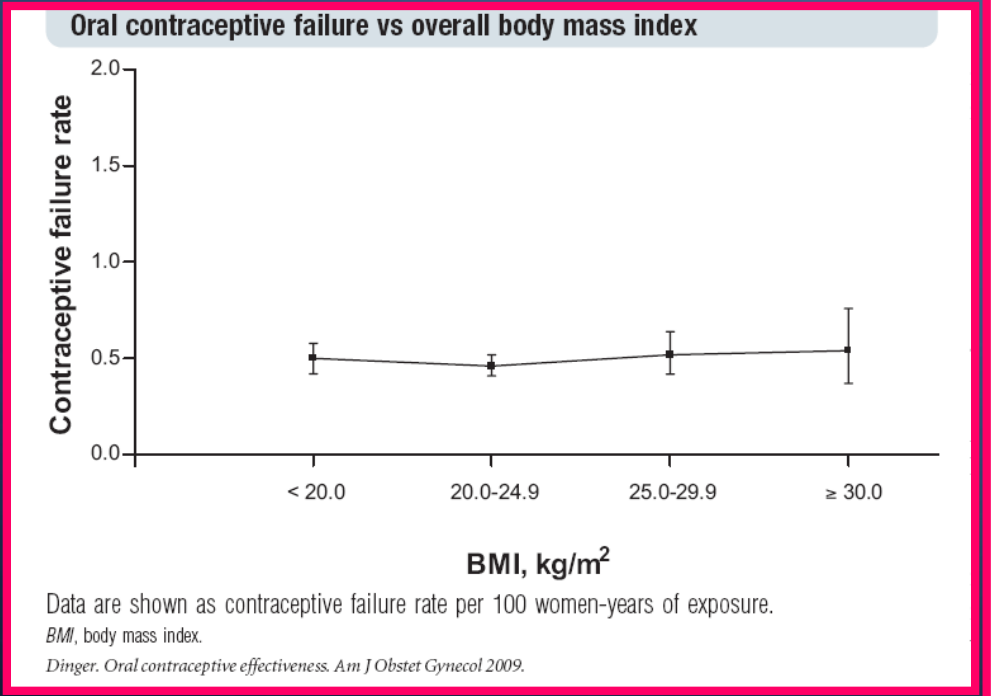
Author	Study type	Concludes obesity increases risk of OCP failure?
Vessey and Painter (2001) [17]	Prospective cohort	No
Holt et al. (2002) [18]	Retrospective cohort	Yes
Holt et al. (2005) [19]	Case-control	Yes
Brunner and Hogue (2005) [22]	Retrospective cohort	No
Brunner et al. (2007) [23]	Retrospective cohort	No
Brunner et al. (2006) [26]	Case cohort	No
Zhang et al. (2006) (abstract) [27]	Clinical trial	No
Westhoff et al. (2008) (abstract) [28]	Clinical trial	No

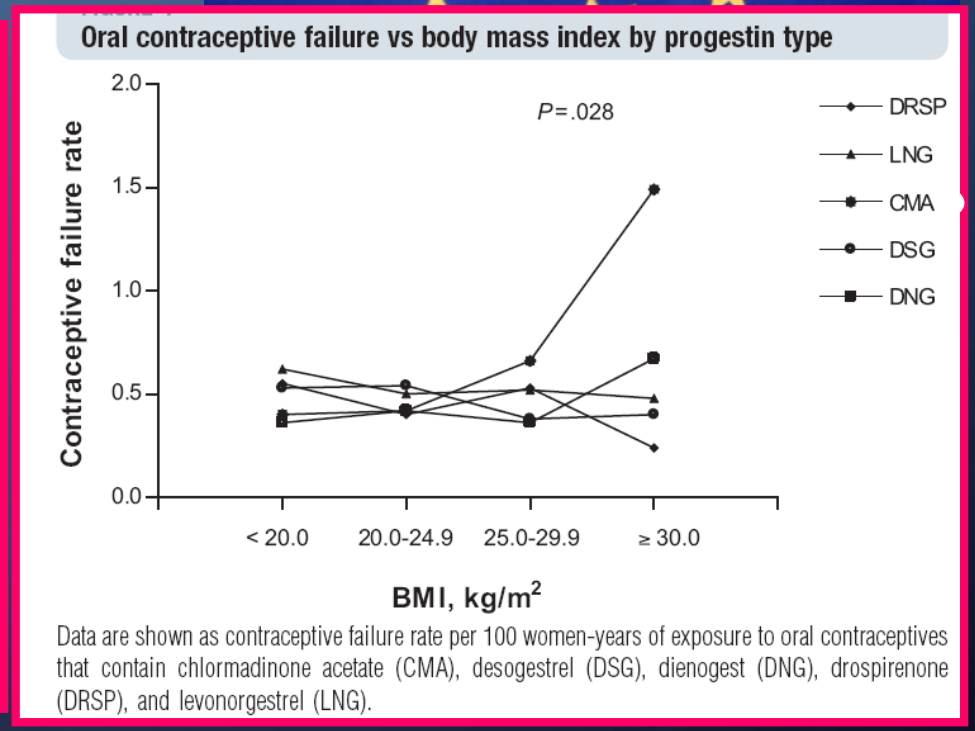
Contraception
an international reproductive health journal

Trussell J et al
Contraception 2009;79:334-38

Obesità ed efficacia (EURAS-OC)

59,510 women observed between 2000 and 2005 in Europe





AJOG American Journal of Obstetrics & Gynecology

Dinger JC et al AJOG 2009;201

Obesità ed efficacia
Systematic Review 2016

Hormonal contraceptives for contraception in overweight or obese women (Review)

Lopez LM, Grimes DA, Chen-Mok M, Westhoff C, Edelman A, Helmerhorst FM

THE COCHRANE COLLABORATION®

Efficacy of oral contraceptives (EPs or Ps) is similar in obese women when the recommended regimen is followed.

Anello vaginale

Variable	Normal weight Mean (ng/L, SD[1])	Obese Mean (ng/L, SD)	*P* value
EE			
Week 1	21.8 (17.5, 27.1)	14.8 (12.5, 17.5)	.008
Week 2	23.5 (19.6, 28.2)	14.9 (12.5, 17.8)	.001
Week 3	21.9 (17.9, 26.6)	14.8 (12.7, 17.3)	.004
ENG			
Week 1	1349 (1179, 1542)	1190 (968, 1464)	.35
Week 2	1360 (1196, 1547)	1311 (1106, 1553)	.75
Week 3	1275 (1116, 1457)	1240 (1041, 1477)	.39

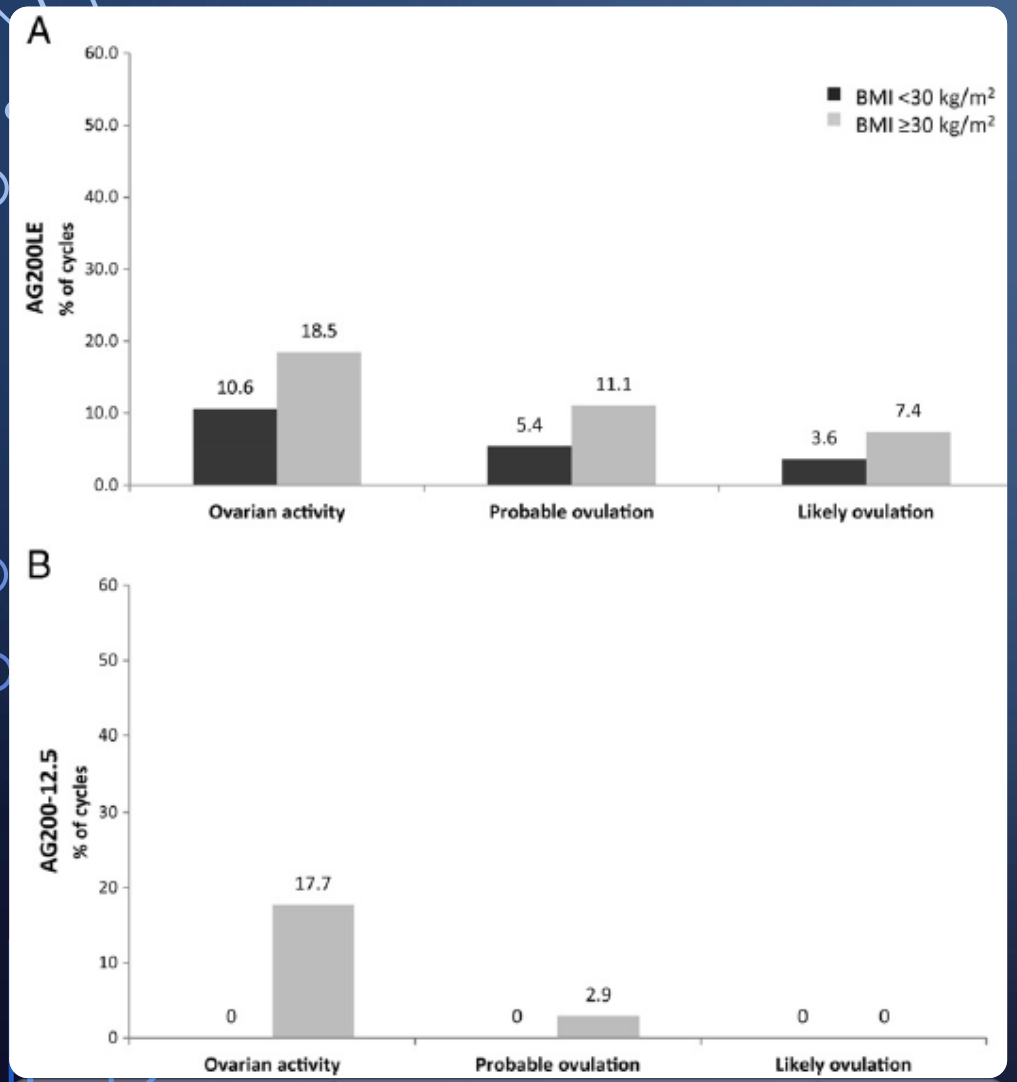
Maximum follicular diameter	Overall n = 37	Normal weight n = 18	Obese n = 19	*P* value
Week 1				
≥8 mm	11 (30)	5 (28)	6 (32)	.80
≥13 mm	4 (11)	3 (17)	1 (5)	.26
Week 2				
≥8 mm	5 (14)	4 (22)	1 (5)	.13
≥13 mm	4 (11)	3 (17)	1 (5)	.26
Week 3				
≥8 mm	4 (11)	2 (11)	2 (11)	.95
≥13 mm	4 (11)	2 (11)	2 (11)	.95

Although obese women had lower EE levels during vaginal ring use, they had excellent suppression of ovarian follicle development, similar to normal weight women. **This predicts that ring effectiveness will be similar in women with a BMI up to 39.9.** The lower serum EE levels in the obese women may explain the greater reported bleeding or spotting days.

AJOG American Journal of Obstetrics & Gynecology

Westhoff CL et al AJOG 2012;39

Patch



Data comparing pregnancy rates in obese versus nonobese women using a contraceptive patch are limited. A pooled analysis of three pivotal studies of a contraceptive patch [ethinyl estradiol (EE) and norelgestromin transdermal system (Ortho Evra®)] reported that body weight over 90 kg was associated with significantly increased pregnancy rates ($p<.001$), but BMI was not

Contraception
an international reproductive health journal

Foegh M et al
Contraception 2013;87:201-211

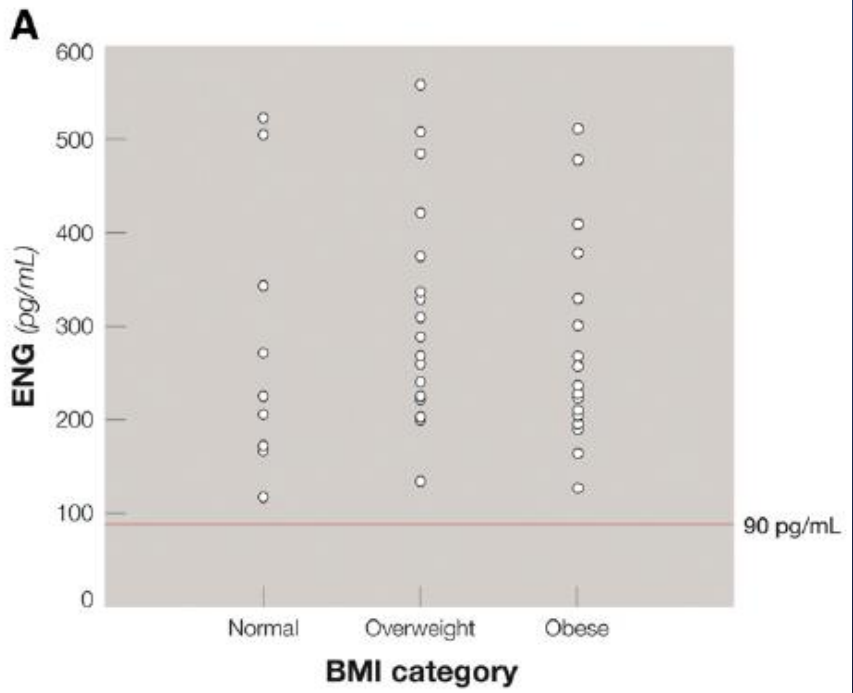
Impianto ETN

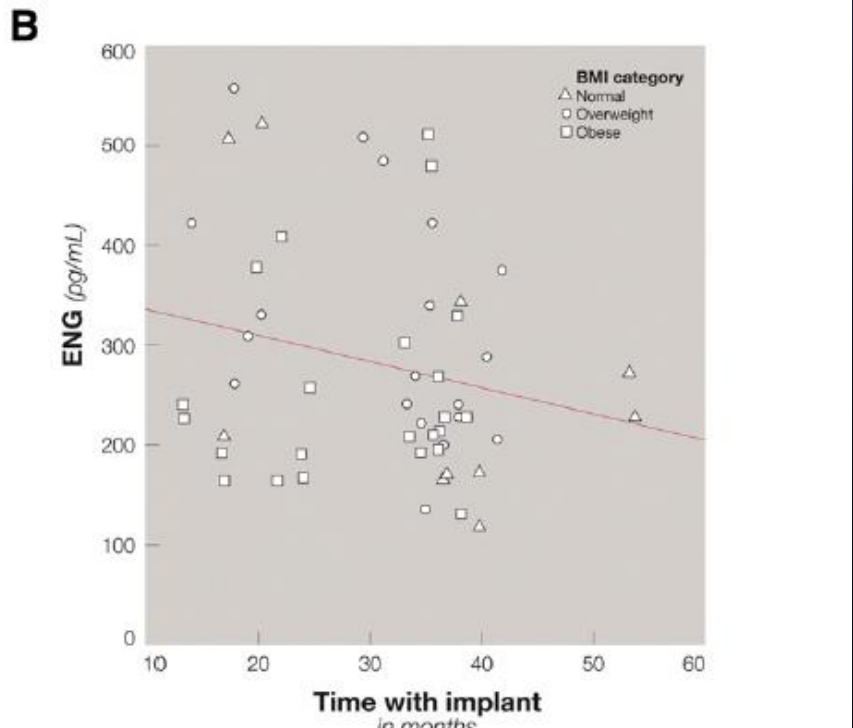
Contraception
an international reproductive health journal

Morrell KM et al
Contraception 2016;93:263-265

EXPERT OPINION
ON DRUG METABOLISM & TOXICOLOGY

Grandi G, Cagnacci A & Volpe A.
Exp Opinion Drug Metab Toxicol 2014;10:1-10





Sindrome metabolica

- I criteri NCEP: ATP III (National Cholesterol Education Program: Adult Treatment Panel III) 2005 per la sindrome metabolica sono i seguenti: presenza di 3 o più dei seguenti criteri:

- Obesità addominale (circonferenza vita: uomini >102 cm, donne >88 cm)

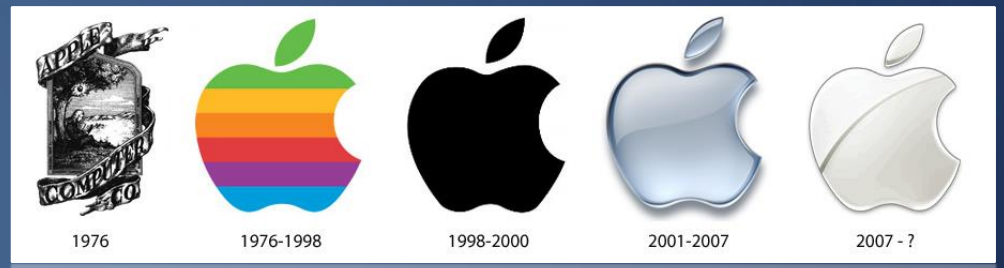
- Ipertrigliceridemia (>150 mg/dl), oppure trattamento farmacologico in atto per ipertrigliceridemia

- Basso colesterolo HDL (uomini <40 mg/dl, donne <50 mg/dl), o terapia farmacologica specifica

- Iperglicemia (a digiuno >100 mg/dl) o terapia farmacologica specifica, o precedente diagnosi di diabete mellito di tipo 2

- Ipertensione arteriosa (>130 mmHg di sistolica e >85 mmHg di diastolica), oppure trattamento farmacologico in atto

Come sono cambiati i contraccettivi ormonali



Administration

Classic 21/7 >> Extended/continuous regimens

Oral >> Others ways of administration

Progestin component

- Androgenic >> Non androgenic >> Anti androgenic

Estrogenic component

- Mestranol >> Ethinyl-estradiol >> Reduction of doses (15 mcg)>> Estradiol

Grandi G, Cagnacci A & Volpe A.
Exp Opinion Drug Metab Toxicol
2014;10:1-10

Problema senza risoluzione in contraccezione combinata?

Rischio tromboembolico

Estrogeno

Potenza estrogenica

Progestinico

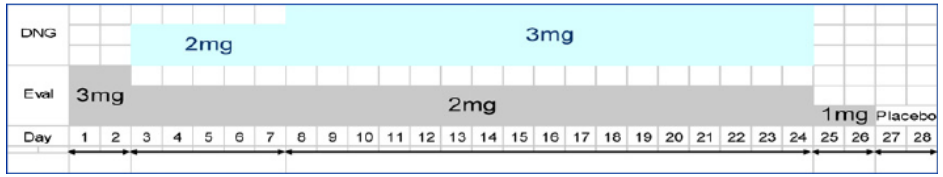
Potenza androgenica

Rischio arterioso
Metabolismo glico-lipidico

L'estradiolo in contraccezione ormonale

- Estradiol Valerate/Dienogest

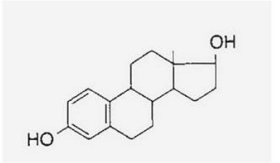
quadriphasic regimen (26+2)



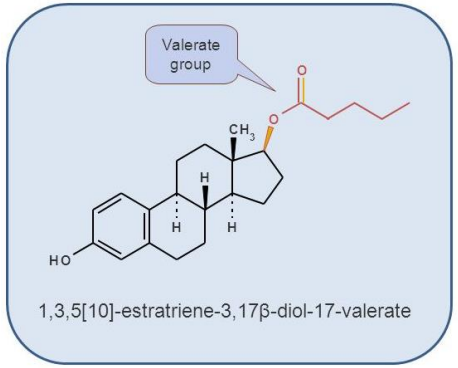
- Estradiol 1.5 mg/
Nomegestrol Acetate 2.5 mg

monophasic regimen (24+4)

Estradiolo ed estradiolo valerato



1,3,5[10]-estratriene-3,17β-diol



1,3,5[10]-estratriene-3,17β-diol-17-valerate

-E2V is the ester of 17β-Estradiol (E2).

-E2V is rapidly and completely metabolized to Estradiol (E2) during the first liver passage.

- E2V is virtually identical to E2 in pharmacokinetic and exactly identical in pharmacodynamic and clinical practice.

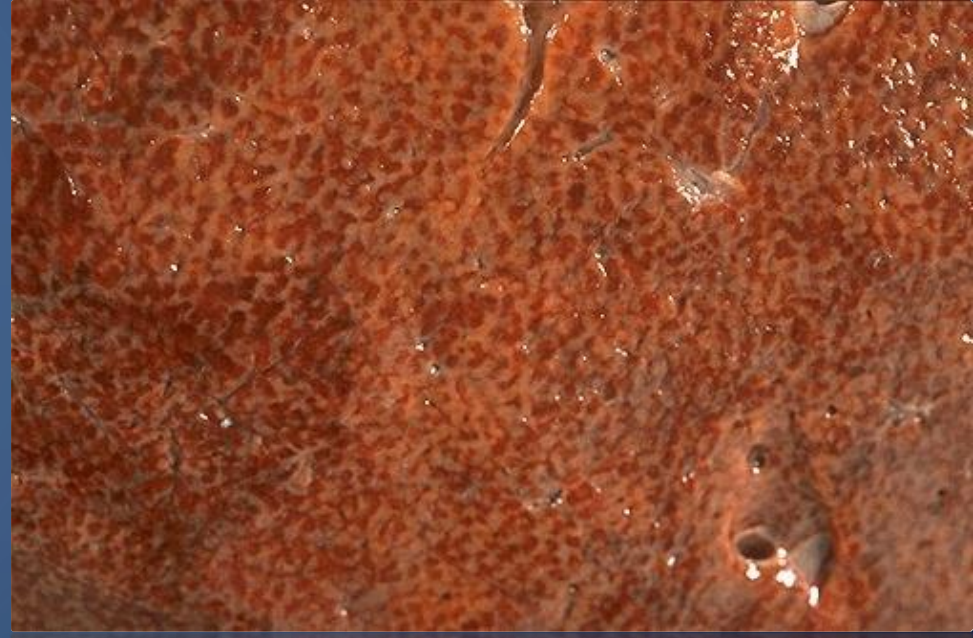
-1 mg of E2V is equivalent to 0.76 mg of E2.

Contraception
an international reproductive health journal

Fruzzetti F et Bitzer J.
Review of clinical experience with estradiol in combined oral contracepives.
Contraception 2010;81:8-15

Impatto epatico

Per il suo radicale etinilico, l'etinil-estradiolo compie molti passaggi epatici.
L'effetto dell'etinil-estradiolo su alcune proteine epatiche è fino a 500-600 volte maggiore dell'estradiolo.



Relative potency of estrogens

Estrogen	FSH	SHBG	CBG	Angiotensinogen
17β-E2	1	1	1	1
EE	120	600	500	350

Contraception
an international reproductive health journal

Fruzzetti F & Bitzer J.
Review of clinical experience with estradiol in combined oral contracepives.
Contraception 2010;81:8-15

Effetto biologico di EE vs E2

- The biological effects of E2V Vs EE can be compared only at specific target-organs level.

Biological effect	E2V effect versus EE effect
Suppression of FSH and ovulation inhibition	E2V 2mg = EE 20 µg
Endometrial stimulation	E2V 2mg = EE 20 µg
Maturation of vaginal epithelium cells	E2V 2mg slightly > EE 20 µg

Contraception
an international reproductive health journal

Endrikat J et al. Contraception 2008; 78: 218-25
Wiegratz I et al. Contraception 2004; 70: 97-106

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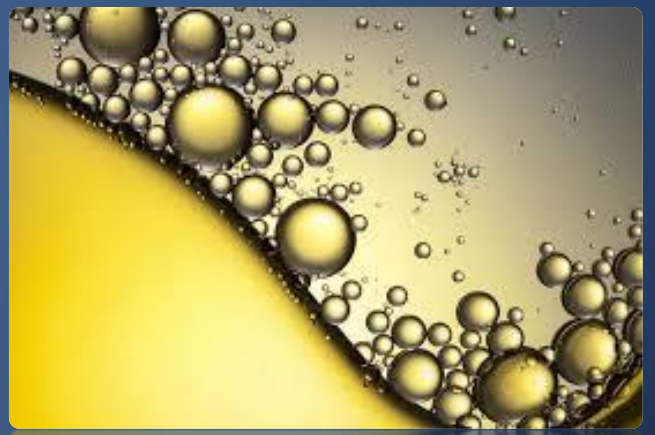


Ipertrigliceridemia
Basso HDL
Iperglicemia

COC e metabolismo glico-lipidico

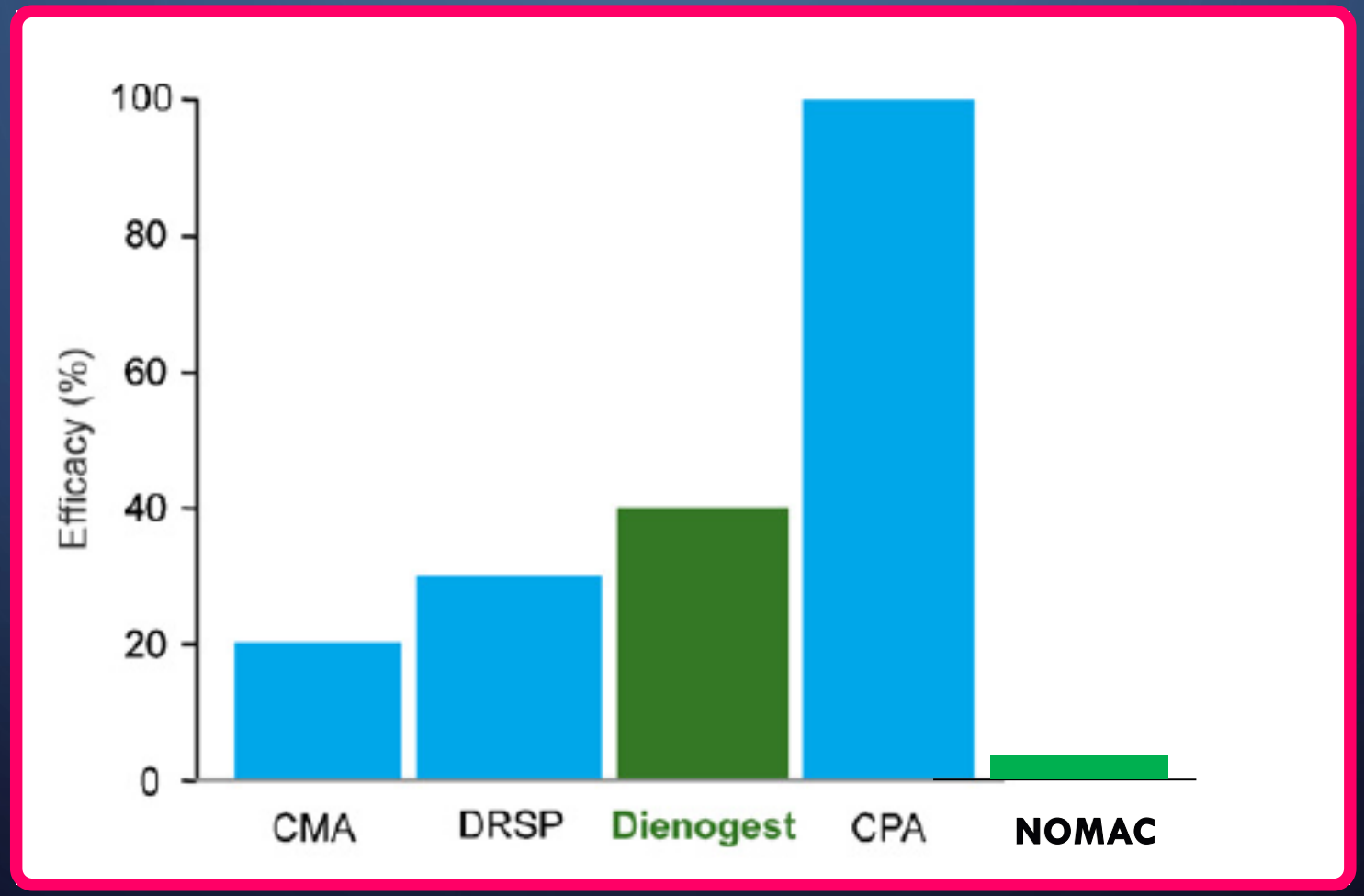
- The effect of a COC on lipid metabolism depends upon the **relative balance between the estrogen and androgen activity of the compound.** Estrogen-balanced COCs tend to decrease LDL-cholesterol and to increase HDL-cholesterol and triglycerides. The opposite occurs with androgen-balanced COCs.

- COCs with **androgenic progestins are also believed to reduce insulin sensitivity (SI).**

Wahl P et al.
Effects of estrogen/progestin potency on lipid/lipoprotein cholesterol.
N Engl J Med 1983; 308:862-7

1928 LAND·JOURNAL
NEJM

Attività anti-androgenica dei progestinici



E2V-DNG vs EE/LNG e metabolismo lipidico

METHODS:

In a randomized, open-label study conducted in Germany over seven cycles, healthy women aged 18-50 years received E(2)V/DNG (E(2)V 3 mg on days 1-2, E(2)V 2 mg/DNG 2 mg on days 3-7, E(2)V 2 mg/DNG 3 mg on days 8-24, E(2)V 1 mg on days 25-26, placebo on days 27-28; n = 30) or EE/LNG (EE 0.03 mg/LNG 0.05 mg on days 1-6, EE 0.04 mg/LNG 0.075 mg on days 7-11, EE 0.03 mg/LNG 0.125 mg on days 12-21, placebo on days 22-28; n = 28). The primary variables were the mean intraindividual relative changes from baseline to cycle 7 in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels. Changes in other lipid parameters, haemostatic parameters, sex hormone-binding globulin (SHBG), cortisol-binding globulin (CBG), carbohydrate metabolism parameters, blood pressure and body weight were also assessed.

RESULTS:

Mean ± SD HDL cholesterol increased by 7.9% ± 21.8% with E(2)V/DNG and decreased by 2.3% ± 14.4% with EE/LNG. Mean ± SD LDL cholesterol decreased by 6.5% ± 15.9% with E(2)V/DNG and by 3.0% ± 17.4% with EE/LNG. Mean ± SD prothrombin fragment 1 + 2 and D-dimer levels remained essentially unchanged in the E(2)V/DNG group (-0.6% ± 30.3% and -2.1% ± 43.5%, respectively), but increased in the EE/LNG group (by 117.3% ± 358.0% and 62.9% ± 99.5%, respectively). Changes in other hepatic-induced parameters (SHBG, CBG) and carbohydrate metabolism were generally less pronounced with E(2)V/DNG versus EE/LNG. Body weight and blood pressure remained stable throughout the study in both treatment groups. Both formulations were well tolerated, with no serious adverse events reported.

CONCLUSION:

E(2)V/DNG had a minimal impact on metabolic and haemostatic parameters, and a more favourable effect than EE/LNG on lipid markers.

Junge et al, Clin Drug Investig 2011;31:573-84

E2V/DNG vs EE/CMA e metabolismo lipidico

ORIGINAL ARTICLE

Modification of body composition and metabolism during oral contraceptives containing non-androgenic progestins in association with estradiol or ethinyl estradiol

Giovanni Grandi, Ilaria Piacenti, Annibale Volpe, and Angelo Cagnacci

Department of Obstetrics Gynecology and Pediatrics, Obstetrics and Gynecology Unit, Azienda Policlinico of Modena, Modena, Italy

Gynecol Endocrinol 2014;30:676-80

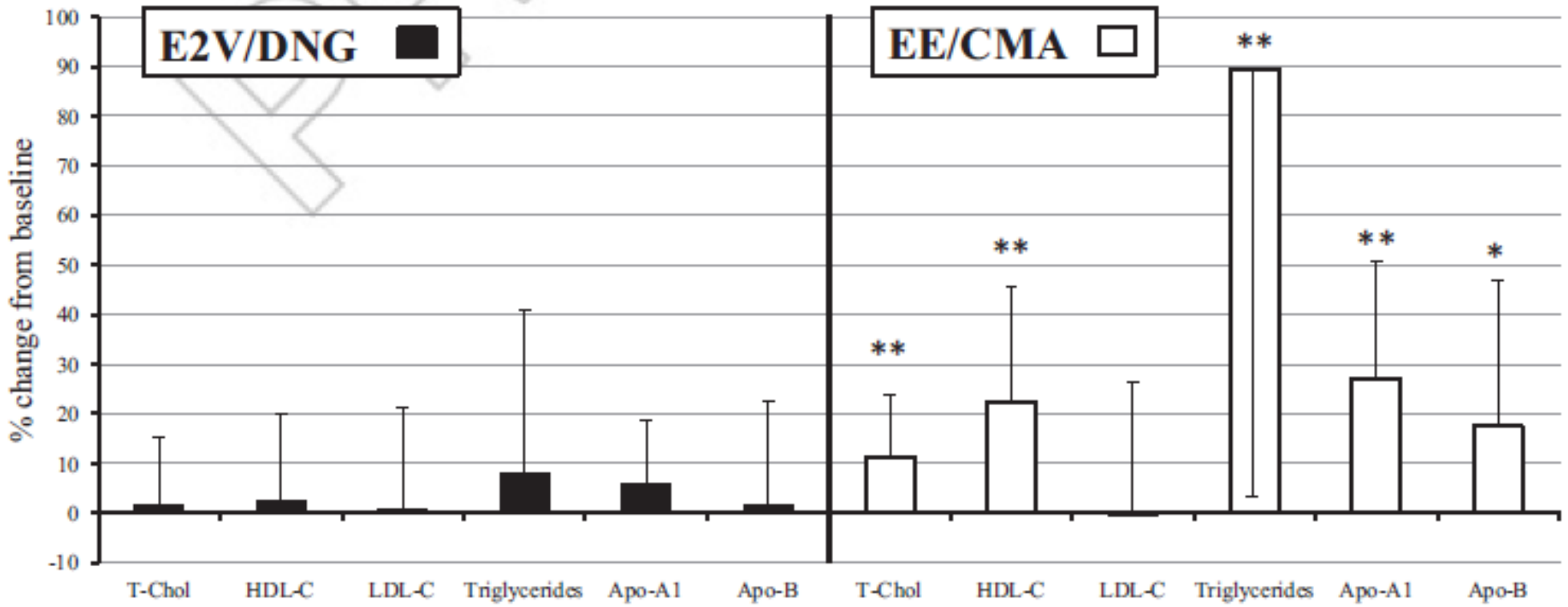
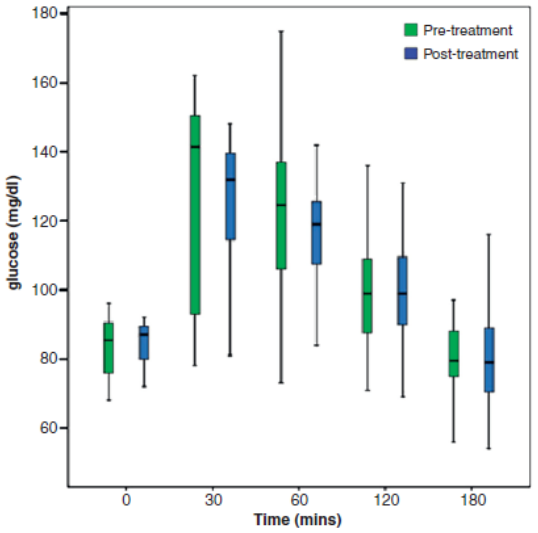
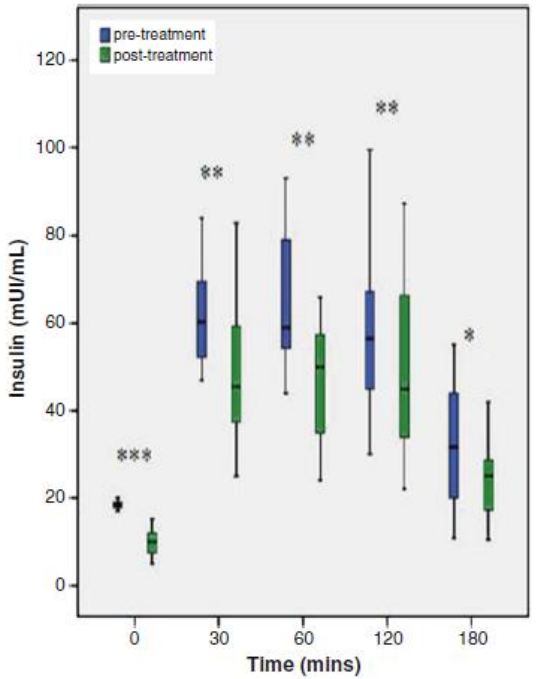
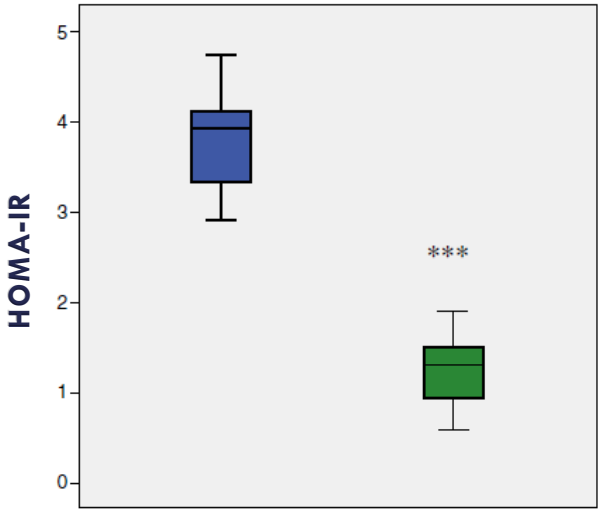


Figure 1. Mean (±SD) percent change from baseline to cycle three in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, Apo-A1 and Apo-B in women treated with estradiol valerate/dienogest (E2V/DNG) or ethinyl estradiol/chlormadinone acetate (EE/CMA). $*p<0.05$; $**p<0.01$ versus basal.

E2V/DNG e metabolismo glucidico







Contraception
an international reproductive health journal

De Leo V et al,
Contraception 2013:88;364-368

	E2V/DNG ($n = 16$)		
	Before	During	p
Glucose, mmol/L	4.92 ± 0.49	4.94 ± 0.41	0.717
Insulin, pmol/L	34.68 ± 17.40	41.40 ± 19.68	0.650
HOMA-IR	1.13 ± 0.69	1.18 ± 0.69	0.642

Grandi G et al,
Gynecol Endocrinol 2014;30:676-80

GYNECOLOGICAL ENDOCRINOLOGY

Sindrome metabolica

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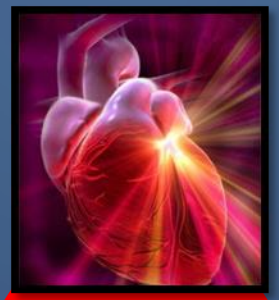
- Ipertensione arteriosa (>130 mmHg di sistolica e >85 mmHg di diastolica), oppure trattamento farmacologico in atto

Ipertensione

Rischio cardiovascolare



Versante venoso

- Trombosi venosa profonda

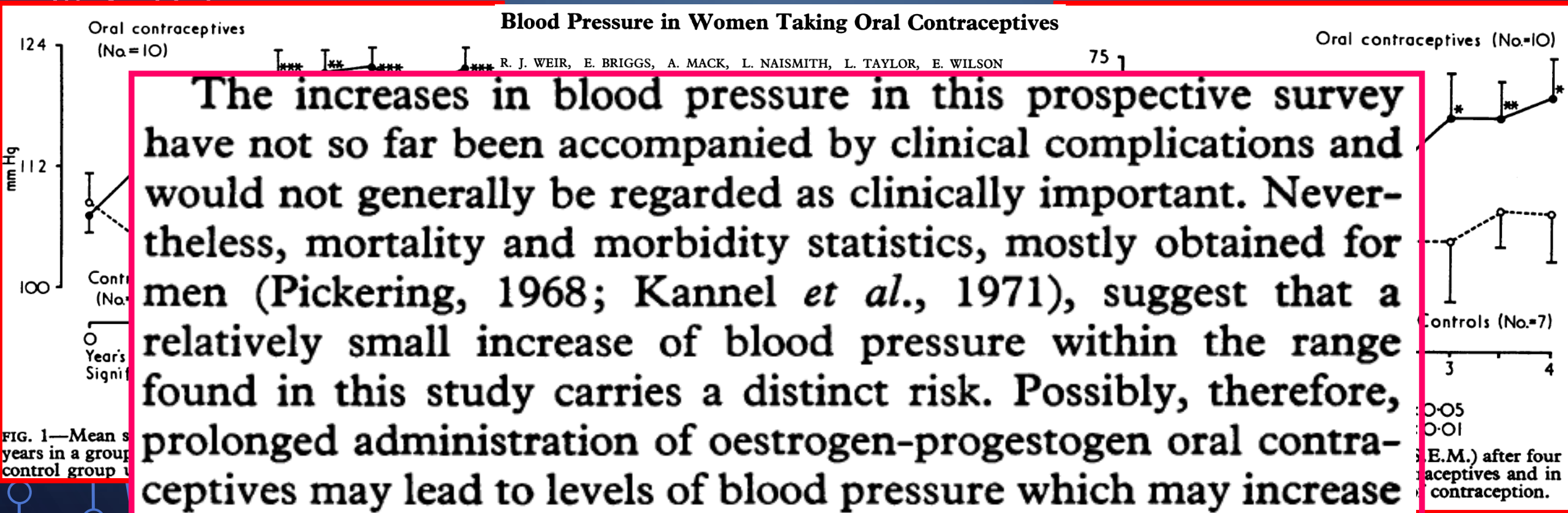
Versante arterioso

- Ictus trombotico
- Infarto del miocardio

Farley TMM et al. Hormonal contraception and risk of cardiovascular disease. Contraception 1998; 57: 211-230

Contraception
an international reproductive health journal

Estrogeni di sintesi e PA



Blood Pressure in Women Taking Oral Contraceptives

R. J. WEIR, E. BRIGGS, A. MACK, L. NAISMITH, L. TAYLOR, E. WILSON

Oral contraceptives (No.=10)

124

112

100

mm Hg

75

Oral contraceptives (No.=10)

Controls (No.=7)

3

4

FIG. 1—Mean s
years in a group
control group

E.M.) after four
aceptives and in
contraception.

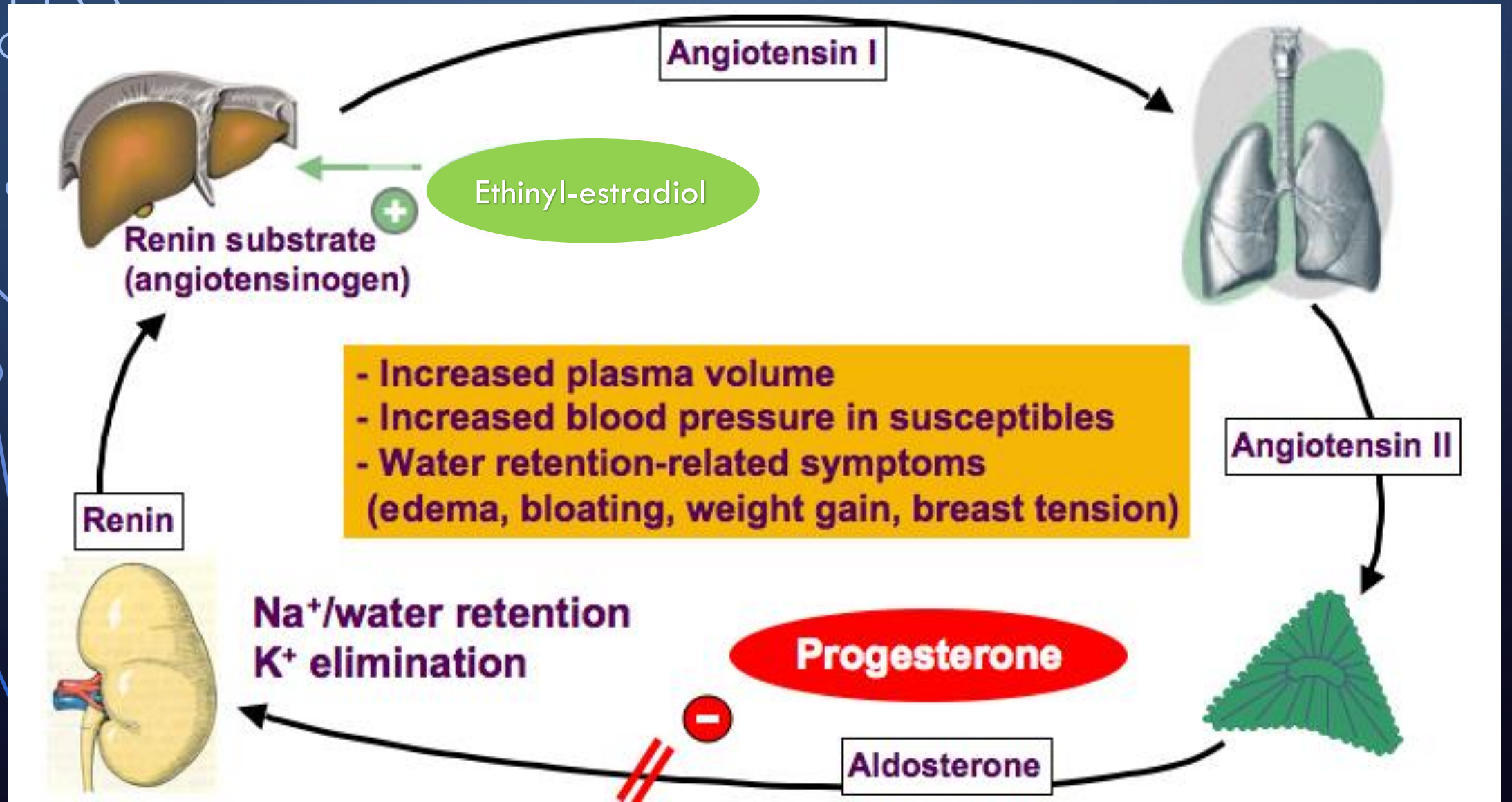
O·05
O·01

The increases in blood pressure in this prospective survey have not so far been accompanied by clinical complications and would not generally be regarded as clinically important. Nevertheless, mortality and morbidity statistics, mostly obtained for men (Pickering, 1968; Kannel *et al.*, 1971), suggest that a relatively small increase of blood pressure within the range found in this study carries a distinct risk. Possibly, therefore, prolonged administration of oestrogen-progestogen oral contraceptives may lead to levels of blood pressure which may increase morbidity and affect life expectancy.

and 8·5 mm Hg respectively after four years. The largest increases in individual cases were 36 mm Hg systolic and 20 mm Hg diastolic. Blood pressure returned to pre-treatment levels within three months after oral contraceptives had been stopped. These changes in blood pressure were unrelated to the progestogenic potencies of the preparations being taken.

BMJ
British Medical Journal

Estrogeni – Progesterone e regolazione PA

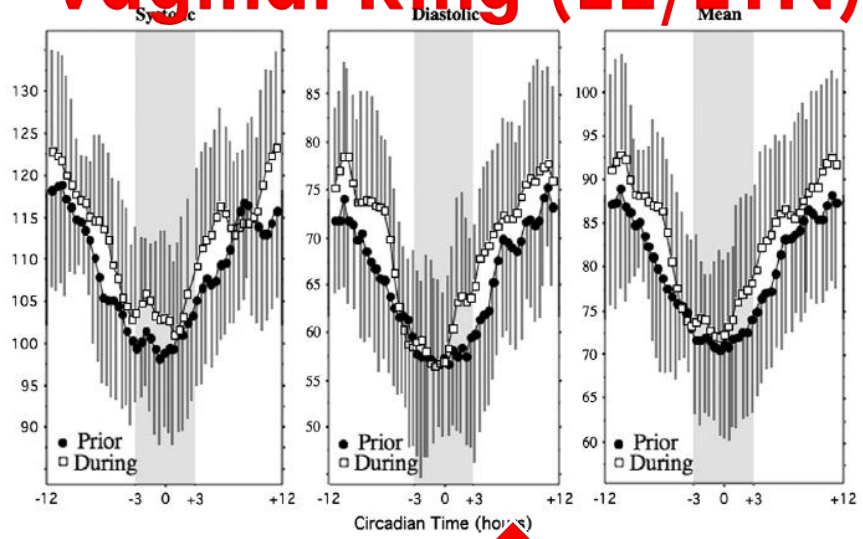


PA e anello vaginale

Cagnacci A et al,
Contraception 2013;88:539-43

Contraception
an international reproductive health journal

Vaginal Ring (EE/ETN)



24 h diastolic PA

24 h mean PA

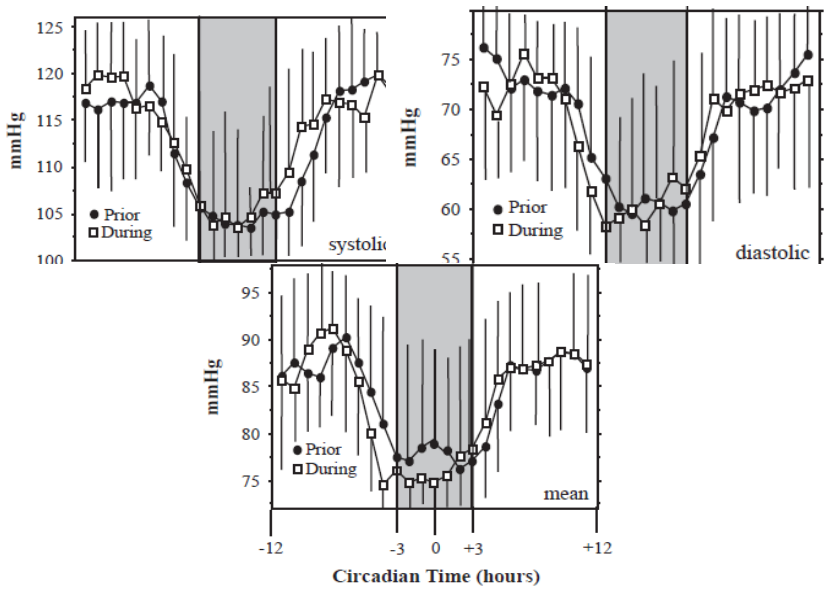
24 h heart rate

PA e EE/DRSP COC

Cagnacci A et al, Contraception 2013; 88:413-17

Contraception
an international reproductive health journal

30 mcg EE/3 mg DRSP

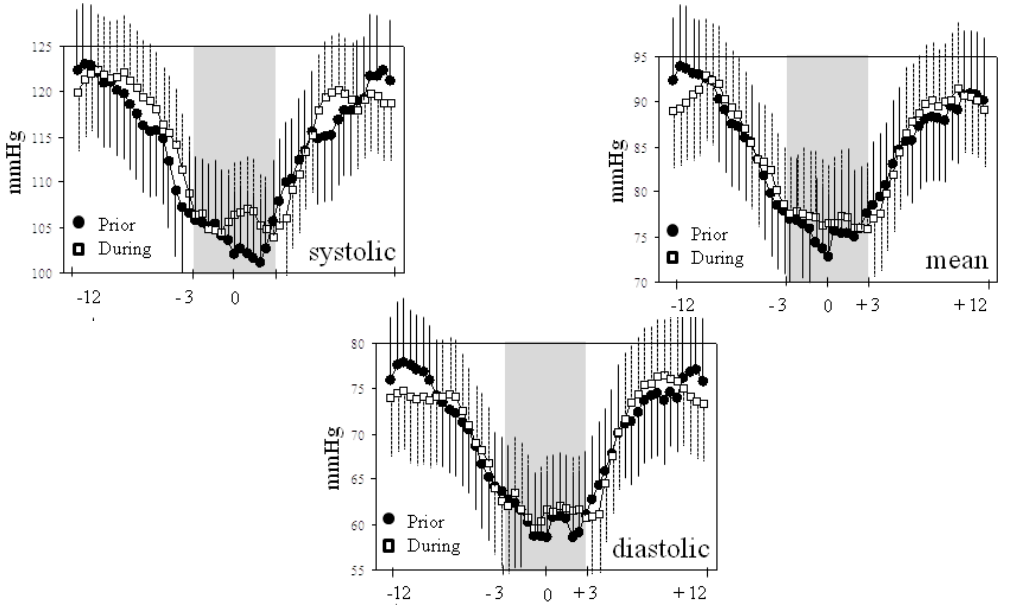


No modification of 24 h PA

↑ **24 h heart rate**

PA e E2V/E2 COC

E2V or E2 based COCs



No modification of 24 h PA

No modification of 24 h heart rate

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Grandi G et al,
Contraception 2014;90:529-34

PA e E2V/DNG vs E2/NOMAC

	E2V/DNG (n=11)				E2/NOMAc (n=7)				Between-group
	Before	During	Net	p	Before	During	Net	p	p
24 h									
Systolic BP (mmHg)	113.09±6.94	114.91±9.47	1.82±9.63	.544	113.45±8.23	114.84±9.19	1.39±6.53	.594	.918
Diastolic BP (mmHg)	69.06±5.96	69.39±10.5	0.33±8.43	.902	69.05±7.99	68.65±8.45	−0.40±5.89	.862	.846
Mean (mmHg)	84.22±5.08	85.35±8.41	1.13±7.41	.624	83.75±8.01	83.62±8.19	−0.13±4.91	.950	.699
HR (beats/min)	74.53±6.20	73.36±8.71	−1.17±6.54	.567	75.12±1.93	75.11±4.88	−0.01±5.01	.994	.697
Daytime									
Systolic BP (mmHg)	116.07±6.88	117.85±9.45	1.78±9.53	.549	117.61±9.20	116.83±8.85	−0.78±5.56	.724	.531
Diastolic BP (mmHg)	71.93±5.89	72.16±10.56	0.22±8.32	.931	72.64±9.13	71.40±8.82	−1.24±7.53	.679	.712
Mean (mmHg)	87.08±4.70	88.25±8.64	1.17±7.28	.606	87.35±9.09	85.94±8.23	−1.41±5.77	.542	.441
HR (beats/min)	78.53±8.57	77.77±10.69	−0.76±9.02	.787	80.76±4.25	78.72±8.11	−2.04±6.02	.404	.745
Nighttime									
Systolic BP (mmHg)	104.83±7.70	106.77±10.09	1.95±10.22	.542	101.95±6.98	104.15±10.88	2.19±6.26	.391	.956
Diastolic BP (mmHg)	61.14±7.31	61.90±10.89	0.76±9.55	.797	59.14±5.63	61.05±8.91	1.91±5.74	.412	.779
Mean (mmHg)	76.77±8.25	77.41±8.99	0.64±9.43	.827	73.77±6.02	75.85±8.67	2.08±5.11	.322	.717
HR (beats/min)	71.13±5.08	69.98±7.48	−1.16±4.58	.421	69.82±4.23	70.63±3.95	0.82±5.45	.706	.687

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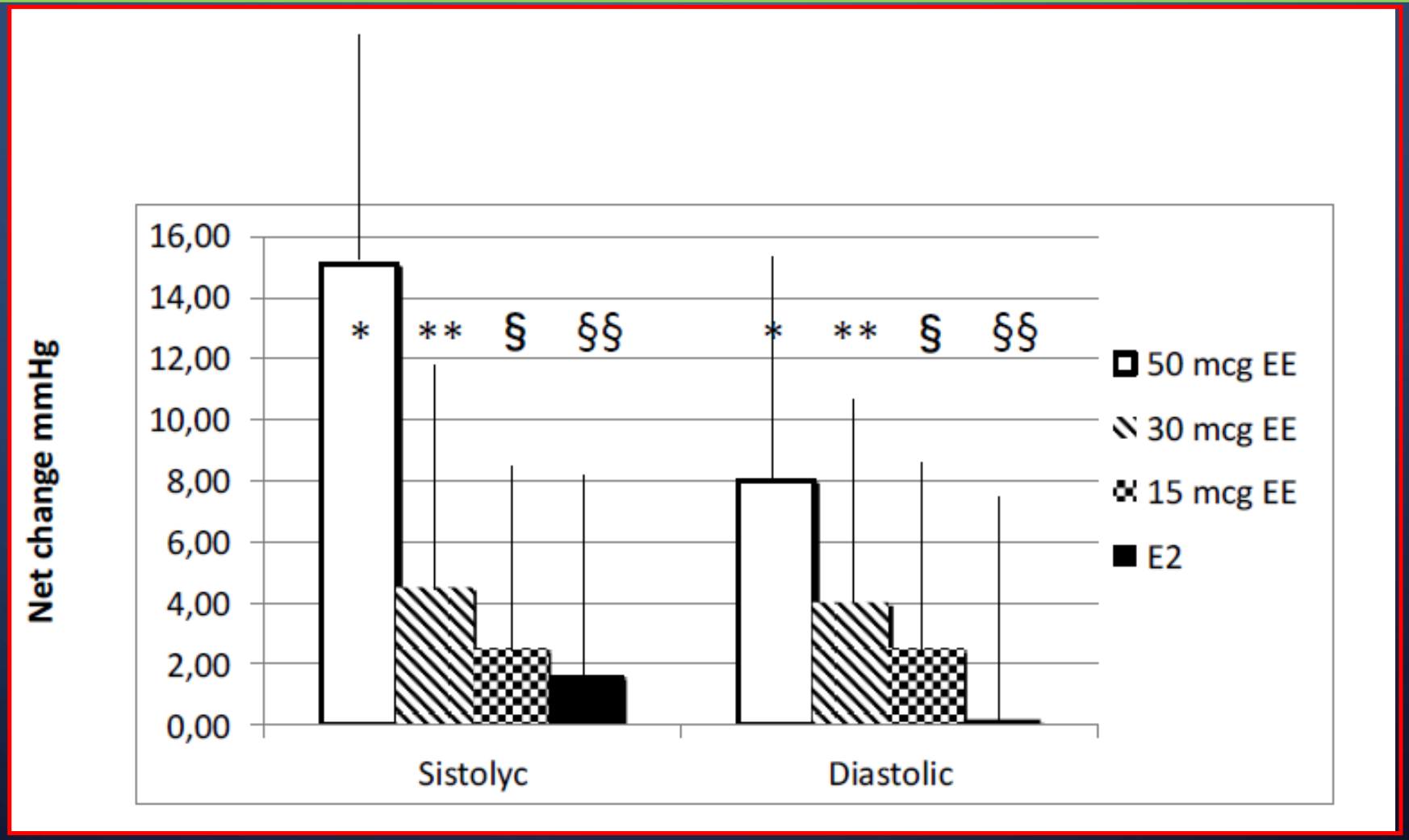
Grandi G et al, Contraception 2014;90:529-34

Pressione arteriosa ed evoluzione estrogenica



Grandi G, Napolitano A, Cagnacci A.
Exp Opinion Drug Metab Toxicol 2016

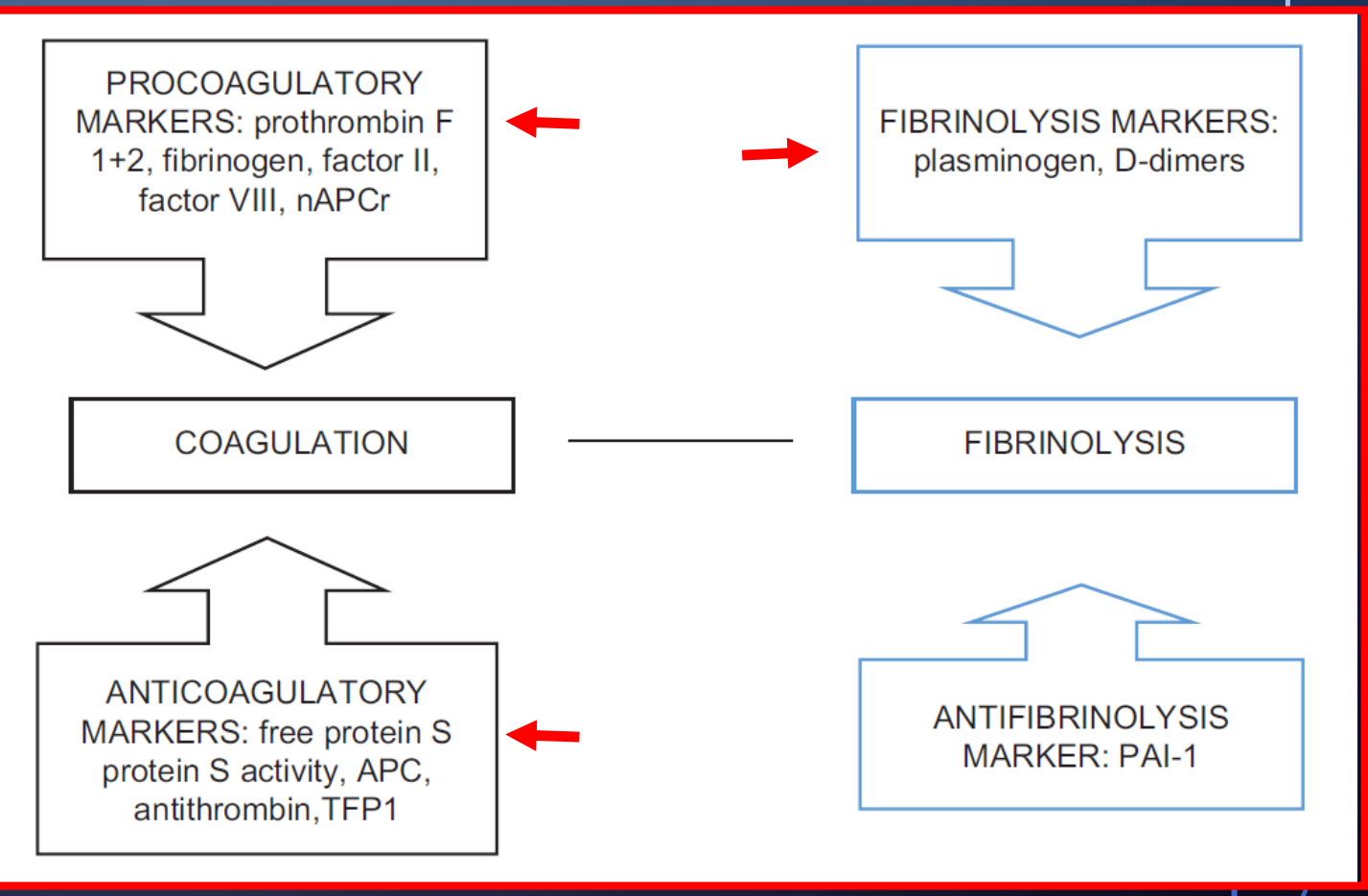
COCs ed emostasi

Table 2 Haemostatic changes during COC use (adapted from reference 17).

Factor	*Change during COC use*
Procoagulant factors	
Fibrinogen, V, VII, VIII, IX, X, XII	↑
XI	= or ↑
von Willebrand factor	=
Anticoagulant proteins	
Antithrombin	↓
Protein C	= or ↑
Protein S	↓
Resistance to APC	↑
Markers of thrombin formation	
F 1 + 2, TAT, fibrinopeptide A, D-dimer	↑
Fibrinolytic factors	
TAFI, PAI-1, PAI-2, t-PA	↑ ↓

↑, increase; ↓, decrease; =, no change (vs. non-use of COCs).

TAT, thrombin–antithrombin complex; TAFI, thrombin-activatable fibrinolysis inhibitor; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator.



Lete I et al, Eur J Contracept Reprod HealthCare 2015; 2015;20:329-43.

E2 e markers procoagulativi

Table 3 Effects of E_2-based COCs (E_2V/DNG and E_2/NOMAC) and DRSP-containing COCs on haemostasis, lipid and carbohydrate metabolism. EE/LNG was used as the comparator.

Marker	*EE/DRSP*[54]	*E_2V/DNG*[48,49]	*E_2/NOMAC*[33,50]
Haemostatic markers			
F 1 + 2	–	NS	↓*
D-dimer	–	↓*†	↓*‡
APC ratio	–	NS	↓*
Protein S (activity)	–	NS	NS

Lete I et al, Eur J Contracept Reprod HealthCare 2015;20:329-43.

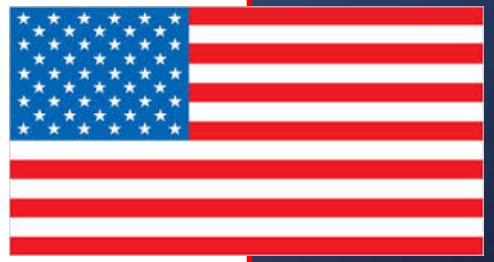
ELSEVIER

Contraception 94 (2016) 328–339

Contraception

Original research article

Impact of estrogen type on cardiovascular safety of combined oral contraceptives☆,☆☆,★



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Received 14 March 2016; revised 14 June 2016; accepted 17 June 2016

Abstract

Objectives: The International Active Surveillance study "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) investigated the cardiovascular risks associated with the use of a combined oral contraceptive (COC) containing dienogest and estradiol valerate (DNG/EV) compared to established COCs in a routine clinical setting.

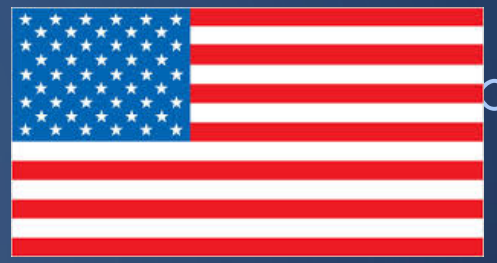
Study Design: Transatlantic, prospective, noninterventional cohort study conducted in the United States and seven European countries with two main exposure groups and one exposure subgroup: new users of DNG/EV and other COC (oCOC), particularly levonorgestrel-containing COCs (LNG). All self-reported clinical outcomes of interest (OoI) were validated via attending physicians and relevant source documents. Main OoI were serious cardiovascular events (SCE), particularly venous thromboembolic (VTEs) events. Comprehensive follow-up procedures were implemented. Statistical analyses were based on Cox regression models.

Results: A total of 50,203 new COC users were followed up for up to 5.5 years (mean value, 2.1 years). Overall 20.3% and 79.7% of these women used DNG/EV and oCOC (including 11.5% LNG users), respectively. A low loss to follow-up of 3.1% was achieved. Based on 47 (VTE) and 233 (SCE) events, the primary analysis (European data set) yielded adjusted hazard ratios for DNG/EV vs. oCOC of 0.4 and 0.5, respectively. The upper bounds of the 95% confidence intervals were 0.98 (VTE) and 0.96 (SCE). The corresponding hazard ratios for DNG/EV vs. LNG showed similar point estimates but the confidence intervals included unity.

Conclusion: DNG/EV is associated with similar or even lower cardiovascular risk compared to oCOC and LNG.

Implication Statement: A COC containing DNG and EV is associated with similar or even lower cardiovascular risk compared to COCs containing levonorgestrel or other progestogens.

INAS-SCORE



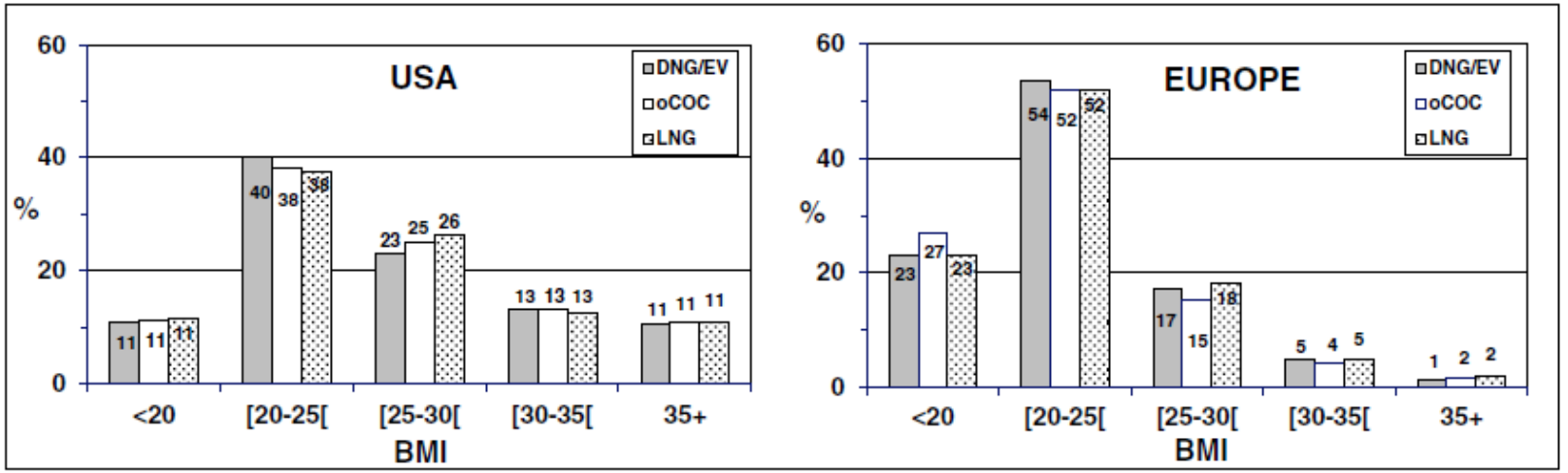


Fig. 2. Mean BMI by cohort and region.

Table 4
VTE events: number, incidence and 95% CIs per exposure group.

Data set	DNG/EV		oCOC		LNG		OHC		No use		Total
	n	Incidence[a] (95% CI)	*n*	Incidence[a] (95% CI)	*n*	Incidence[a] (95% CI)	*n*	Incidence[a] (95% CI)	*n*	Incidence[a] (95% CI)	*n*
USA and Europe (confirmed VTE)	9	7.2 (3.3–13.7)	58	9.1 (6.9–11.8)	10	9.9 (4.8–18.3)	1	2.3 (0.1–13.0)	9	3.5 (1.6–6.7)	77

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Dinger JC et al Contraception 2016;94:328-339

INAS-SCORE

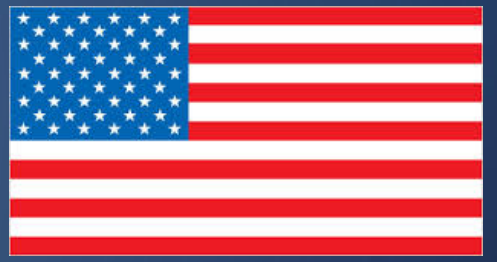

Table 5
VTE incidence rates, HR_{crude} and HR_{adj}, and 95% CIs.

Data set	Exposure	Incidence (events/10,000 WY)		HR (DNG/EV vs. comparators)			
		Point estimate	95% CI	Crude estimate	95% CI	Adjusted[a] estimate	95% CI
USA and Europe (confirmed VTE)	DNG/EV	7.2	3.3–13.7	–	–	–	–
	oCOC	9.1	6.9–11.8	0.8	0.4–1.6	0.5	0.2–1.0
	LNG	9.9	4.8–18.3	0.7	0.3–1.8	0.5	0.2–1.3
Europe							
Confirmed VTE (primary analysis)	DNG/EV	7.4	3.4–14.1	–	–	–	–
	oCOC	8.3	5.7–11.7	0.9	0.4–1.8	0.4	0.2–1.0[b]
	LNG	8.2	3.0–17.9	0.8	0.3–2.4	0.5	0.2–1.5
Confirmed and potential VTE	DNG/EV	9.1	4.5–16.2	–	–	–	–
	oCOC	10.4	7.4–14.0	0.8	0.4–1.6	0.5	0.3–1.0[b]
	LNG	9.6	3.9–19.8	0.9	0.3–2.3	0.5	0.2–1.5

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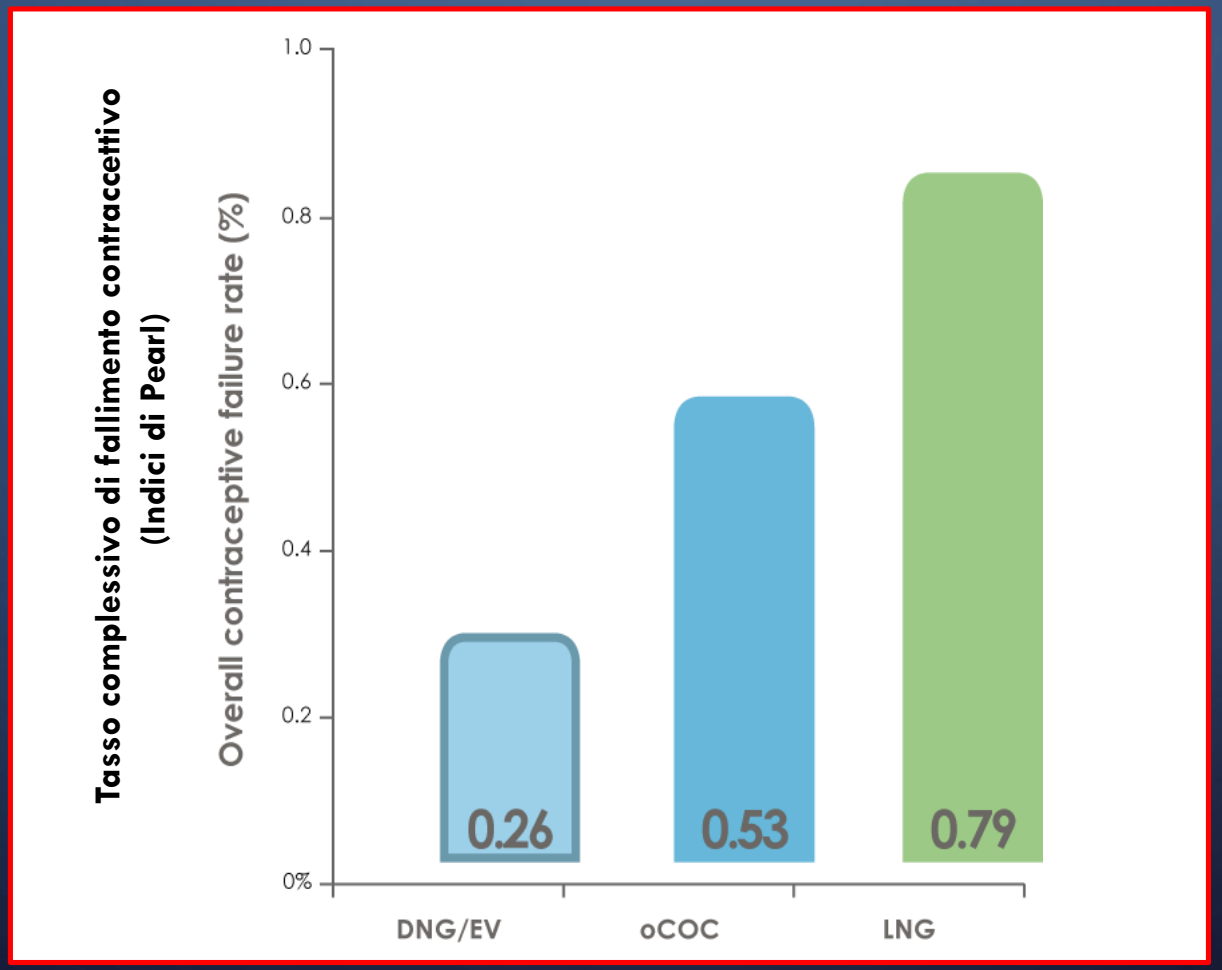
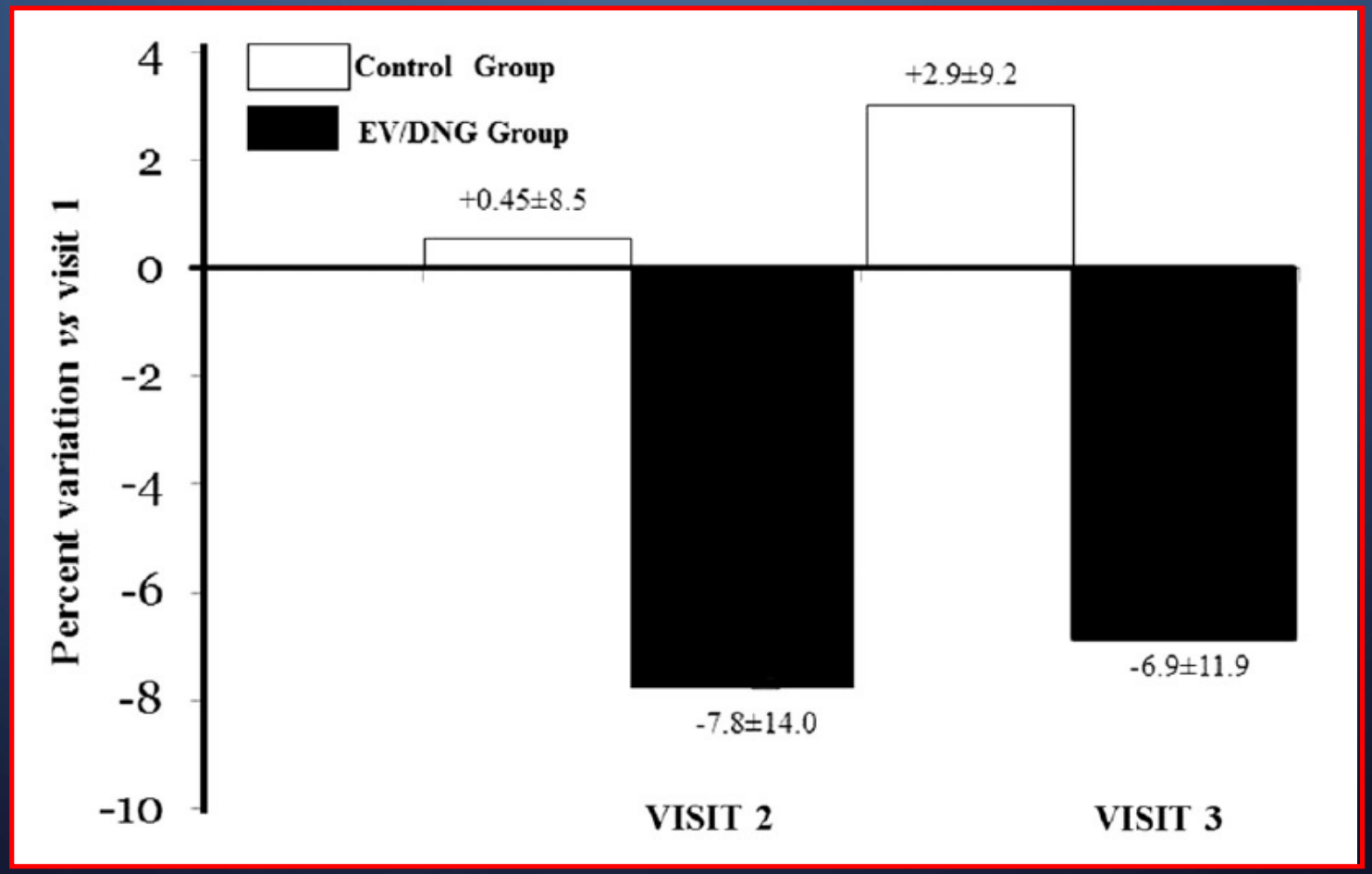
Dinger JC et al Contraception 2016;94:328-339

INAS-SCORE Efficacia contraccettiva



Barnett C et al Eur J Contracept Reprod HealthCare 2017;22:17-23

E2V/DNG e transizione menopausale



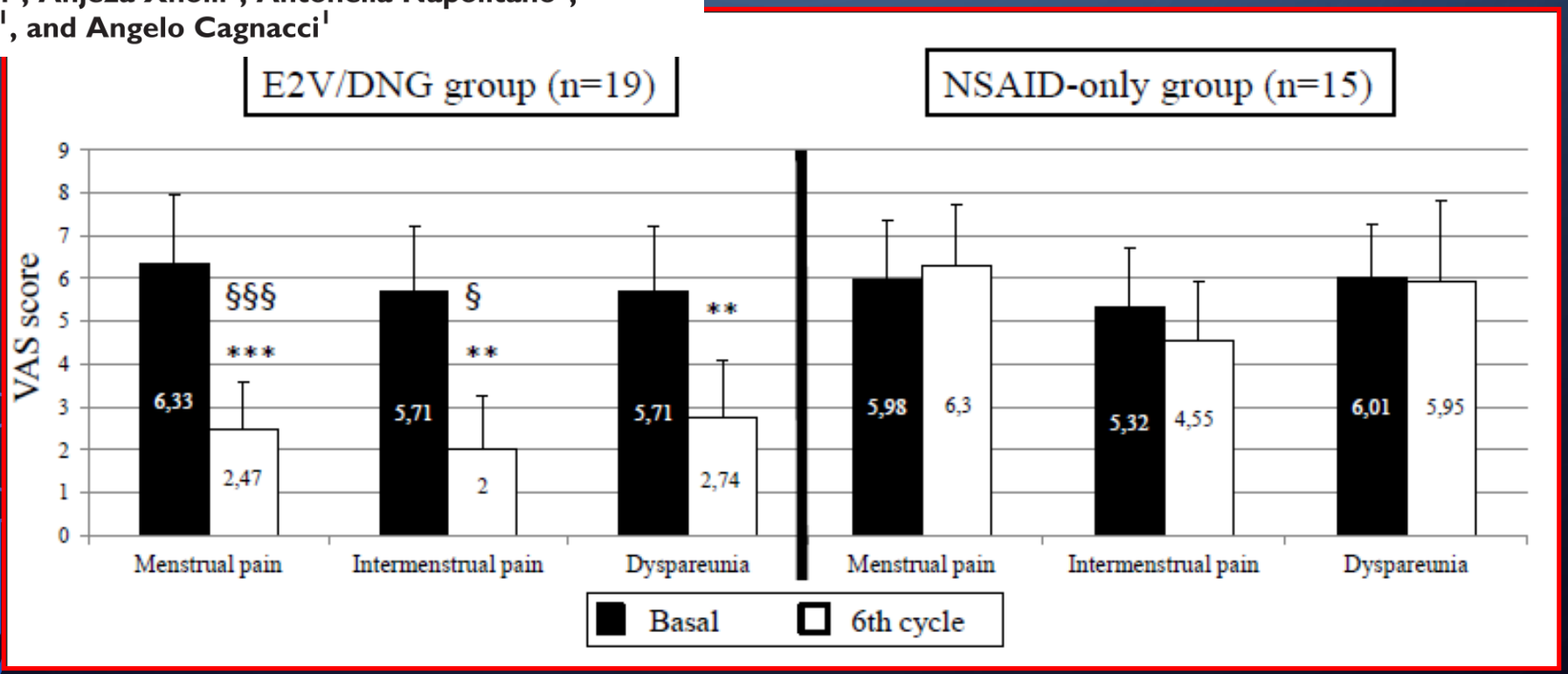
Paoletti A et al, Gynecol Endocrinol 2016;32:61-4

Endometriosi – Dolore pelvico

Pelvic Pain and Quality of Life of Women With Endometriosis During Quadriphasic Estradiol Valerate/Dienogest Oral Contraceptive. A Patient-Preference Prospective 24-Week Pilot Study

Giovanni Grandi[1], Anjeza Xholli[1], Antonella Napolitano[1], Federica Palma[1], and Angelo Cagnacci[1]

Reprod Sciences 2015;22:626-32



Endometriosi
Qualità di vita

Pelvic Pain and Quality of Life of Women With Endometriosis During Quadriphasic Estradiol Valerate/Dienogest Oral Contraceptive. A Patient-Preference Prospective 24-Week Pilot Study

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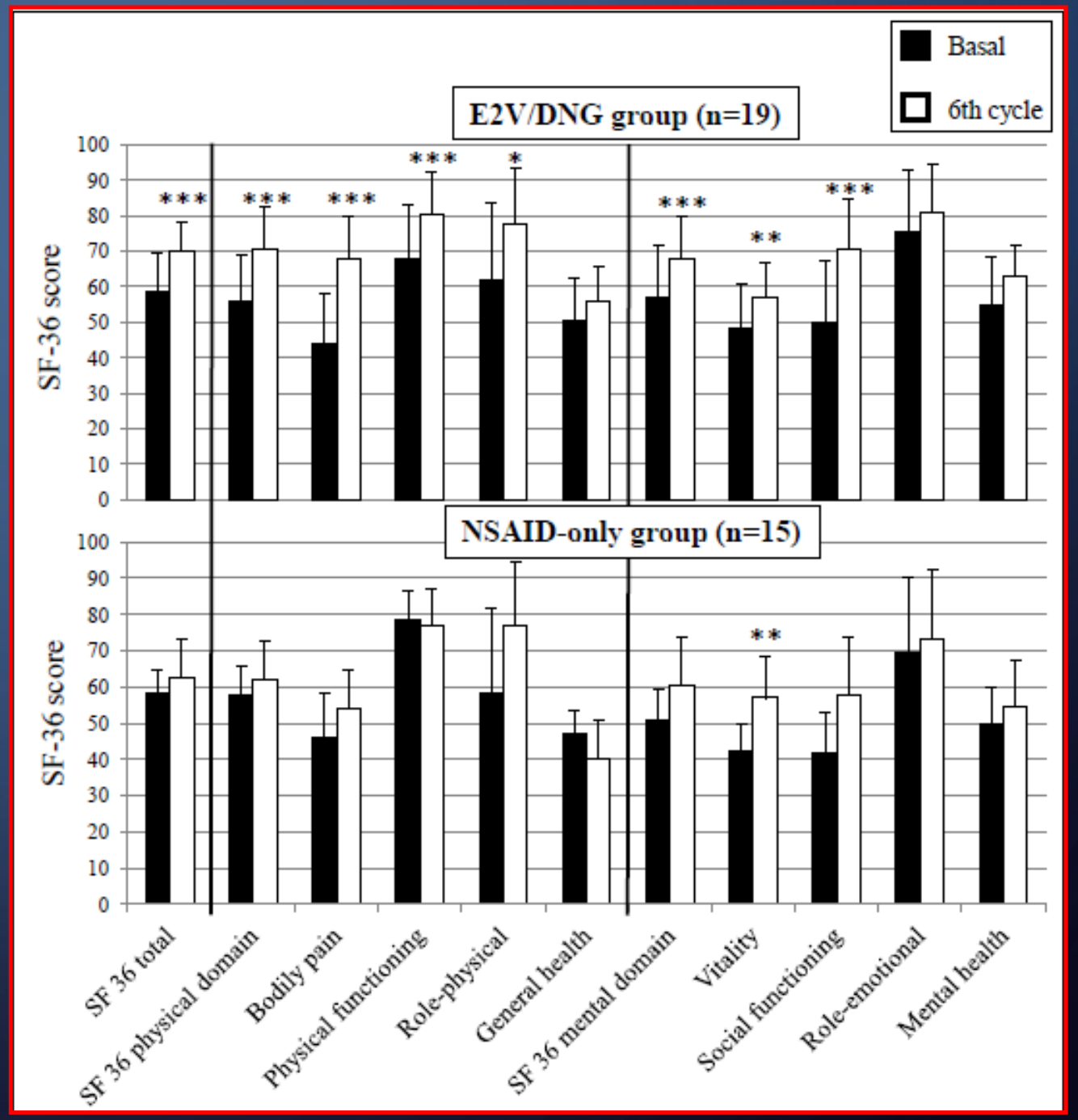
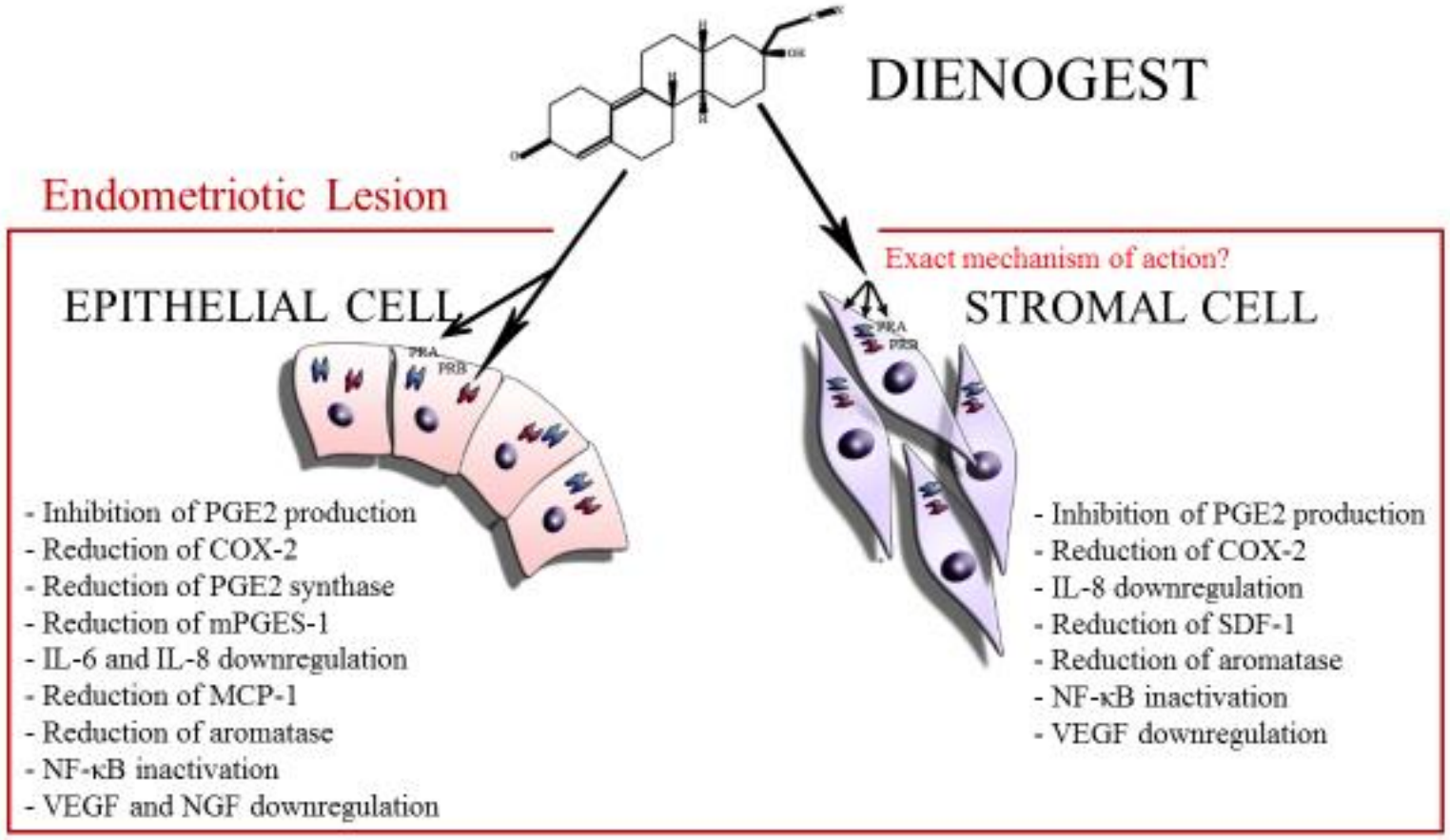


Dienogest ed effetto anti-infiamatorio

Does dienogest influence the inflammatory response of endometriotic cells? A systematic review

Giovanni Grandi[1,3] · Michael Mueller[2,3] · Nick A. Bersinger[2,3] · Angelo Cagnacci[1] · Annibale Volpe[1] · Brett McKinnon[2,3]

Inflamm Res 2016;65:183-192



E2-NOMAC Vs E2V/DNG 2012-2017?

L'estradiolo in contraccezione ormonale

- Estradiol 1.5 mg/ Nomegestrol Acetate 2.5 mg
  monophasic regimen (24+4)

- Estradiol Valerate/Dienogest
  quadriphasic regimen (26+2)

Grandi G, Facchinetti F.
News of Women's Health 2016;dicembre

Tabella 1. Similarità e differenze dal punto di vista clinico dei contraccettivi a base di estradiolo (E2) o del suo estere estradiolo valerato (E2V) presenti in commercio.
+ vantaggio (considerando i dati esistenti in letteratura e la plausabilità farmacologica); – nessun vantaggio, non dati positivi.

	E2/NOMAc (monofasico)	E2/DNG (quadrifasico)
Effetto neutro su lipidi, glucidi ed SHBG	+++	+++
Rischio di accumulo (in caso di ridotta eliminazione)	+++	+
Attività progestazionale	+++	+++
Attività anti–gonadotropinica	+++	+
Attività glucorticoide	–	–
Attività mineralocorticoide	–	–
Attività anti–androgenica	+	+++
Efficacia contraccettiva in caso di compresse dimenticate	+++	–
Possibilità di regimi continuativi	+++	+
Possibilità di non avere sanguinamento da sospensione	+	+

Estradiolo naturale:
Una possibile soluzione del problema

Rischio tromboembolico

Estrogeno

Potenza estrogenica

Progestinico

Potenza androgenica

Rischio arterioso
Metabolismo glico-lipidico

Estradiolo naturale:
Una possibile soluzione del problema

Estrogeno	Progestinico
Potenza estrogenica	Potenza androgenica