

La contraccezione in perimenopausa

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The Stages of Reproductive Aging in women

Menarche — FMP (0)

Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67–69]

Harlow et al., CLIMACTERIC 2012;15:1–10

ISSUES IN WOMEN OVER 40 YRS

Health problems:

- Menorrhagia
- Irregular bleedings
- PMS
- Bone loss
- Fibroids
- Increase of cancer risk

Contraceptive needs:

- Delayed childbearing
- High abortion rate
- Chromosomal abnormalities

Goals for Contraception in women over 40 years

- Prevention of pregnancy
- Impact hormonal fluctuations associated with perimenopause
- Provide additional noncontraceptive benefits

Raccomandazioni per l'uso di contraccettivi in donne di età riproduttiva avanzata

Organizzazione	Raccomandazione
American college of Obstetricians and Gynecologists	Continuare CHCs fino a 50-55 yrs
American Society for Reproductive Medicine	Uso fino a 12 mesi dopo la ultima mestruazione se la donna vuole evitare la gravidanza
CDC	Da usare >44 se la donna vuole evitare la gravidanza
North American Menopause Society	Uso fino a 1 aa dopo ultima mestruazione se la donna vuole evitare la gravidanza

Attenzione generale alle condizioni mediche

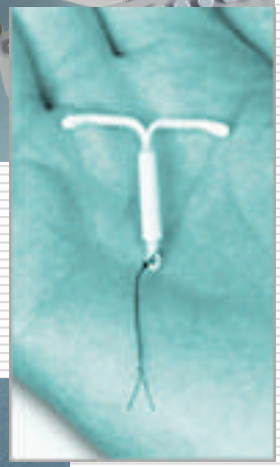
www.cdc.gov/reproductive health/contraception/contraception_guidance.htm

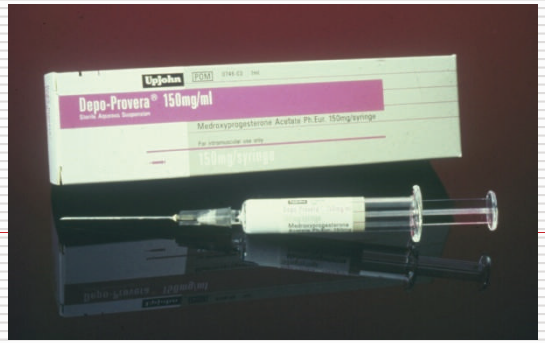
Shifren JL, 2014; Lichtmacher A, 2014; Curtis KM, 2016

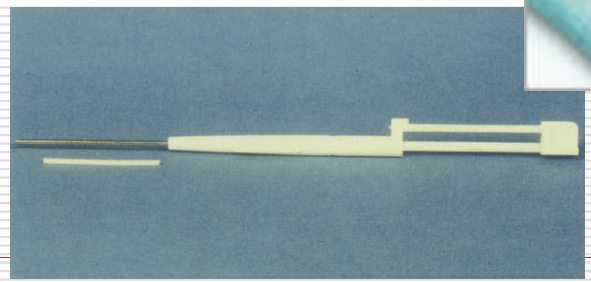
I contraccettivi ormonali

- La pillola EP
- Il cerotto EP
- L'anello vaginale EP
- la pillola P
- L’impianto P sottocutaneo
- La spirale a rilascio di P









Medical Eligibility Criteria for Contraceptive Use, 2010

BOX 1. Categories of medical eligibility criteria for contraceptive use

1 = A condition for which there is no restriction for the use of the contraceptive method.
2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

U.S. Medical Eligibility Criteria for Contraceptive Use, June 18, 2010 / Vol. 59 / No. RR-4

COCs: Who Should Not Use (WHO Class 4)

COCs should not be used if a woman:

- **Is a smoker and age 35 years or older**
- Has blood clotting disorders (deep vein thrombophlebitis or pulmonary embolus)
- Has ischemic heart disease or stroke (current or history of)
- Is jaundiced (symptomatic viral hepatitis or cirrhosis)
- Has diabetes (> 20 years duration)
- **Has headaches (migraine)**
- **Has high blood pressure (> 180/110)**
- Has breast cancer
- Has liver tumors
- Has to undergo major surgery with prolonged bed rest
- Is pregnant (known or suspected)
- Is breastfeeding (< 6 weeks postpartum)

***Source*: WHO 1996.**

COCs: Conditions Requiring Precautions (WHO Class 3)

COCs are not recommended unless other methods are not available or acceptable if a woman:

- Has **unexplained vaginal bleeding** (only if serious problem suspected)
- Has **high blood pressure** (> 160/100 and < 180/110)
- Has a history of breast cancer
- Has symptomatic gall bladder disease
- Is taking drugs for epilepsy (phenytoin or barbiturates) or tuberculosis (rifampin)
- Is < 3 weeks postpartum (even if not breastfeeding)

***Source*: WHO 1996.**

classifications for hormonal contraceptive methods and intrauterine devices

AGE	COC/P /R	POP	DMPA	implants	LNG-IUD	Cu-IUD
Age < 40 yrs	1	1	1	1	1	1
Age ≥40 yrs	2	1	(2)1	1	(2)1	(2)1
SMOKING						
Age <35 yrs	2	1	1	1	1	1
Age ≥35 yrs						
i. <15 Cigarettes/day	3	1	1	1	1	1
ii. ≥15 Cigarettes/day	4	1	1	1	1	1
OBESITY						
BMI ≥30	2	1	1	1	1	1

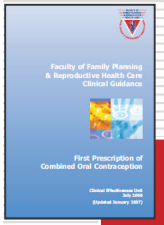
U.S. Medical Eligibility Criteria for Contraceptive Use, June 18, 2010 / Vol. 59 / No. RR-4

classifications for hormonal contraceptive methods & IUDs

Condition	COC/P/R	POP	DMPA	Implants	LNG-IUD	Cu-IUD
Hypertension						
a. Adequately controlled hypertension	3†	1†	2†	1†	1	1
b. Elevated blood pressure levels (properly taken measurements)						
i. Systolic 140–159 mm Hg or diastolic 90–99 mm Hg	3	1	2	1	1	1
ii. Systolic ≥160 mm Hg or diastolic ≥100 mm Hg§	4	2	3	2	2	1
c. Vascular disease	4	2	3	2	2	1
History of high blood pressure during pregnancy (where current blood pressure is measurable and normal)	2	1	1	1	1	1

Condition	COC/P/R	POP	DMPA	Implants	LNG-IUD	Cu-IUD
Diabetes						
a. History of gestational disease	1	1	1	1	1	1
b. Nonvascular disease						
i. Noninsulin-dependent	2	2	2	2	2	1
ii. Insulin-dependent§	2	2	2	2	2	1
c. Nephropathy/retinopathy/ neuropathy§	3/4†	2	3	2	2	1
d. Other vascular disease or diabetes of >20 yrs' duration§	3/4†	2	3	2	2	1

U.S. Medical Eligibility Criteria for Contraceptive Use, June 18, 2010 / Vol. 59 / No. RR-4



Criteri di eligibilità



	EP	P
Ipertensione Controllata 140-150/90-99 >160/100	 3 3 4	 1 1 2
Obesità 30-34 35-39 >40	 2 3 4	 1 1 1
Dislipidemia	2/3	2
Familiarità per trombofilia	2 (WHO) >35 aa 2? 3 (UK)	1 1
Emicrania senza aura	<35 aa, 2 >35 aa, 3	1 1
Fumo di sigaretta	<35 aa, 2 >35 aa, 3/4	1 1

COCs: i punteggi si sommano

- **Età**
- **Fumo**
- **Peso corporeo**
- **Storia familiare**
- **Storia personale**

Contraccezione progestinica

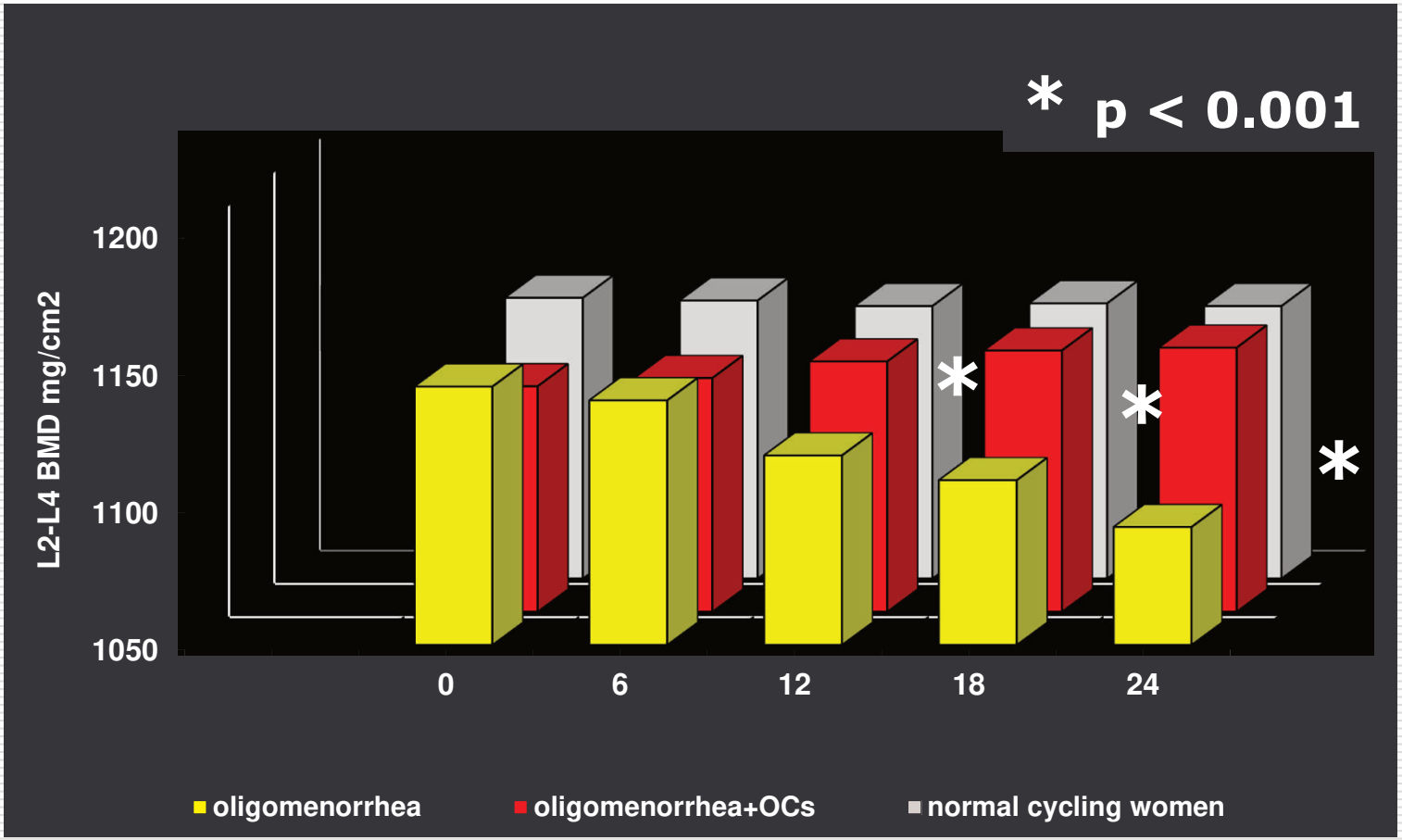
- i.m
- orale
- Impianti sottocutanei
- Intrauterina

Noncontraceptive Benefits of OCs in perimenopausal women

- **Cycle-related:**
  - **Irregular cycles**
  - **Menorrhagia**
  - **Anemia**
  - **Functional ovarian cysts**
  - Dysmenorrhea
- **Prevention of:**
  - **Bone loss**
  - Fibrocystic/benign breast disease
  - Pelvic inflammatory disease (PID)
  - Ectopic pregnancy
- **Cancer reduction:**
  - **Ovarian**
  - **Endometrial**
  - **Colorectal**
- **Treatment of:**
  - **Perimenopausal symptoms**
  - Acne
  - Hirsutism

Adapted from Grimes DA et al, eds. *Modern Contraception: Updates from* The Contraception Report. Emron;1997:1-100

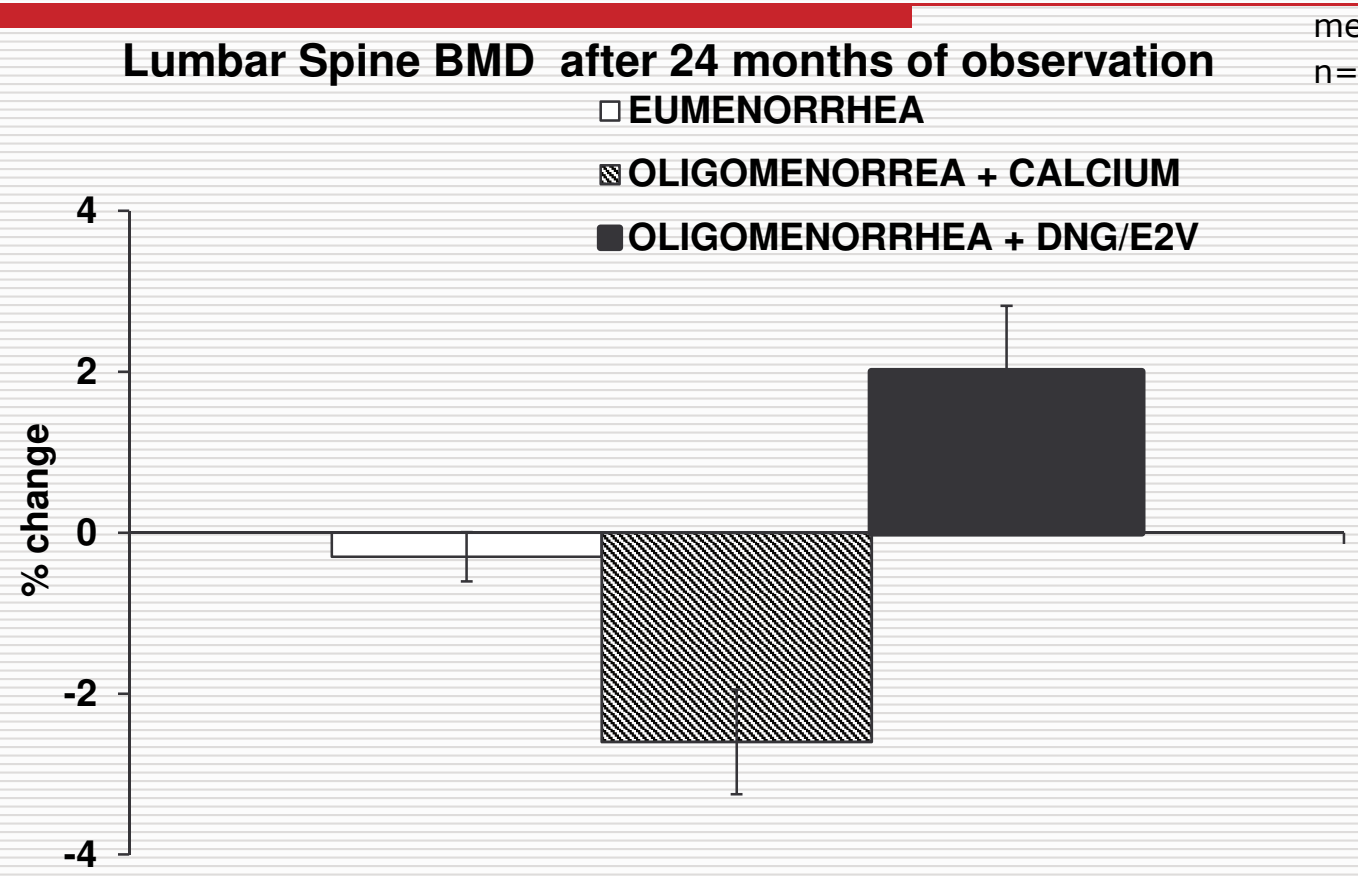
Noncontraceptive Benefits of Ocs
BMD in premenopausal women



from Gambacciani et al, Obstet Gynecol 1994

LS-BMD in Perimenopausal Women

mean age 49.5 ± 2.1 yr
n= 25 in each group



Gambacciani, Levancini , Menopause Review 2014

Hormonal contraception

cancer risk

Modification of the Associations Between Duration of Oral Contraceptive Use and Ovarian, Endometrial, Breast, and Colorectal Cancers

Prospective NIH Diet and Health Study (enrolled 1995-1996, followed until 2011); All analyses included at least 100 000 women who reported OC use (> 10yrs)

- ovarian cancer
  - long-term OC use [≥10 years] HR 0.60 0.47-0.76 $P < .001$
- endometrial cancer
  - long-term OC use HR, 0.66 (0.56-0.78) $P < .001$
    - Smokers HR 0.47 (0.25-0.88)
    - obese BMIs 0.36 (0.25-0.52)
    - exercised rarely HR 0.40 (0.29-0.56).
- Associations between OC use and breast and colorectal cancers were predominantly null.
- Oral contraceptive use may be beneficial for chemoprevention for a range of women with differing baseline cancer risks.

JAMA Oncology, April 12, 2018

LNG-IUS and Cancer Risk

population-based prospective cohort study
104,318 women from the Norwegian Women and Cancer Study
9144 of whom were ever users and 95,174 of whom were never users of LNG-IUS

Site-specific cancer incidence rates and relative risks comparing ever users (person-years [PY] = 107,701) and never users (PY = 1,197,734) of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the Norwegian Women and Cancer Study.

Cancer type	LNG-IUS user status	Cancer cases	Incidence rate per 100,000 PY (95% CI)	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)
Epithelial ovarian	Ever	18	16.7 (9.9, 26.4)	0.49 (0.30, 0.82)	0.53 (0.32, 0.88)[a]
	Never	457	38.1 (34.7, 41.8)		
Endometrial	Ever	15	13.9 (7.8, 23.0)	0.19 (0.11, 0.40)	0.22 (0.13, 0.40)[b]
	Never	839	70.0 (65.4, 74.9)		
Breast	Ever	297	275.7 (245.3, 309.0)	1.02 (0.90, 1.15)	1.03 (0.91, 1.17)[c]
	Never	3373	281.6 (272.2, 291.3)		
Combined (ovarian, breast, endometrial)	Ever	330	306.4 (274.2, 341.3)	0.84 (0.74, 0.94)	0.86 (0.77, 0.97)[d]
	Never	4669	389.7 (378.7, 401.2)		

ever users of LNG-IUS had a strongly reduced risk of ovarian and endometrial cancer compared to never users, with no increased risk of breast cancer

Jareid et al., Gynecol Oncol.2018 Apr;149(1):127-132

Mortality among contraceptive pill users:

the Royal College of General Practitioners' Oral Contraception Study

Hannaford et al., BMJ 2010

- **Participants 46112 w**. observed for up to 39 years, resulting in **378 006 w/yrs** of observation among never users of OCs and 819 175 among ever users.
- **Ever users of OCs had a RR 0.88, CI 0.82-0.93 compared with never users**
- **12 % significant reduction of death from any cause**
- **Significantly lower rates of death from:**
  - **all cancers** (large bowel/rectum, uterine body, and ovarian cancer)
  - **all circulatory disease; ischaemic heart disease; and all other diseases.**

Estimated absolute reduction in all cause mortality among ever users of OCs

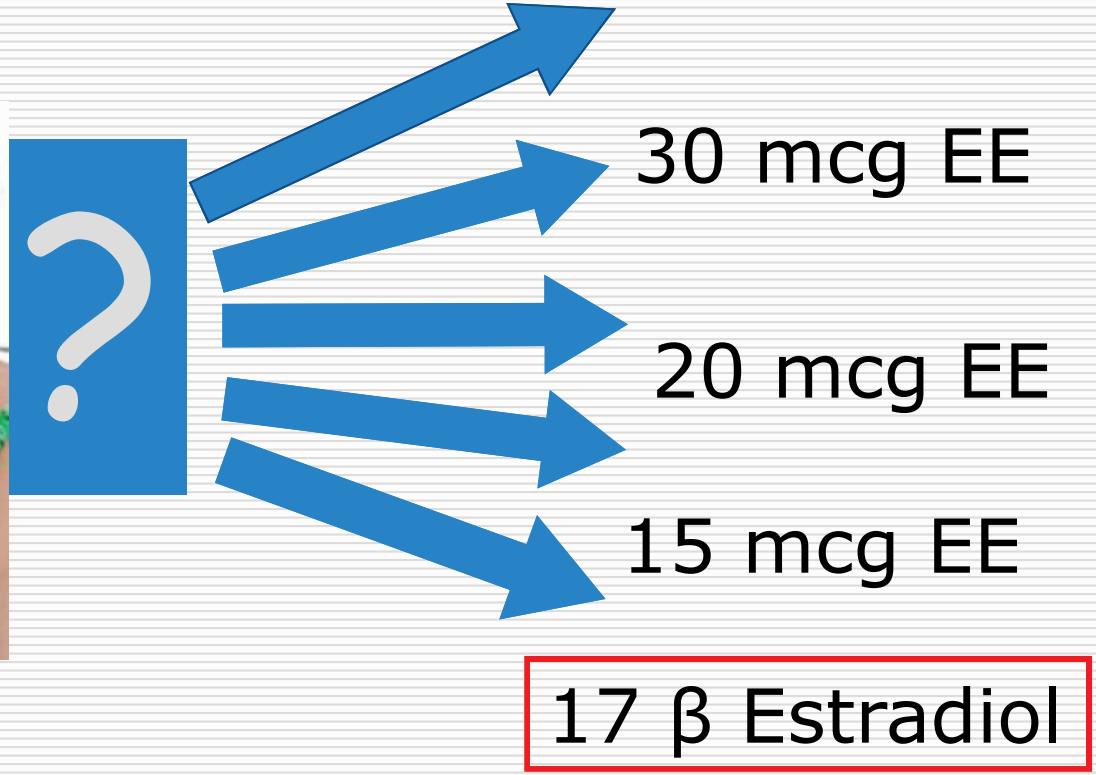
52 per 100 000 w/yrs.

Ocs: thrombosis risk

Role of dose

DVT risk and oral estrogen dose





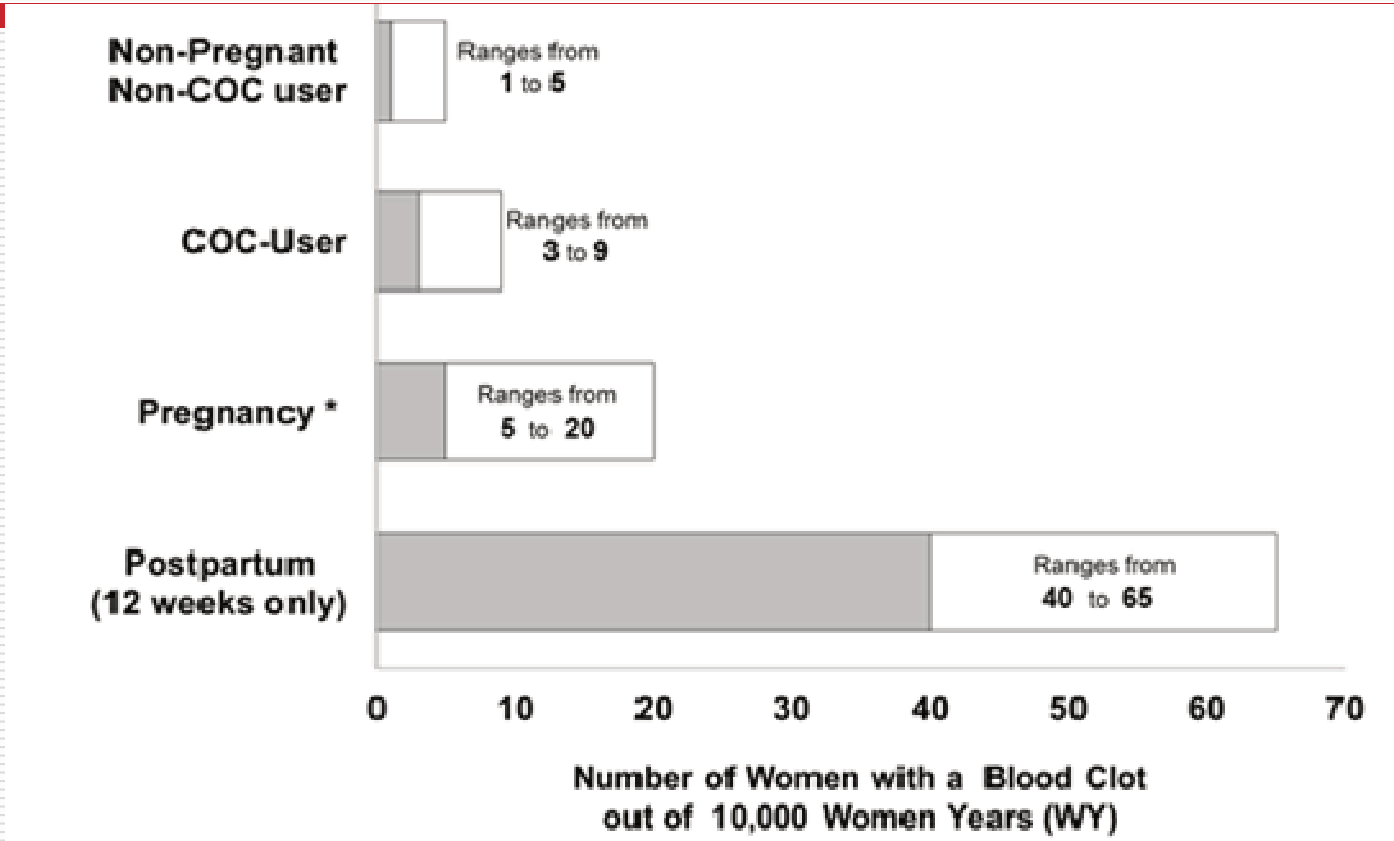
Annual incidence of VTEs is Age dependent

- 1 in 100,000 persons younger than 20 years
- 1 in 10,000 persons aged 20 to 40 years
- 1 in 1,000 persons aged 41 to 75 years
- 1 in 100 persons older than 75 years.

Gomes M.P. V., Deitcher S.R. Arch Intern Med. 2004;164:1965-1976

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Rischio di trombosi venosa



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

PILLOLA E VALUTAZIONE DEL RISCHIO TROMBOTICO

- ANAMNESI
- ESAME OBIETTIVO
- SCREENING DELLA COAGULAZIONE (?)

Indagini ematochimiche e contraccezione ormonale

SOGC WHO RCOG ANAES FFPRH NICE

ACOG ANA

- Tutte le linee guida indicano di non eseguire gli esami ematochimici di screening
- La maggior parte delle linee guida indicano la necessità di effettuare
  - accurata anamnesi
  - misurare la PA e il peso

Combined Hormonal Contraceptives and First Venous Thrombosis in Young French Women: Impact of Thrombotic Family History

Justine Hugon-Rodin,[1,2,4] Marie-Hélène Horellou,[3,4] Jacqueline Conard,[3,4] Anne Gompel,[2,4] and Geneviève Plu-Bureau[1,2,3,4]

Analisi storia familiare:

RCOG guidelines,2014 : un parente di primo grado con VTE età <45 yrs

HAS guidelines, 2013: parente di primo grado con VTE età <50 yrs o >2 parenti con VTE (generalmente uno di primo grado >50 yrs con ≥1 di secondo grado)

30% in meno di eventi trombotici

June 2017 | Vol. 1, Iss. 6
Journal of the Endocrine Society | 762–771

La contraccezione estro-progestinica in premenopausa
La scelta dell'estrogeno

Contraccezione con Estrogeni Naturali

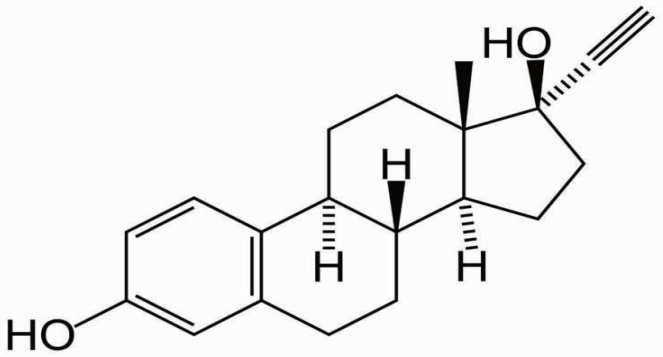
?

Contraccezione con EE, la dose più bassa

Al momento no chiara evidenza di diverse indicazioni d'uso in termini di safety.

In generale tutti i regimi che contengono estrogeni indipendentemente dalla dose, sia di somministrazione tipo di estrogeno dovrebbero essere considerati avere gli stessi benefici o ipotetici rischi, non potendo al momento considerare un metodo sicuramente migliore e più sicuro di un altro (un solo trial documenta la maggiore sicurezza dei CO-E2)

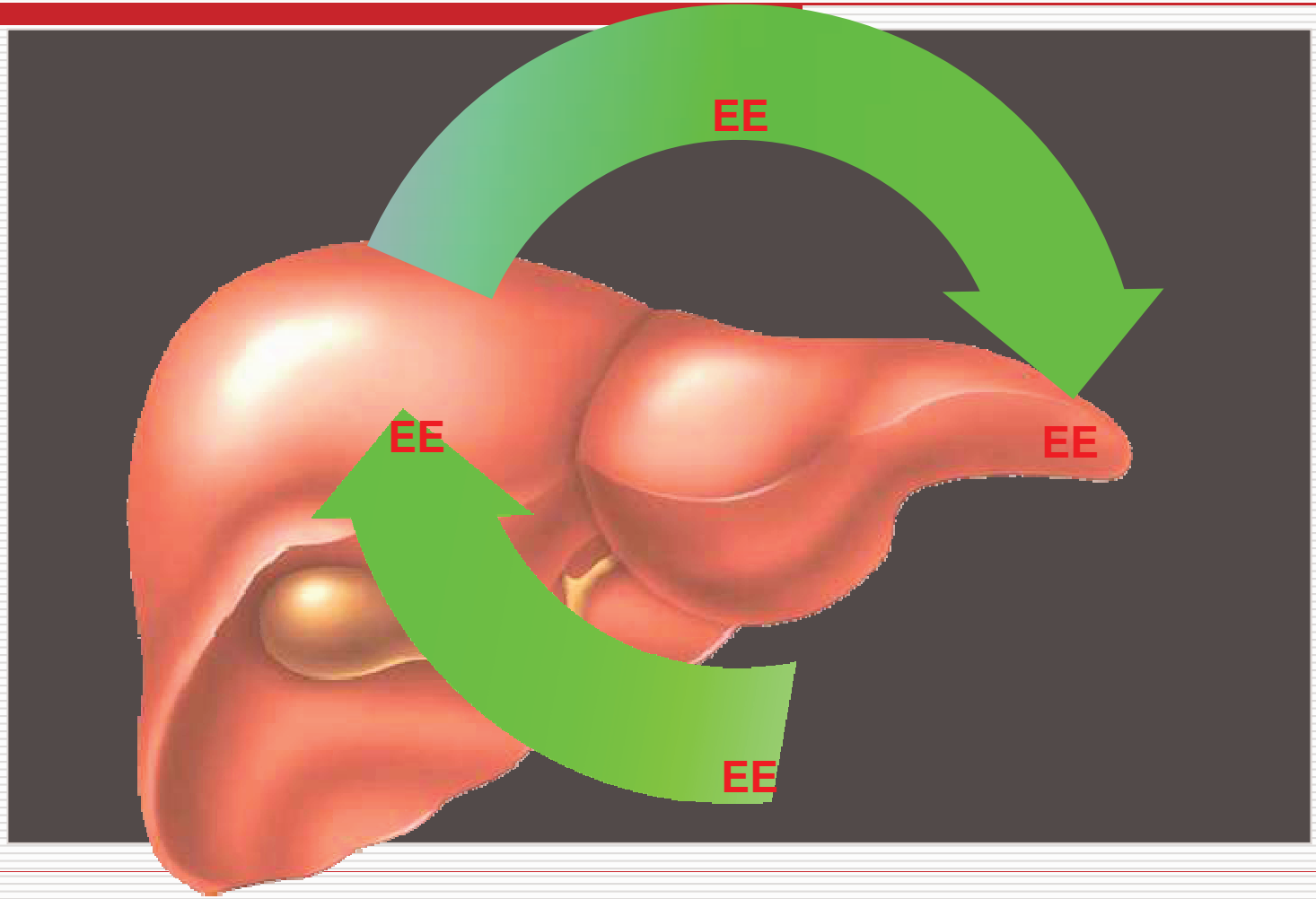
Etinil Estradiolo



- Il gruppo Etinilico C17 previene la inattivazione del gruppo idrossilico C17
- Alti livelli per lungo tempo
- Bassa affinità per SHBG
- **Elevata biodisponibilità : 45-55%**
- **Attivo nell'endometrio nonostante l'azione della 17b HSD 2 indotta dai progestinici**

Lobo RA & Stanczyk FZ., 1994; Fotherby 1996, Kuhnz W et al, 1993 and 1999; Düsterberg B et al, 1999

L’EE va incontro a numerosi passaggi epatici, con un potente effetto sulla sintesi delle proteine



Lobo RA & Stanczyk FZ. Am J Obstet Gynecol 1994

Etinil Estradiolo (EE)

- I limiti dell'EtinilEstradiolo:
  - Effetti sul metabolismo epatico
  - Maggiore esposizione legata alla maggiore biodisponibilità e emivita

HOFFMAN H et al., Exp Toxicol Pathol, 1998, 50 : 458-464

Effetti Metabolici, Estradiolo vs EE

E2 /Nomegestrolo acetato

- Metabolismo lipidi : No effetti
- Metabolismo carboidrati i : No effetti
- Metabolismo coagulazione : Effetti minimi o assenti
- Pressione arteriosa : no modificazioni

Agren U.M. 2011

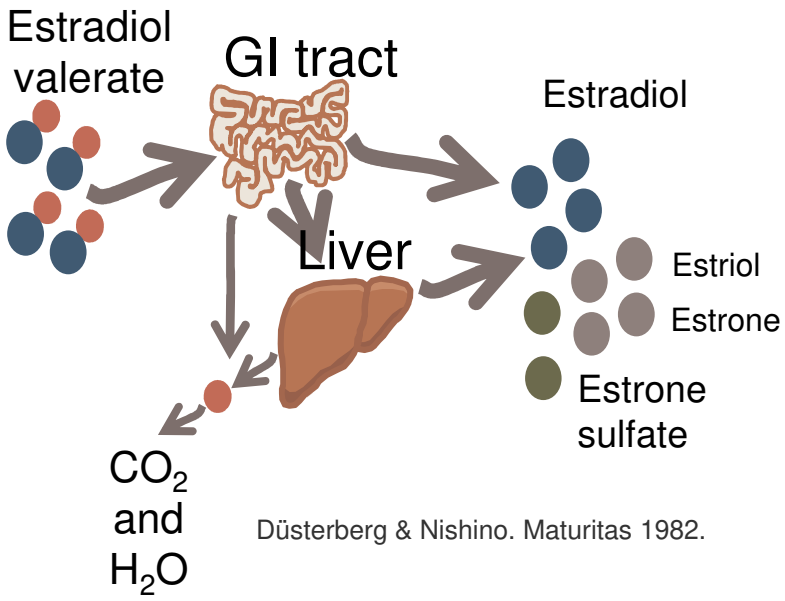


EV/Dienogest

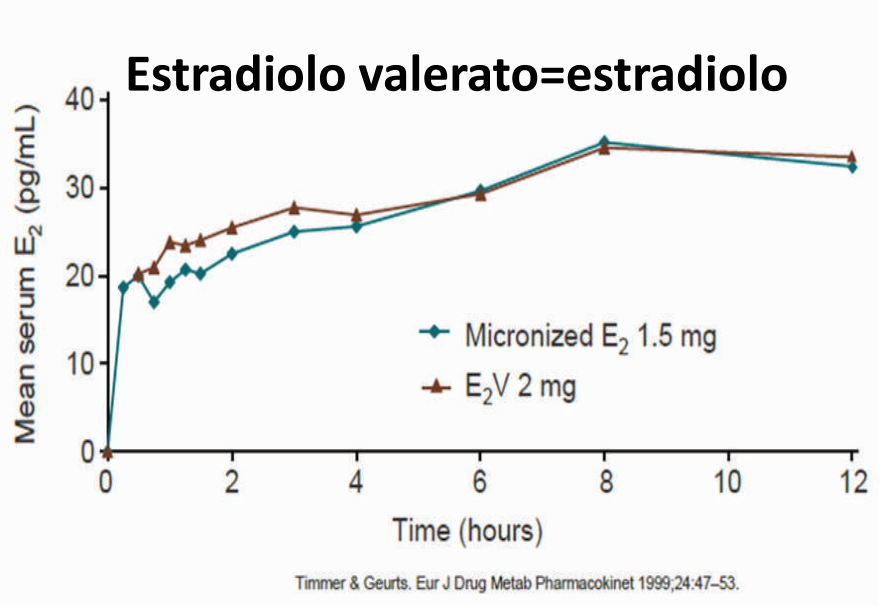
- Metabolismo lipidi : No effetti o aumento HDL
- Metabolismo carboidrati i : No effetti
- Metabolismo coagulazione : Effetti minimi o assenti
- Pressione arteriosa : no modificazioni

Junge V, 2011

Minore /no impatto metabolico degli OCs con EE



Düsterberg & Nishino. Maturitas 1982.



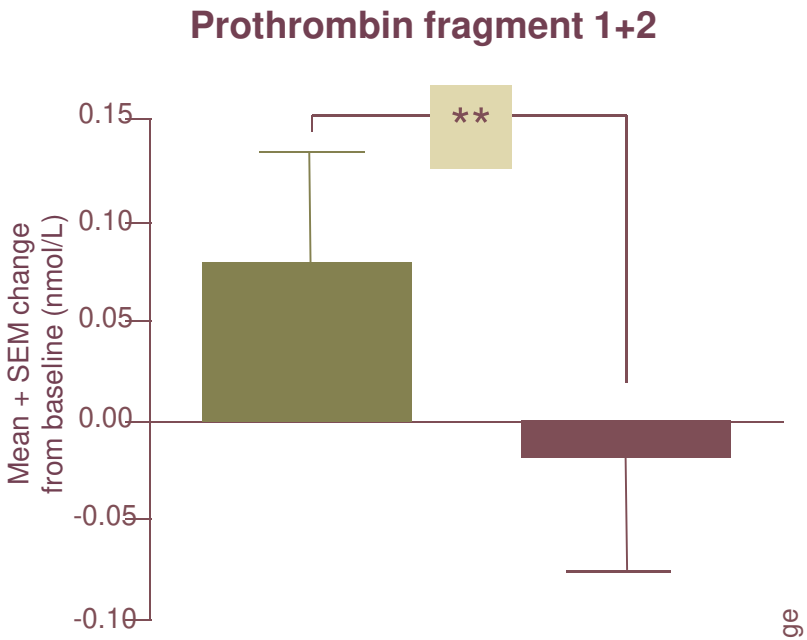
Timmer & Geurts. Eur J Drug Metab Pharmacokinet 1999;24:47–53.

Key messages:

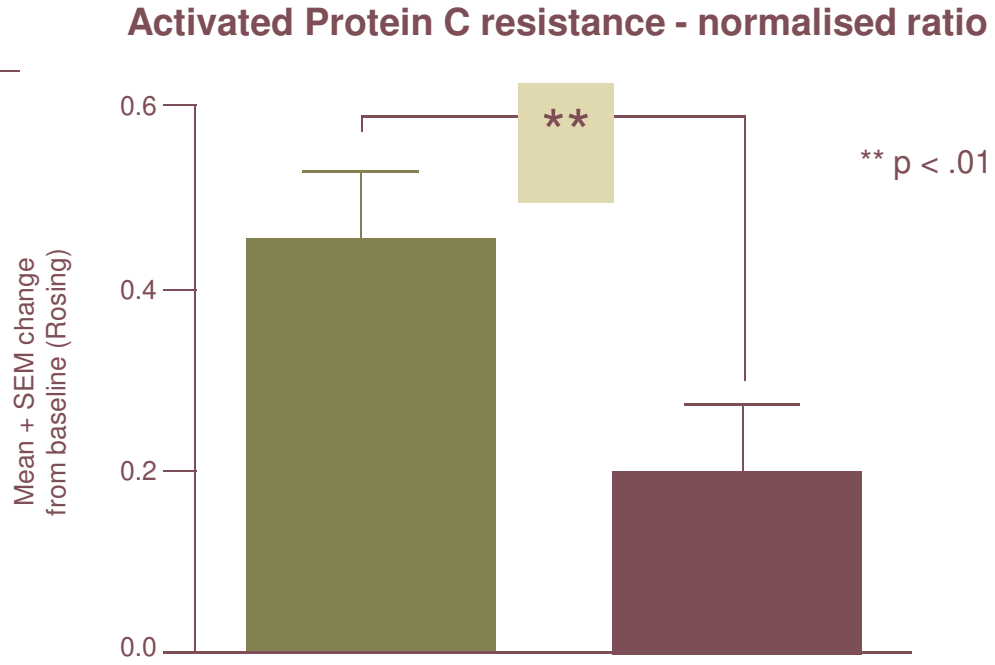
- **Le pillole con estrogeni naturali mostrano simili o minori effetti sui parametri emostatici della formulazione EE/LNG**

- **profili di efficacia e sicurezza del E_2V/DNG , E_2 /NOMAC simili**

E2/NOMAC E EMOSTASI

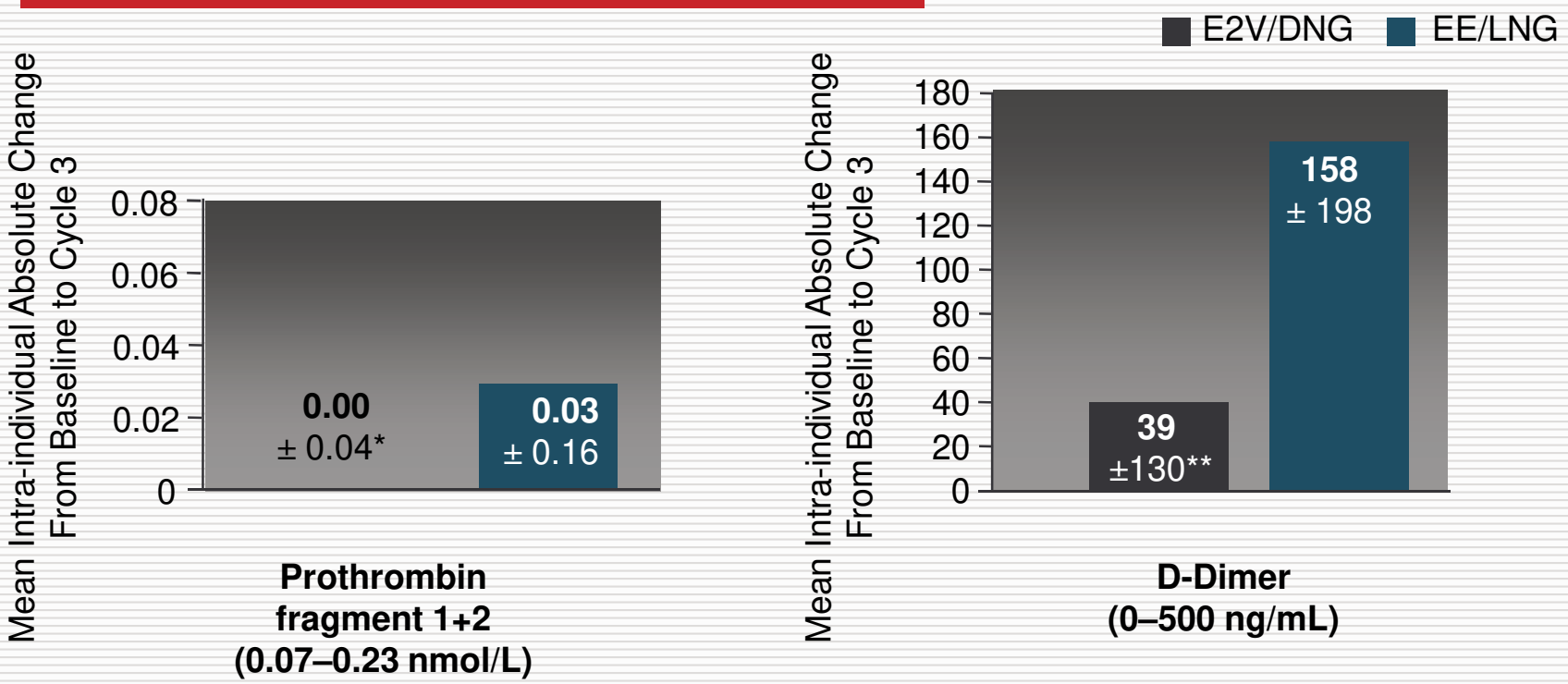






Gaussem P et al, 2011

EV/DNG: Haemostatic profile



*p<0.43; **p<0.01, vs EE/LNG (Microgynon®)

Parke et al. *Hum Reprod.* 2008;**23**(1 Suppl.):i78–79 (abstract plus oral presentation);
Data on file. Clinical Study report number A38220.

ELSEVIER

Contraception 94 (2016) 328–339

Contraception

2016

Original research article

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

Jürgen Dinger[a,*], Thai Do Minh[b], Klaas Heinemann[b]

VTE

Contraceptive	VTE incidence	HR crude (DNG/EV vs comparators	HR adj for risk factors (DNG/EV vs comparators
DNG/EV	7.4/10.000 w/y		
LNG/EE	8.2/10.000 w/y	0.8 (CI , 0.3-2.4)	0.5 (CI, 0.2-1.5)
EE/OC	8.3/10.000 w/y	0.9 (CI, 0.4-1.8)	0.4 (CI, 0.2-1)*

ATI

Contraceptive	ATE incidence	Non user
DNG/EV	0.8/10.000 w/y	2/10.000 w/y
LNG/EE	1.4/10.000 w/y	
EE/OC	3.0/10.000 w/y	

Contraccezione dopo i 40 aa

- Anamnesi personale e familiare
- Esame obiettivo
  - Peso-BMI
  - Misurazione della pressione arteriosa

Vulnerabilità della donna in premenopausa

- Ciclicità mestruale
- SNC
- Metabolico
- Cardiovascolare
- Osso
- BMI
- Maggiore incidenza ETP mammella vs età fertile

Bilanciamento tra benefici e rischi

HRT vs Contraccezione
analogie e differenze

- Anamnesi personale e familiare
- Esame obiettivo
  - Peso-BMI
  - **Pressione arteriosa**

- **Possibile classe 3-4 per OC-combinati**



- Criteri di Selezione della HRT
  - Dosi
  - Vie di somministrazione
  - Scelta del progestinico

Dalla perimenopausa alla menopausa: da necessità contraccettiva a HRT



- Sospendere 1-2 mesi per verificare ricomparsa delle mestruazioni

- Se amenorrea : dosaggio FSH. Interrompere uso contraccettivo se
  - FSH $\geq$ 30 IU/L in due prelievi a distanza di 6-8 settimane in donne di >50 aa
  - Cautela : valori variabili in perimenopausa

Baldwin MK, 2013

Early menopausal transition: HRT?

Contraindicated

HRT does not suppress ovarian function and thus may make some perimenopausal symptoms wors (bleeding)

Spontaneous pregnancy as consequence of FSH suppression by estradiol

Dalla perimenopausa alla menopausa: da necessità contraccettiva a **HRT**, quando

Nel corso d contraccezione:

- IUS-levonorgestrel : scarso impatto su FSH (Halmesmaki K, 2004; Tasci Y 2009).
- Impianto Etonogestrel: scarso impatto su FSH anche dopo 3 aa di uso (Inal MM, 2008)
- EP e POP sopprimono FSH (Beksinska ME, J 2011; Castracane VD, 1995)
- Durante POP, come EP : sospendere e dopo 14 gg dosare FSH
- Diagnosi : FSH>30 UI/ml almeno in due determinazioni a intervallo di 90 gg (Juliato CT, 2007)

Dalla perimenopausa alla menopausa: da necessità contraccettiva a HRT, quando

Determinazioni seriati di FSH possono aiutare perchè la sola amenorrea può non essere attendibile

Una necessità reale e impellente?

E2/NOMAC = E2 1.5 mg/die

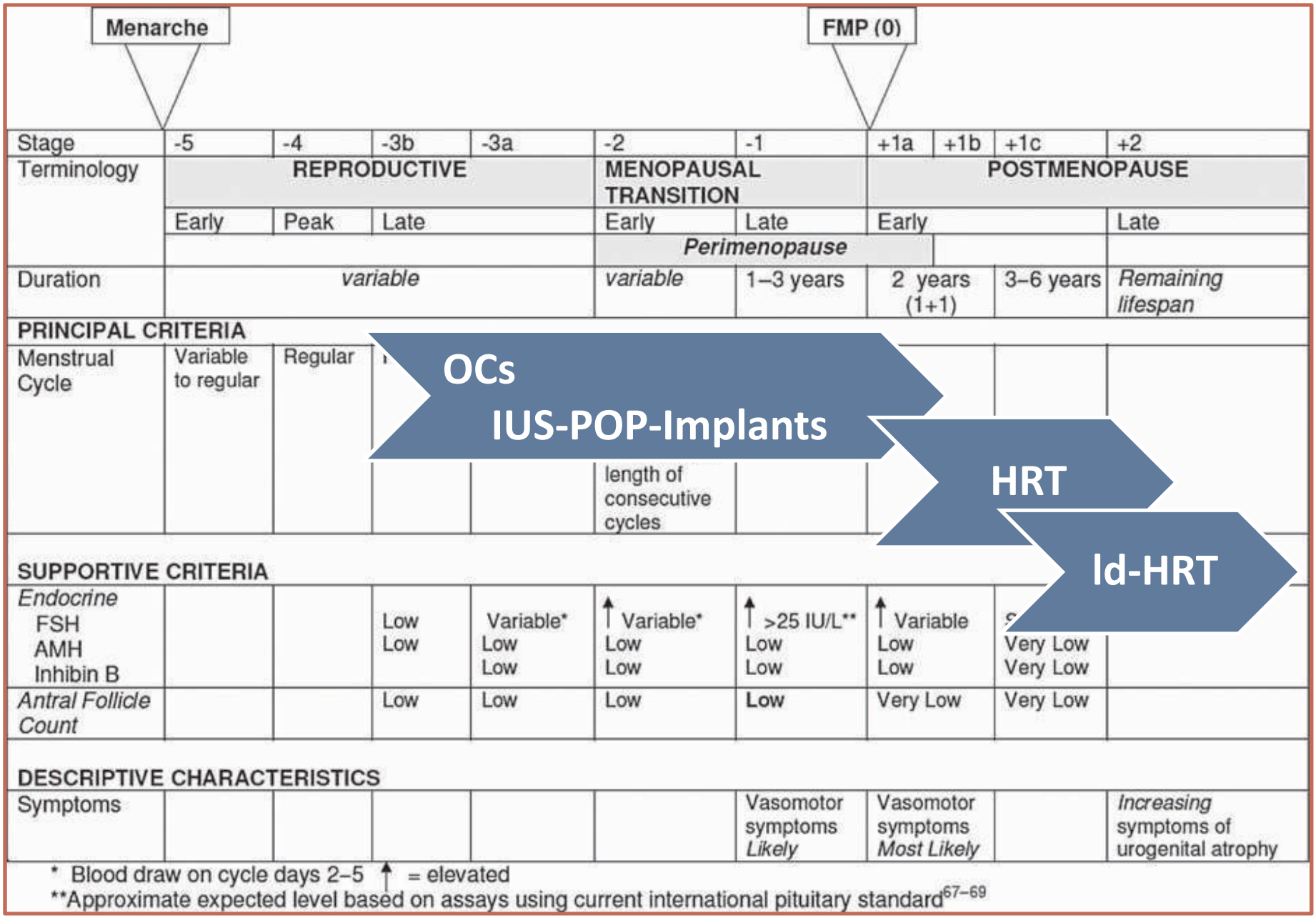
EV/DNG= E2 1- 2 mg/die

1 mg estradiolo=0.75 mg EV

HRT
Dose suggerita inizio menopausa

E2 = 1-2 mg/ die

The Stages of Reproductive Aging in women



Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular			length of consecutive cycles					
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable			
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67–69]

Harlow et al., CLIMACTERIC 2012;15:1–10