

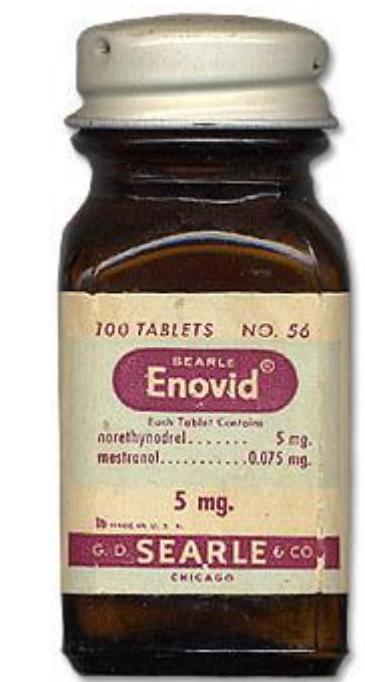
# Contraccuzione ormonale: evoluzione delle formulazioni

Francesco Maria Primiero

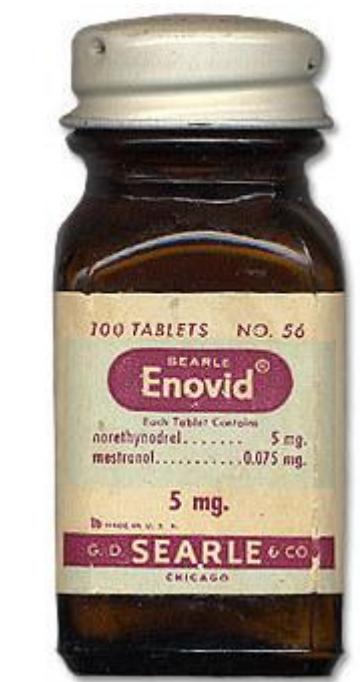
*Dipartimento di Scienze Ginecologico-Ostetriche  
e Scienze Urologiche*  
Sapienza Università di Roma

Ospedale San Pietro Fatebenefratelli, Roma

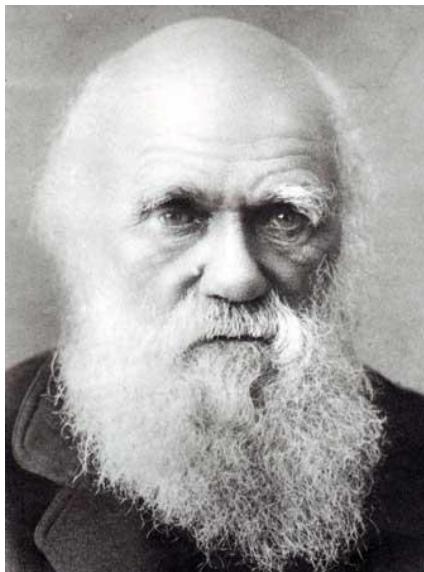
10 giugno 1957: la FDA approva la commercializzazione di Enovid per irregolarità mestruali, comprendenti amenorrea, dismenorrea, menorrhagia, endometriosi, infertilità (the “Rock rebound effect”).



1960: la FDA approva la commercializzazione di Enovid con indicazione contraccettiva.

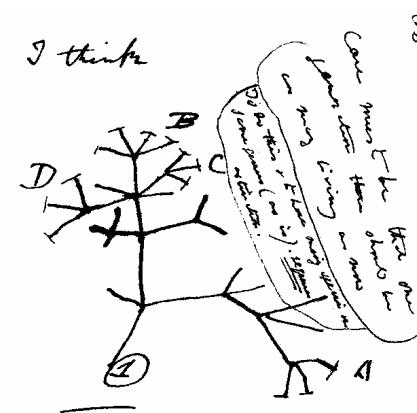


# L'evoluzione chimica dei progestinici



Charles R. Darwin, 1809 -  
1882

F.M. Primiero, 2012



Then between A & B. various  
less & relation. C & B. the  
first generation, B & D  
rather greater distinction  
then genus would be  
formed. - binary relation

Progesterone → Dydrogesterone

Spirolactone

Pregnanes

Estranes

Gonanes

Norpregnanes

Nomegestrol ac.

Nestorone

Trimegestone

Drospirenone

Norethisterone

Ethinodiol d.

Dienogest

Medroxyprogesterone ac.

Chlormadinone ac.

Cyproterone ac.

Megestrolo ac.

Medrogestone

Norgestrel

Levonorgestrel

Norgestrienone

Norgestimate

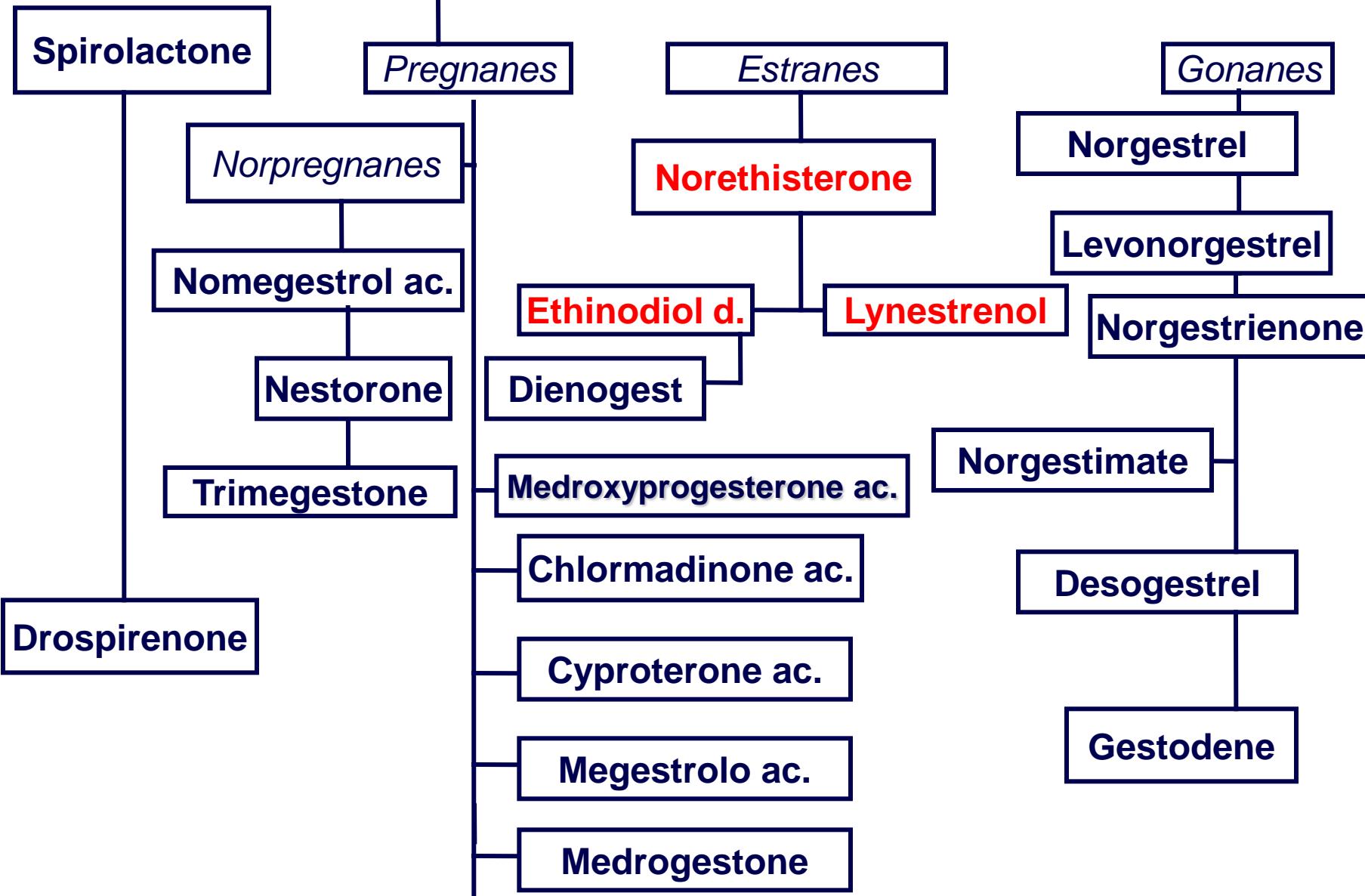
Desogestrel

Gestodene

## C21 derivatives

## 19 Nor derivatives

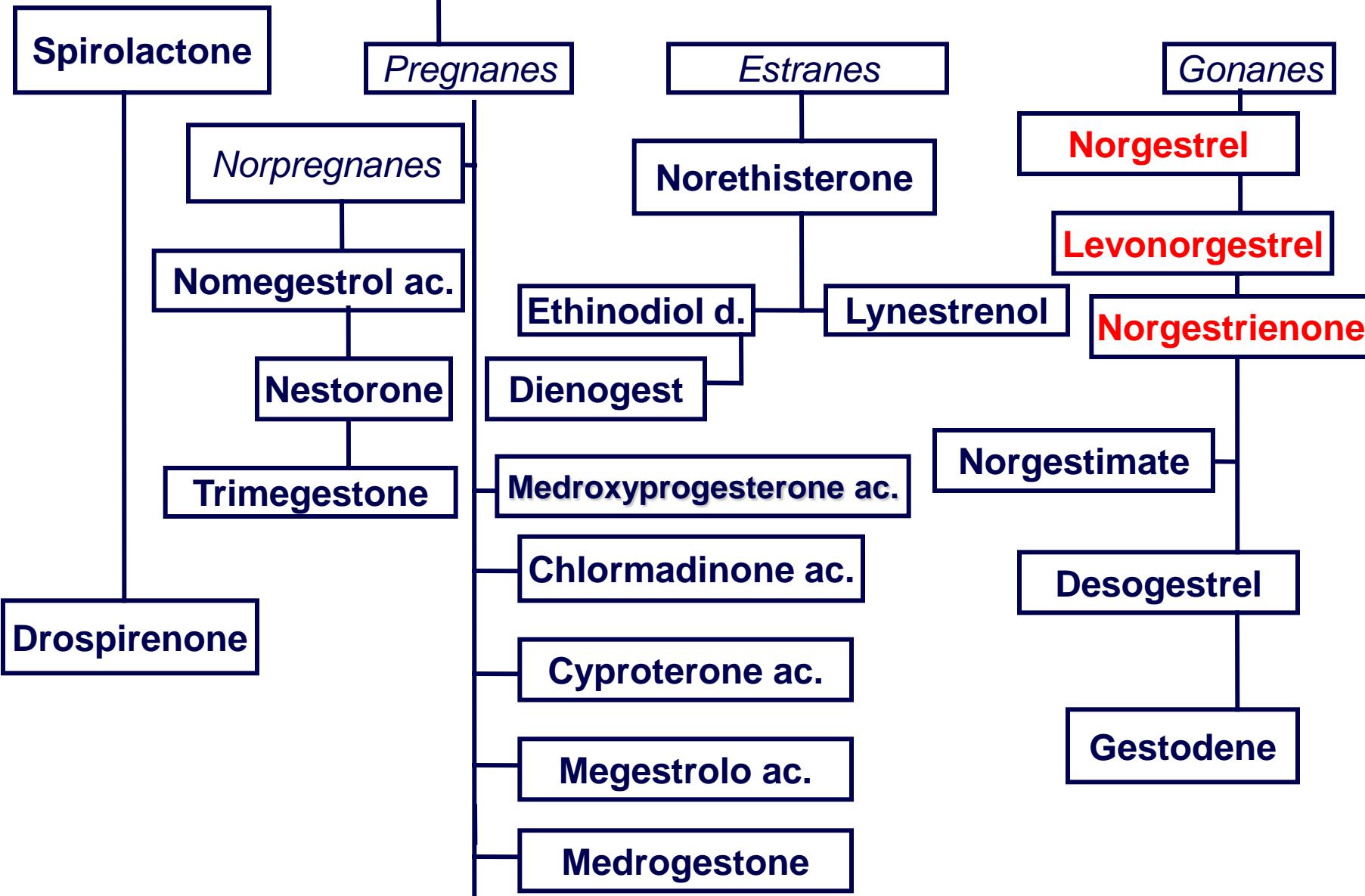
Progesterone → Dydrogesterone

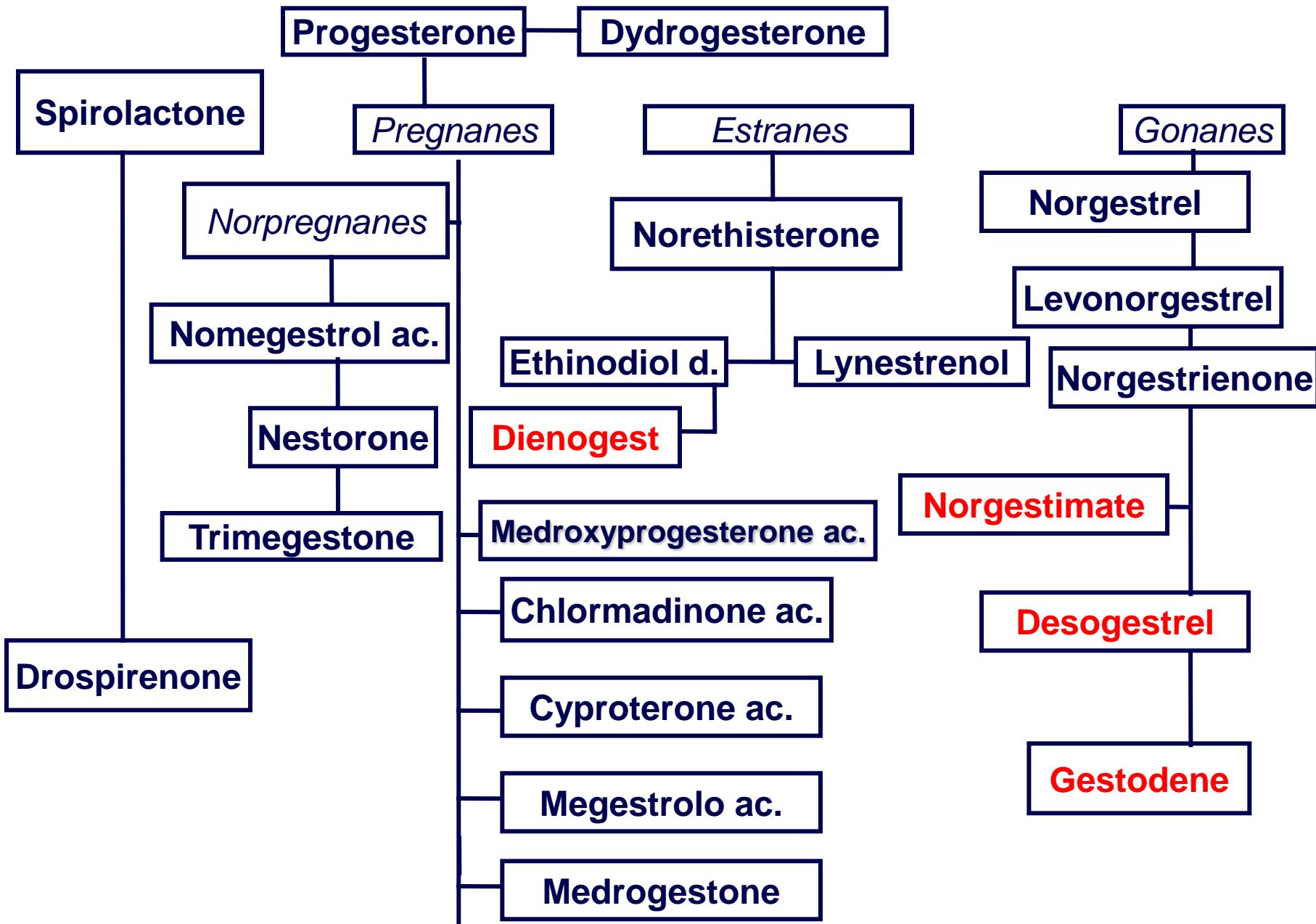


## C21 derivatives

## 19 Nor derivatives

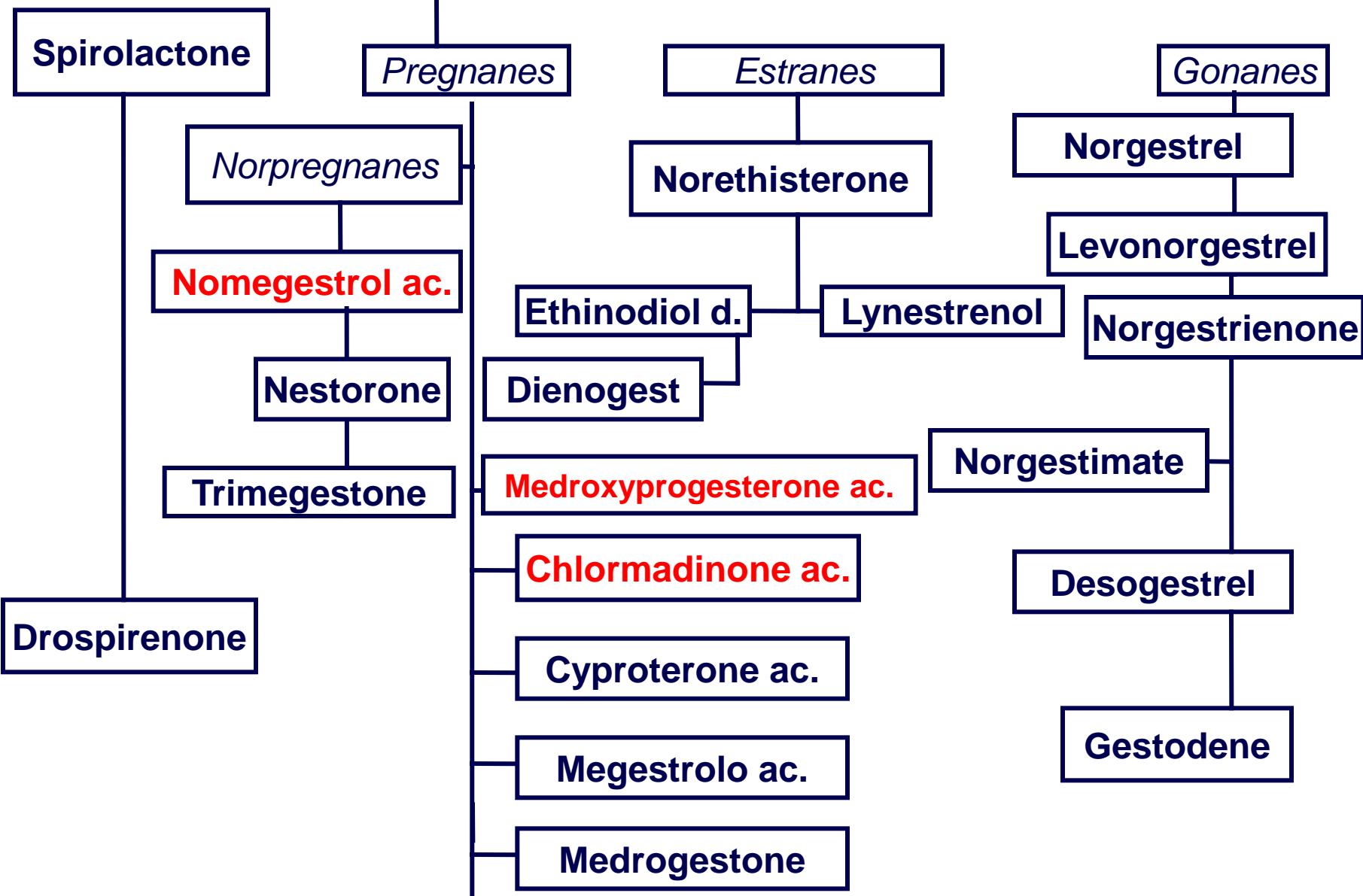
Progesterone → Dydrogesterone





## C21 derivatives

## 19 Nor derivatives



## C21 derivatives

## 19 Nor derivatives

Progesterone → Dydrogesterone

Spirolactone

Pregnanes

Estranes

Gonanes

Norpregnanes

Nomegestrol ac.

Nestorone

Trimegestone

Drospirenone

Norethisterone

Ethinodiol diac.

Dienogest

MAP

Chlormadinone ac.

Cyproterone ac.

Megestrolo ac.

Medrogestone

Norgestrel

Levonorgestrel

Norgestrienone

Norgestimate

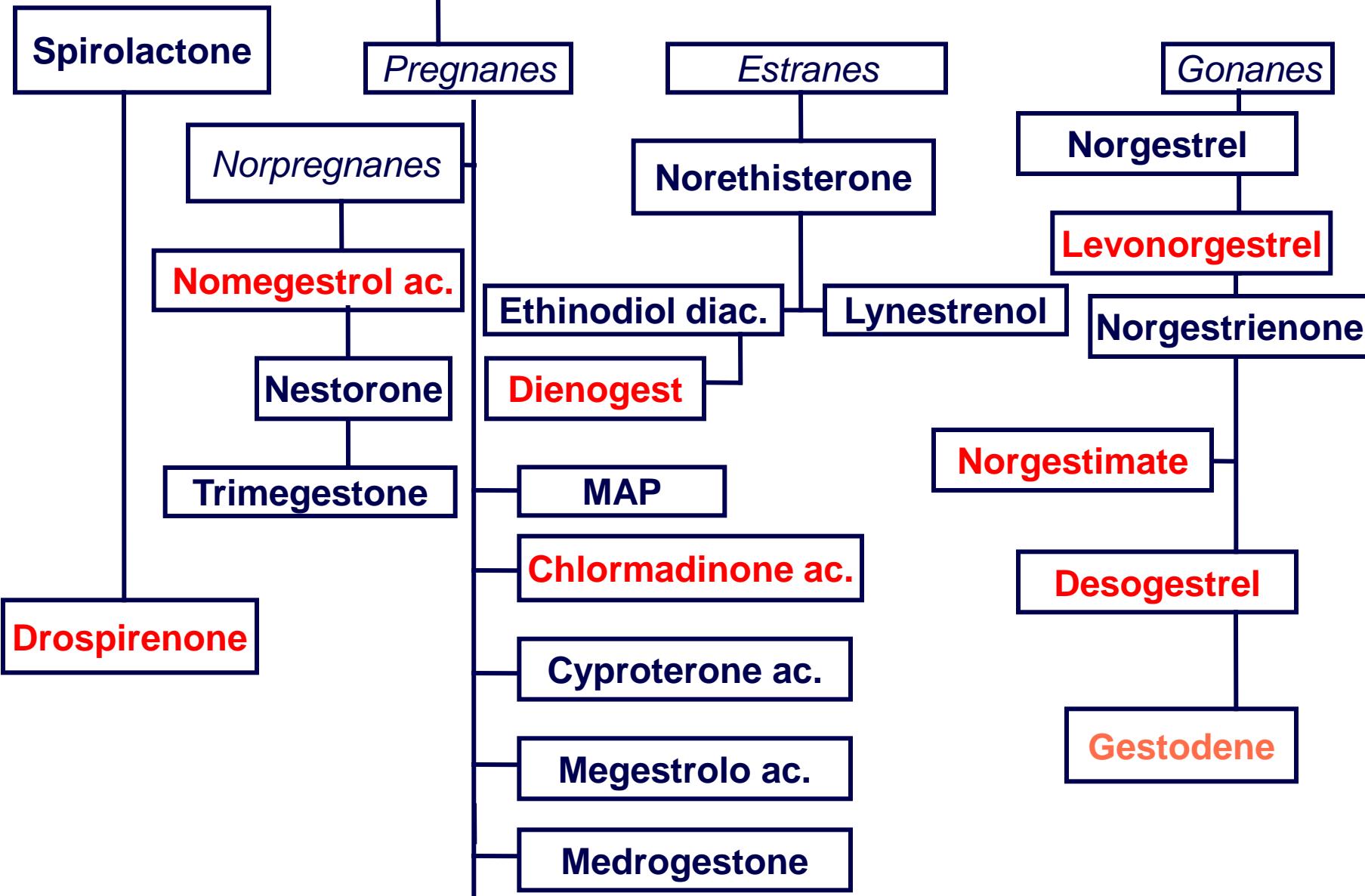
Desogestrel

Gestodene

## C21 derivatives

## 19 Nor derivatives

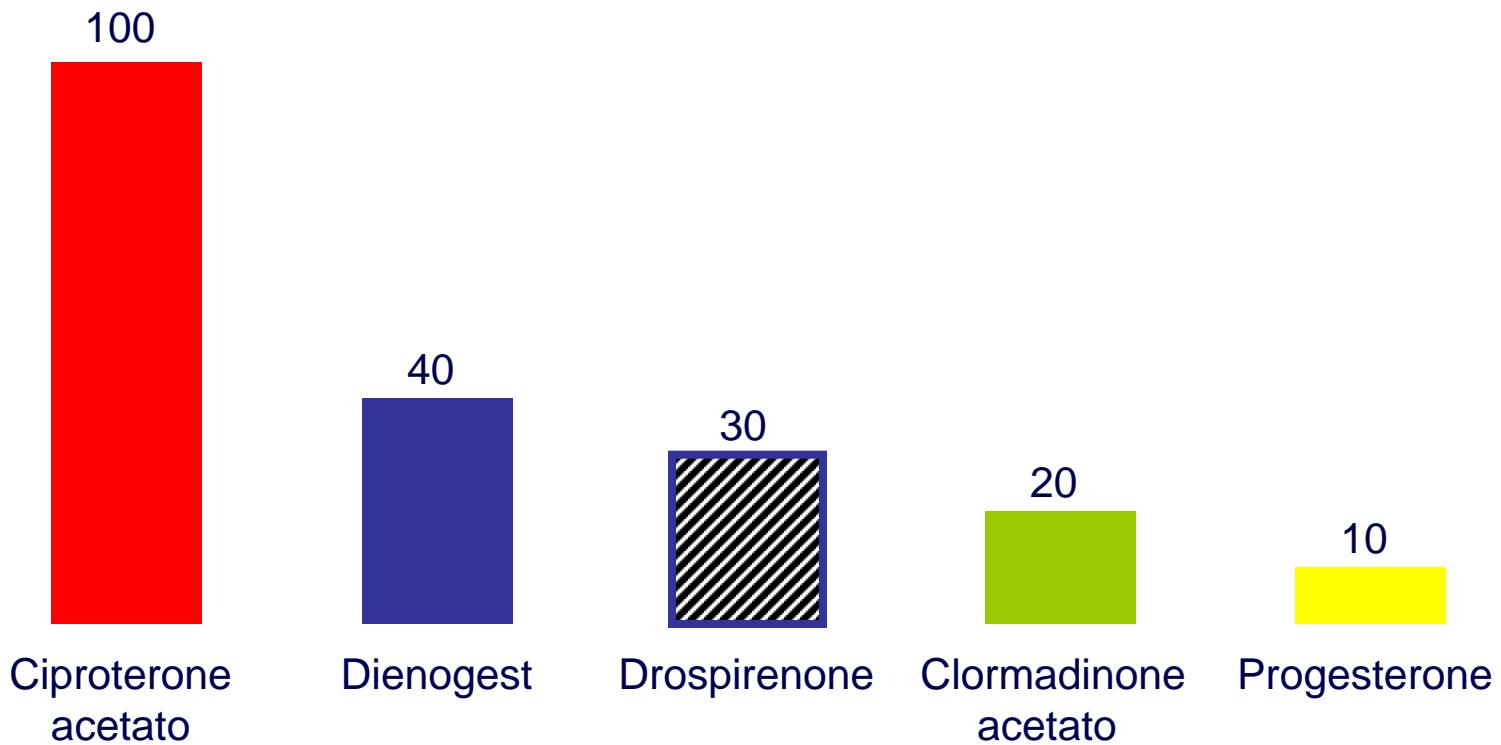
Progesterone → Dydrogesterone



# Profilo farmacologico dei progestinici

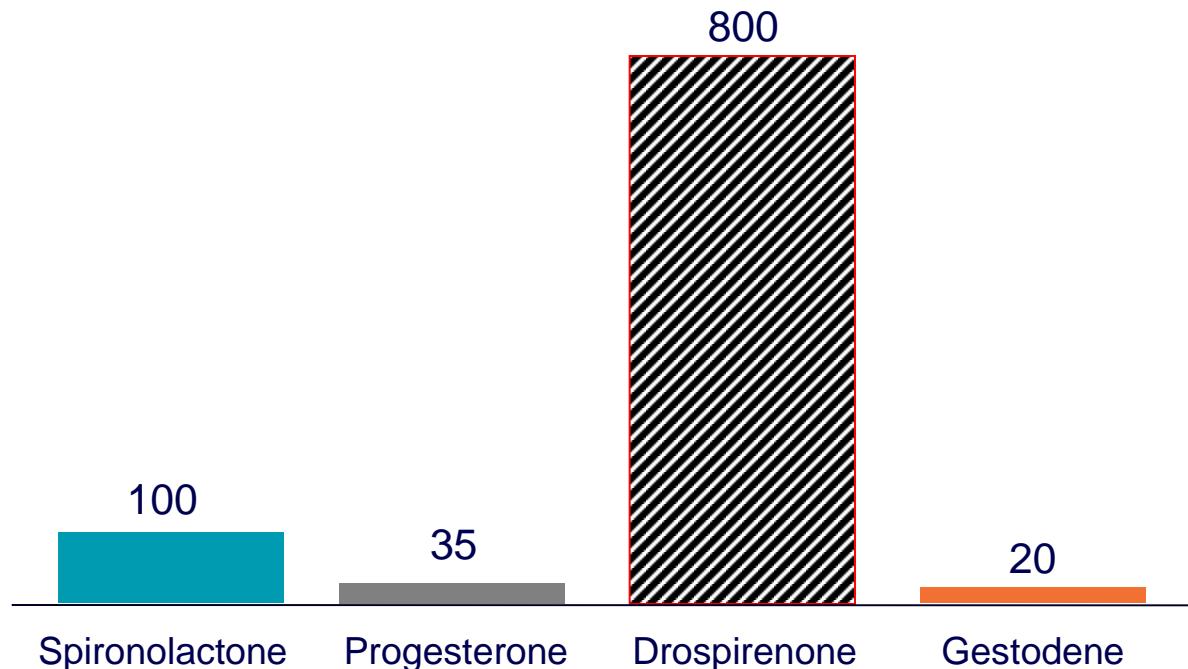
Progesterins	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Chlormadinone acetate	+	-	-	+	+	-
Cyproterone acetate	+	-	-	++	+	-
Dienogest	+/-	+/-	-	+	-	-
Drospirenone	+	-	-	+	-	++
Etonogestrel (3-keto-desogestrel)	+	-	+	-	-	-
Gestodene	+	-	+	-	+/-	+
Levonorgestrel	+	-	+	-	-	-
Medroxyprogesterone acetate	+	-	+/-	-	+	-
Nomegestrol acetate	+	-	-	+/-	-	-
Norethisterone	+	+	+	-	-	-
Norgestimate	+	-	+	-	-	-
Progesterone	+	-	-	+/-	+	+

## Attività antiandrogenica relativa di diversi progestinici



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

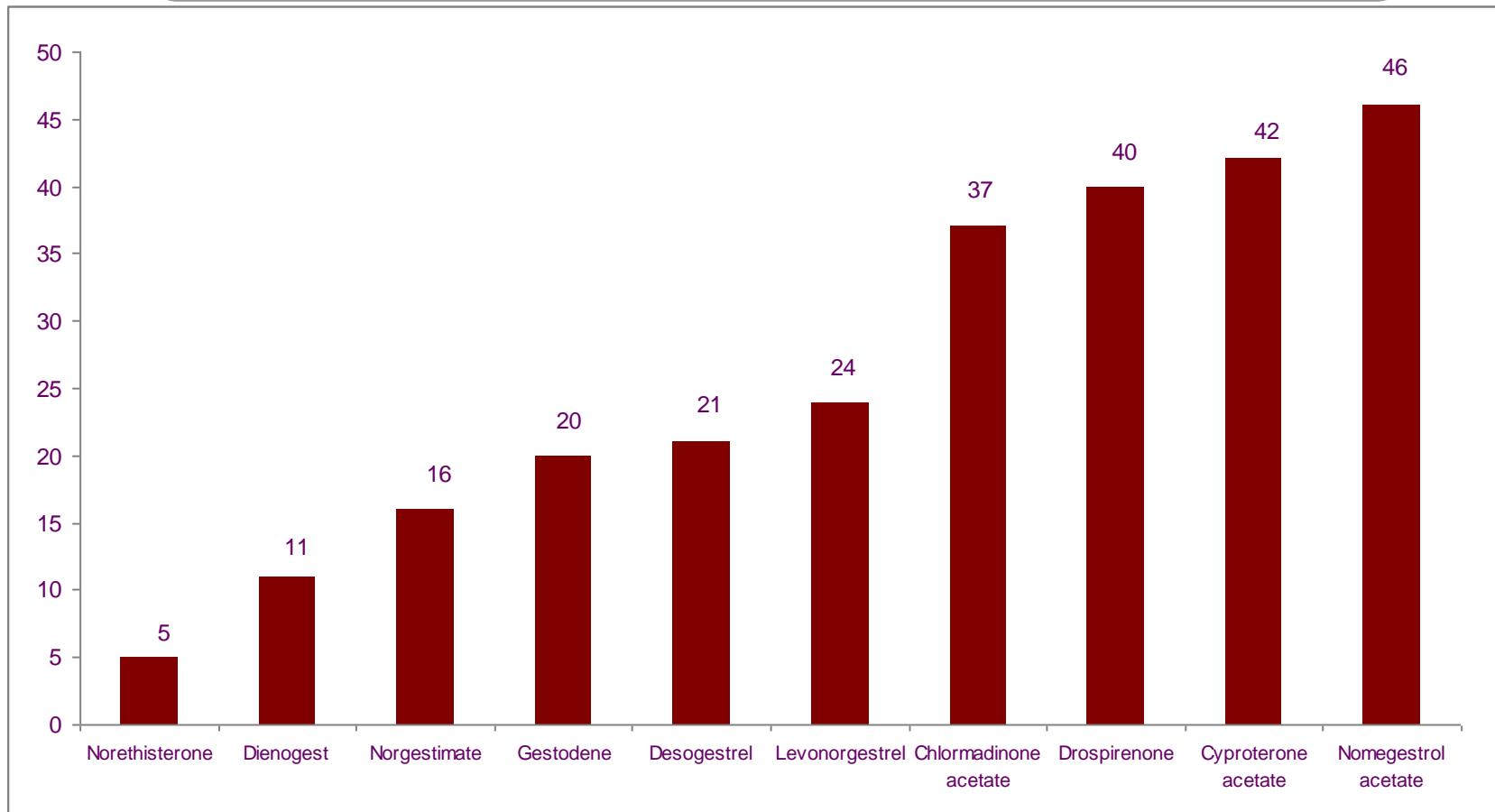
# Attività antimineralcorticoide relativa di diversi progestinici



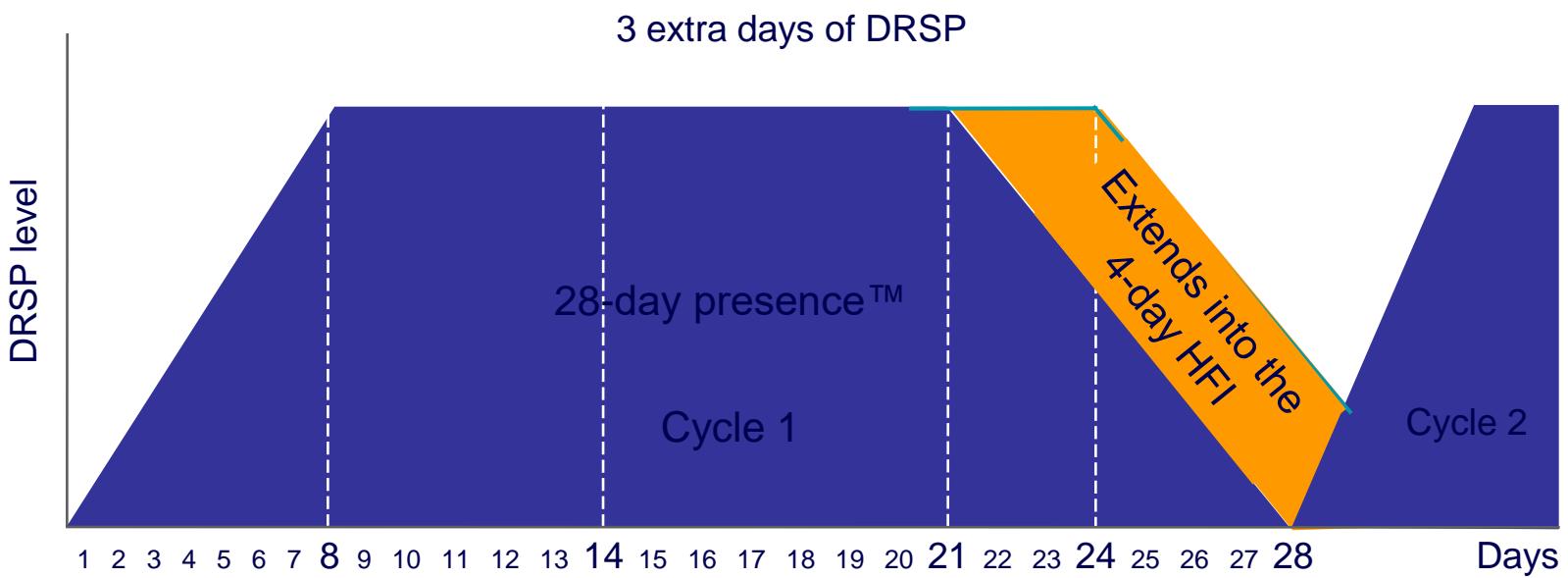
## Ulteriori parametri di caratterizzazione del progestinico

- Emivita
- Interazione con le proteine vetrifici
- Sensibilità agli enzimi catabolici
- MOID (minimal ovulation inhibiting dose)
- Isterotropismo

# Emivita di diversi progestinici



# Emivita del drospirenone e farmacocinetica interciclica



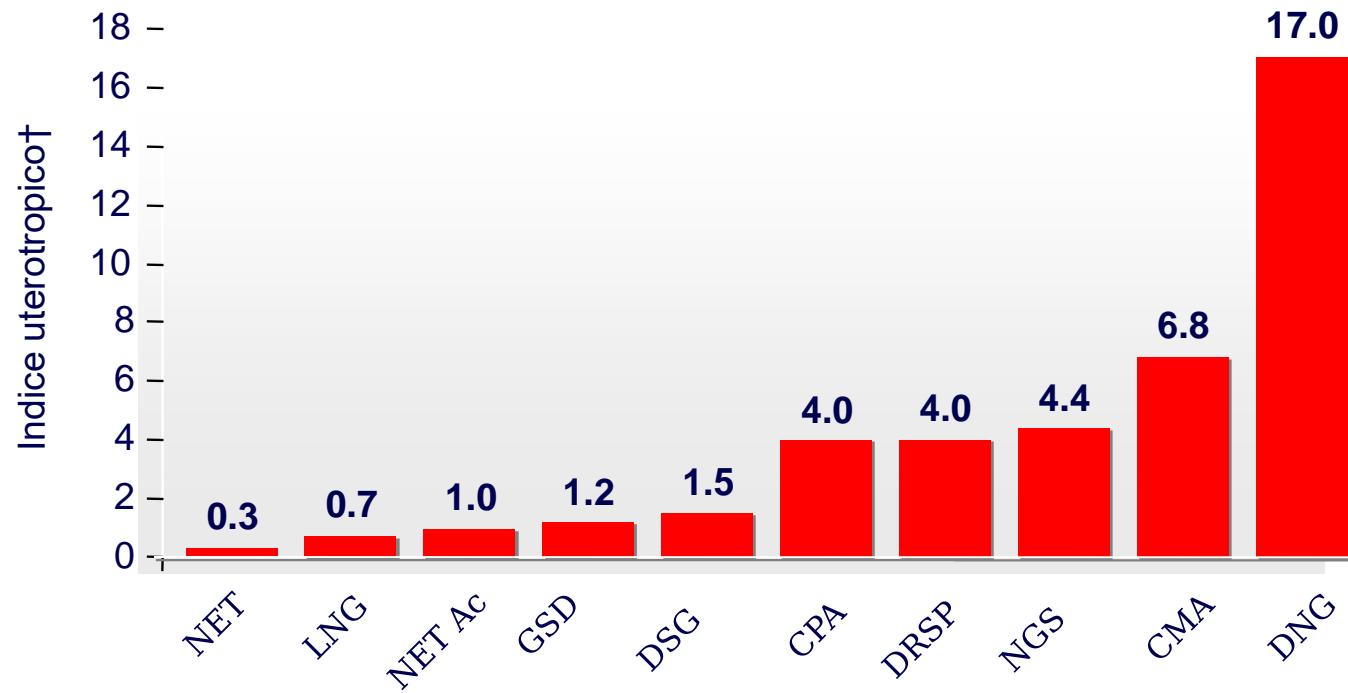
$$\text{DRSP T/2} = 30.9 - 32.5 \text{ hrs}^1$$

1. Blode H, et al. Eur J Contracept Reprod Health Care 2000;5:256–64

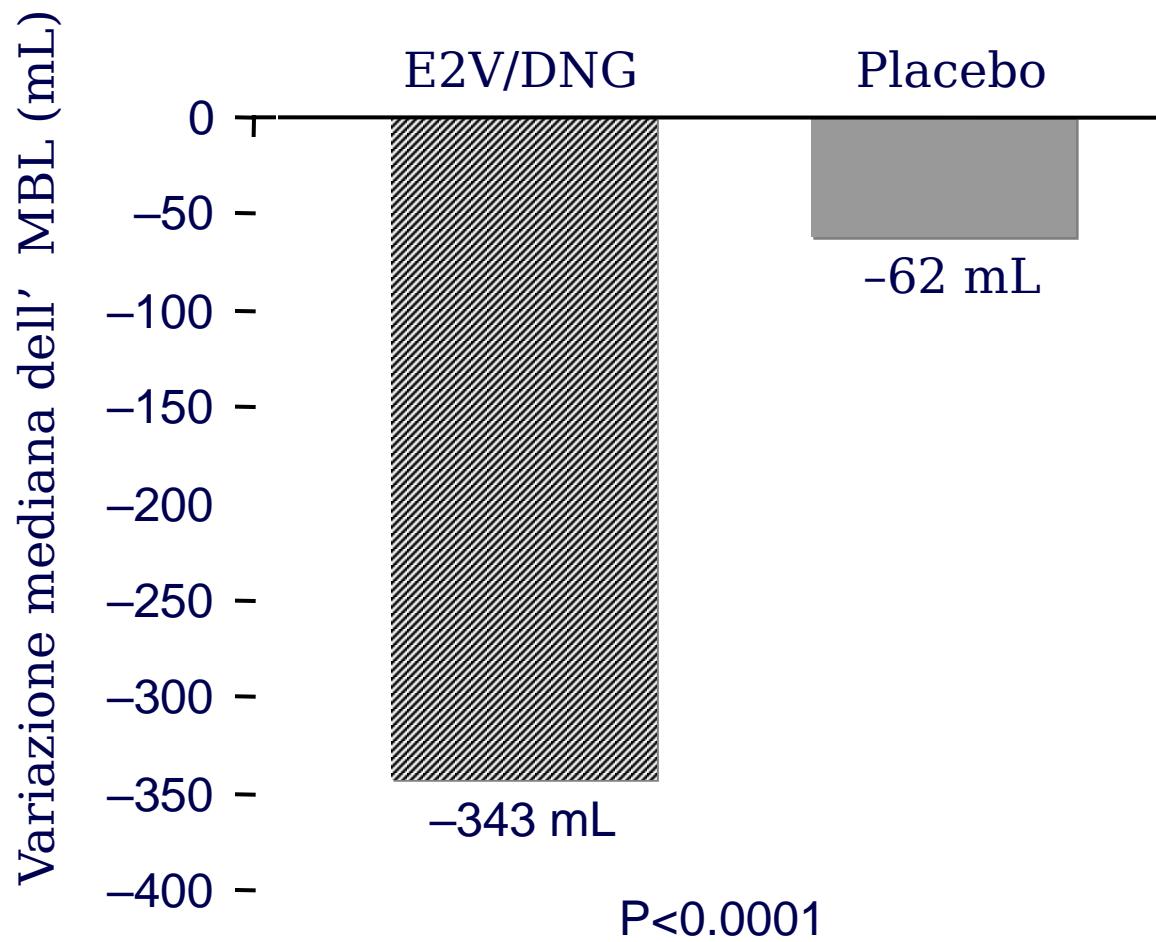
# Interazione dei progestinici con le proteine vettrici

- Effetti sulla sintesi epatica
- Affinità di legame

# Attività uterotropica di diversi progestinici

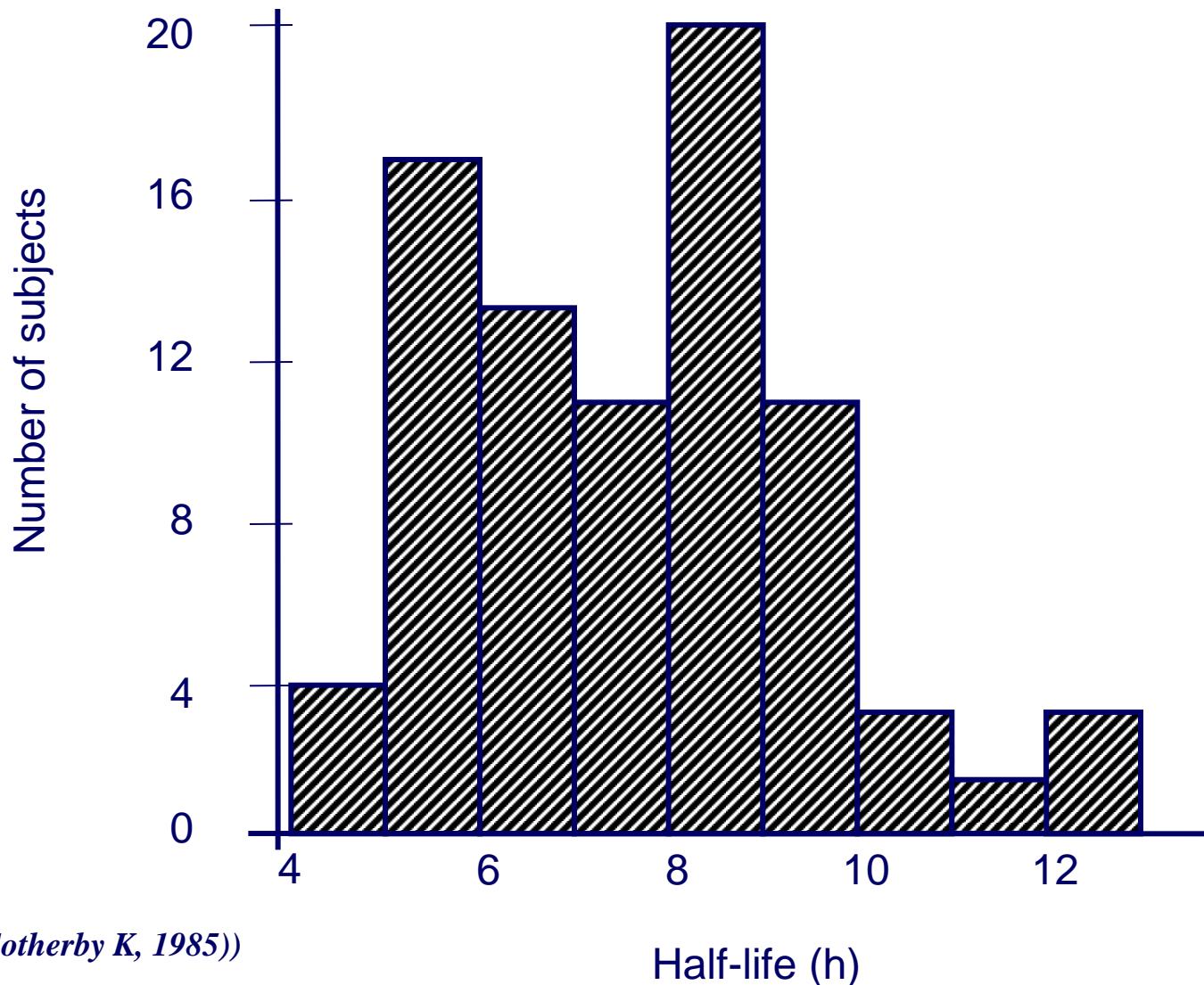


## Variazione mediana nella MBL – dati pooled



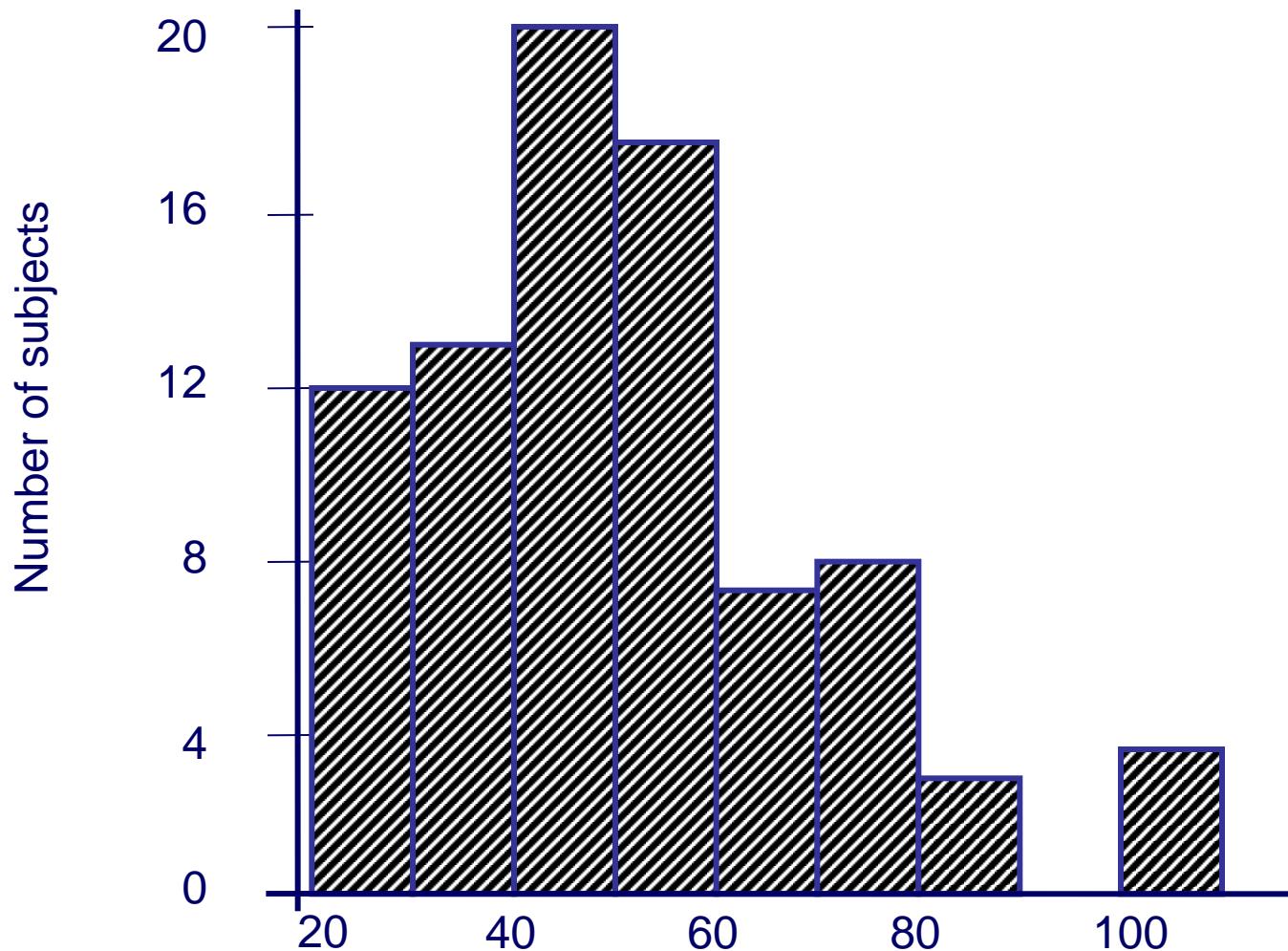


# Range of half-lives of elimination for norethisterone





# Range of bioavailability (area under the serum concentration – time curve) for norethisterone





## Il concetto di minima dose inibente stabilmente l'ovulazione

Progestinico	Dose minima inibente l'ovulazione mg/die p.o.
Progesterone	300
Didrogestrone	>30
Medrogestone	10
Medrossiprogesterone acetato	10
Clormadinone acetato	2
Ciproterone acetato	1
Noretisterone	0.5
Noretisterone acetato	0.5
Linestrenolo	2.0
Etinodiolo diacetato	2.0
Levonorgestrel	0.05
Desogestrel	0.06
Gestodene	0.03
Norgestimate	0.2
Dienogest	1.0
Drospirenone	2.0
Promegestone	0.5
Nomegestrolo acetato	5.0
Trimegestone	0.5

## **EPE e tipo di estrogeno**

**Etinilestradiolo**  
~~Etinilestradiolo~~  
**(EE)**  
~~(EE)~~



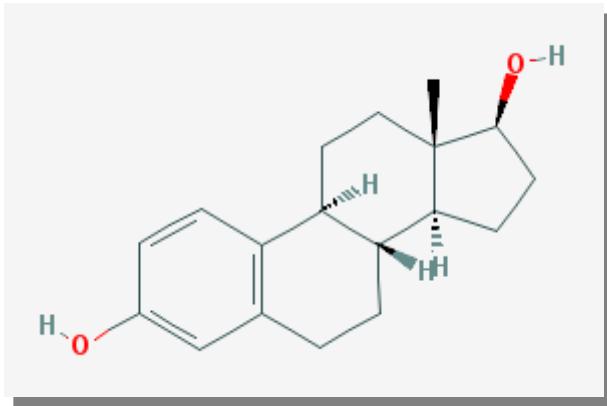
**Estrogeno di sintesi**  
~~Estrogeno di sintesi~~

**Estradiolo valerato**  
~~Estradiolo valerato~~  
**(E<sub>2</sub>V)**  
~~(E<sub>2</sub>V)~~

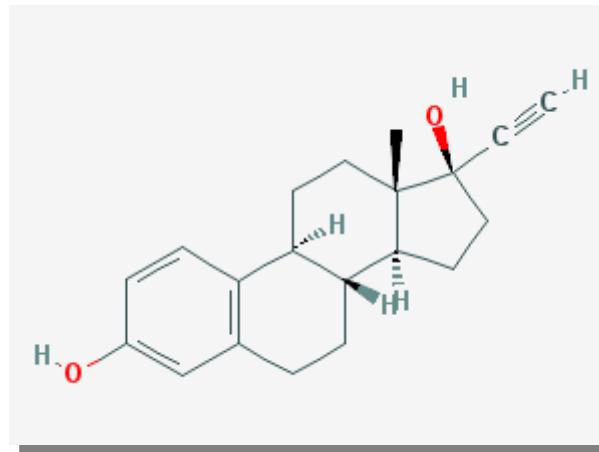
**Estradiolo (E<sub>2</sub>)**  
~~Estradiolo (E<sub>2</sub>)~~



**Estrogeni naturali**  
~~Estrogeni naturali~~

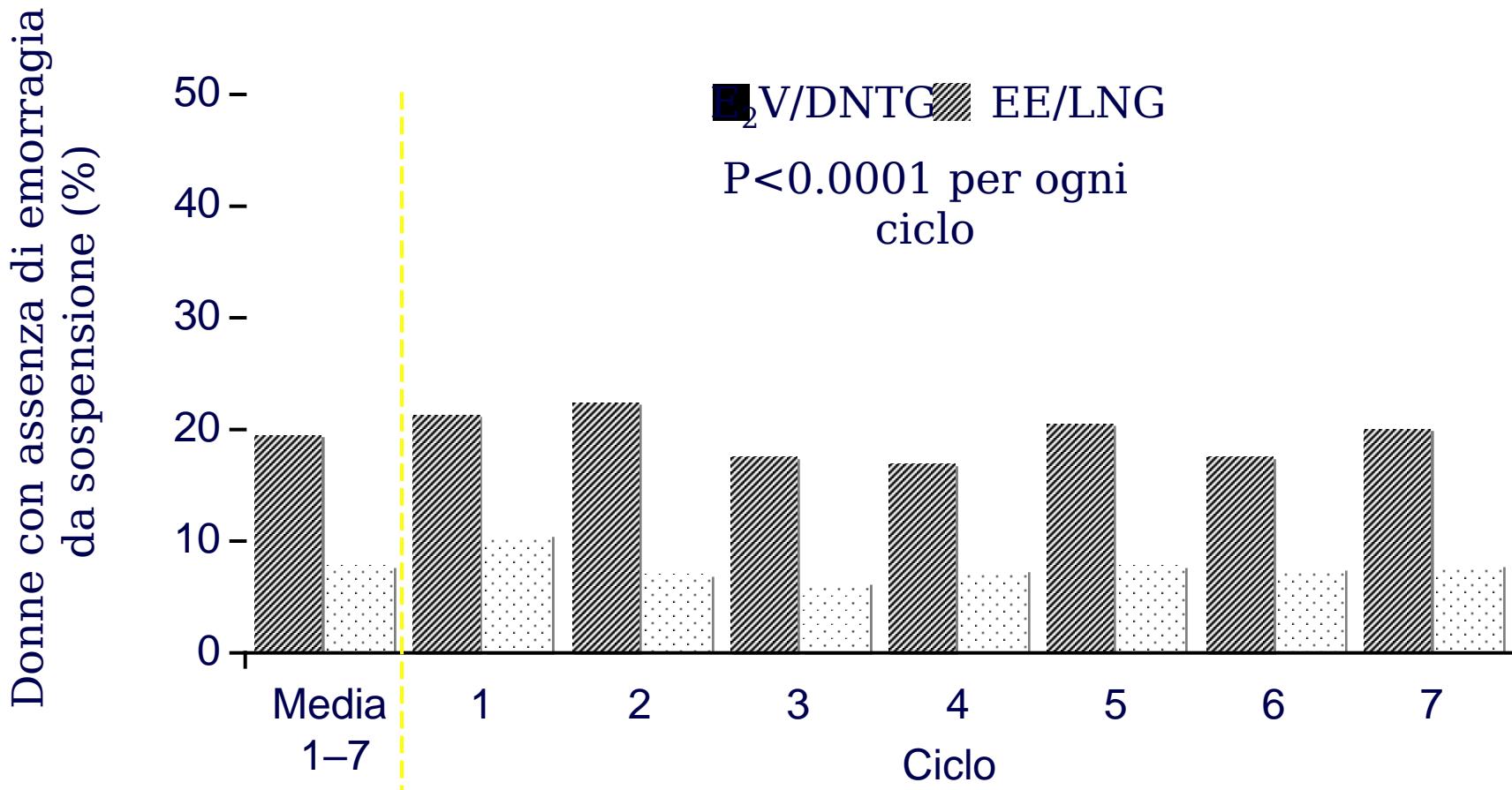


Estradiolo

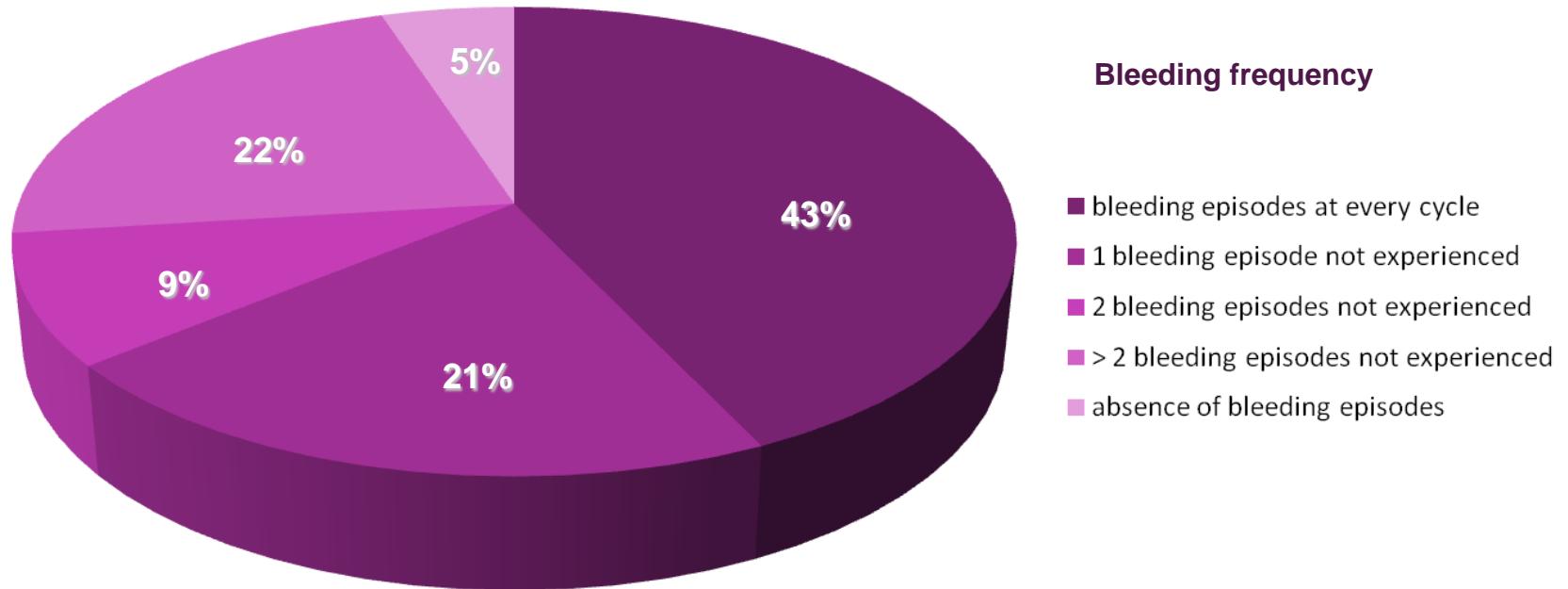


Etinilestradiolo

# E<sub>2</sub>V/DNG: Assenza di emorragia da sospensione



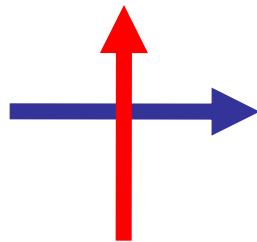
# E2/NOMAC: Assenza di emorragia da sospensione



Ahrendt et al, 2009

# La pillola come strumento di evoluzione

Riproduzione  
incessante



Ovulazione  
incessante

Pillola, ovvero la  
gravidanza fittizia

# Risk of death among ever and never users of OCs\*

Cause of death	Adjusted RR	95% CI
All causes	0.88	0.82 – 0.93
All cancers	0.85	0.78 – 0.93
All circulatory dis.	0.86	0.77 – 0.96
All digestive dis.	0.95	0.71 – 1.27
Violence (suicide)	1.26	0.73 – 2.18
All other dis.	0.84	0.74 – 0.97

\* 46112 women observed for up to 39 years and more than 1000000 wy;  
more than 4600 deaths.

Hannaford PC et al, 2010

# Risk of death among ever and never users of OCs\*

Cancer	Adjusted RR	95% CI
Endometrium	0.43	0.21 – 0.88
Ovary	0.53	0.38 – 0.72
Main gynaecol.	0.63	0.49 – 0.82
CNS - pituitary	0.84	0.47 – 1.50
Site unknown	0.88	0.67 – 1.15
Other cancers	0.83	0.70 – 1.00

\* 46112 women observed for up to 39 years and more than 1000000 wy;  
more than 4600 deaths.

Hannaford PC et al, 2010

# Risk of death among ever and never users of OCs\*

Cancer	Adjusted RR	95% CI
Colon/rectum	0.62	0.46 – 0.83
Gallbladder/liver	0.65	0.30 – 1.39
Lung	1.22	0.96 – 1.53
Melanoma	0.73	0.33 – 1.61
Breast	0.90	0.74 – 1.08
Invasive cervix	1.34	0.74 – 2.44

\* 46112 women observed for up to 39 years and more than 1000000 wy;  
more than 4600 deaths.

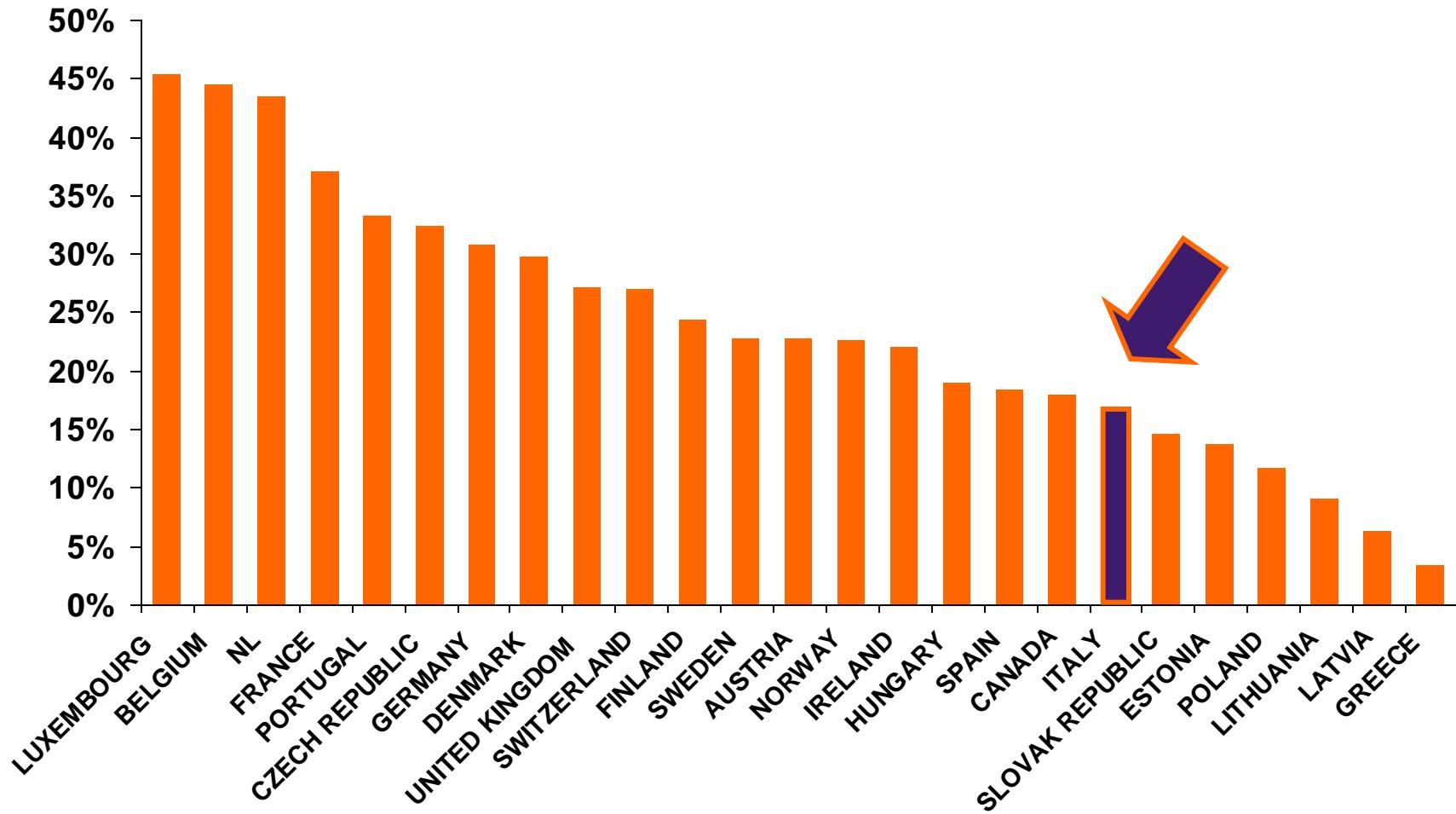
Hannaford PC et al, 2010

# Risk of death among ever and never users of OCs\*

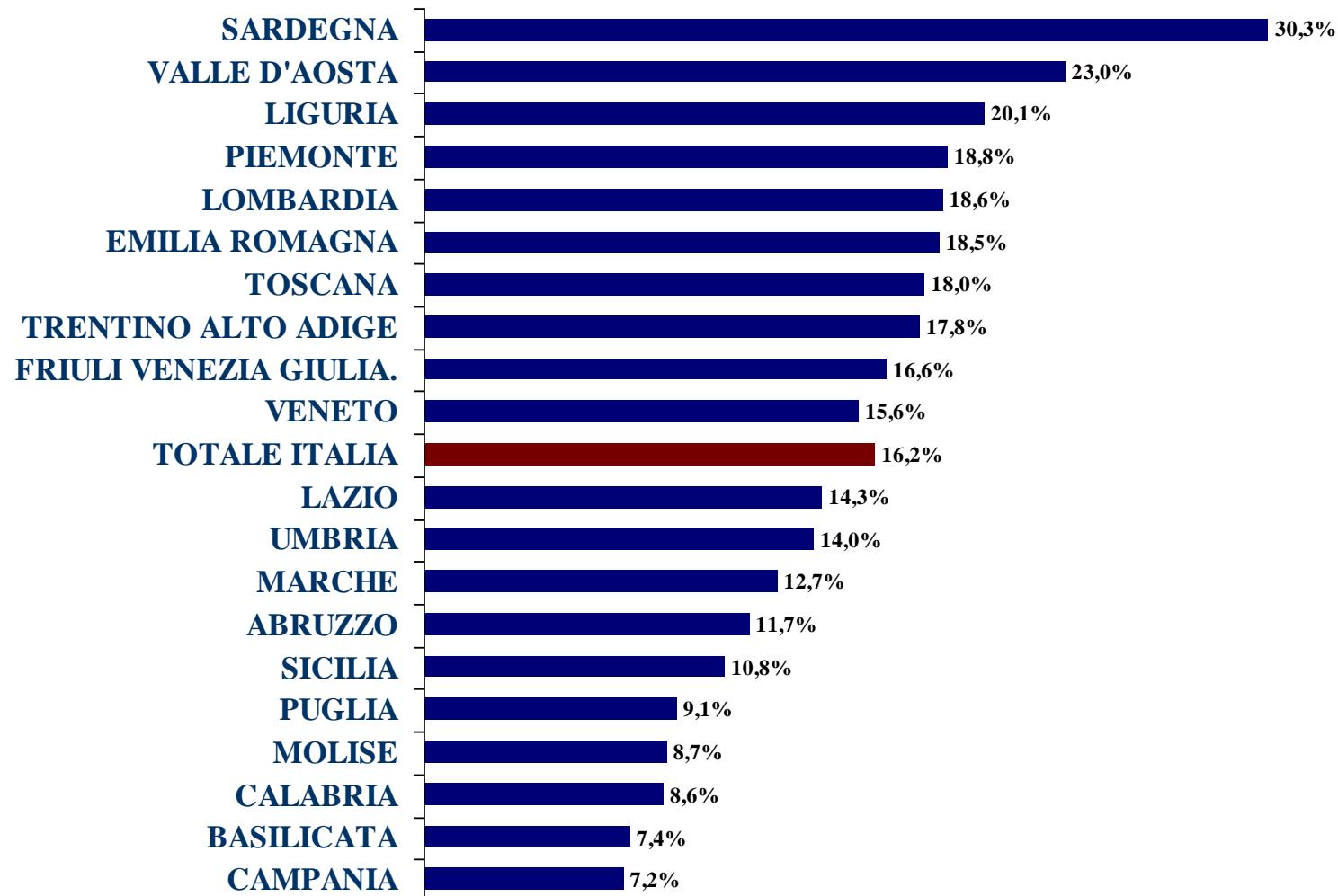
Circulatory dis.	Adjusted RR	95% CI
Ischaemic heart dis.	0.43	0.21 – 0.88
Other heart dis.	0.53	0.38 – 0.72
Cerebrovascular dis.	0.63	0.49 – 0.82
Other circulatory dis.	0.84	0.47 – 1.50

\* 46112 women observed for up to 39 years and more than 1000000 wy;  
more than 4600 deaths.

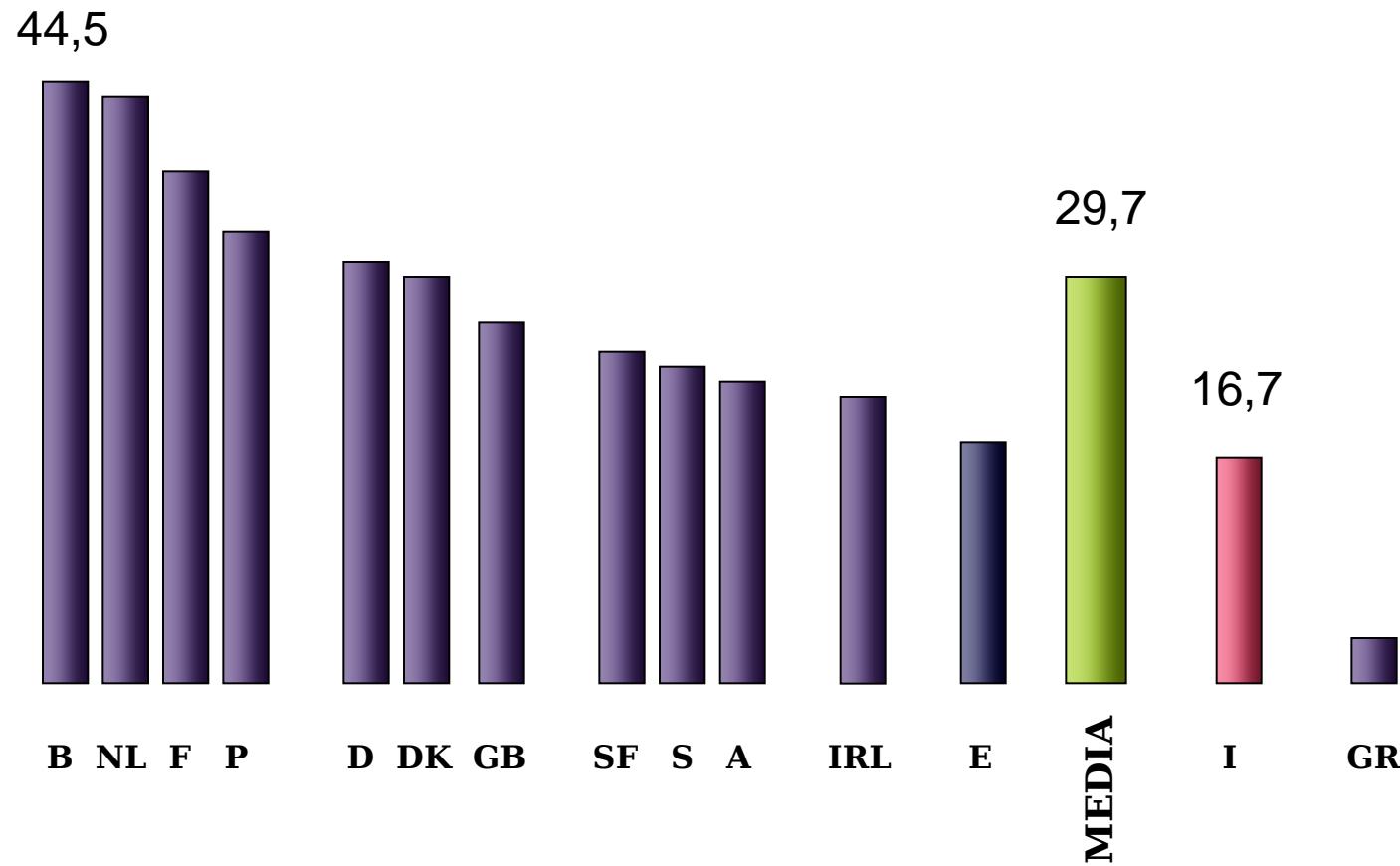
# Diffusione della contraccezione ormonale in Italia e nei paesi europei



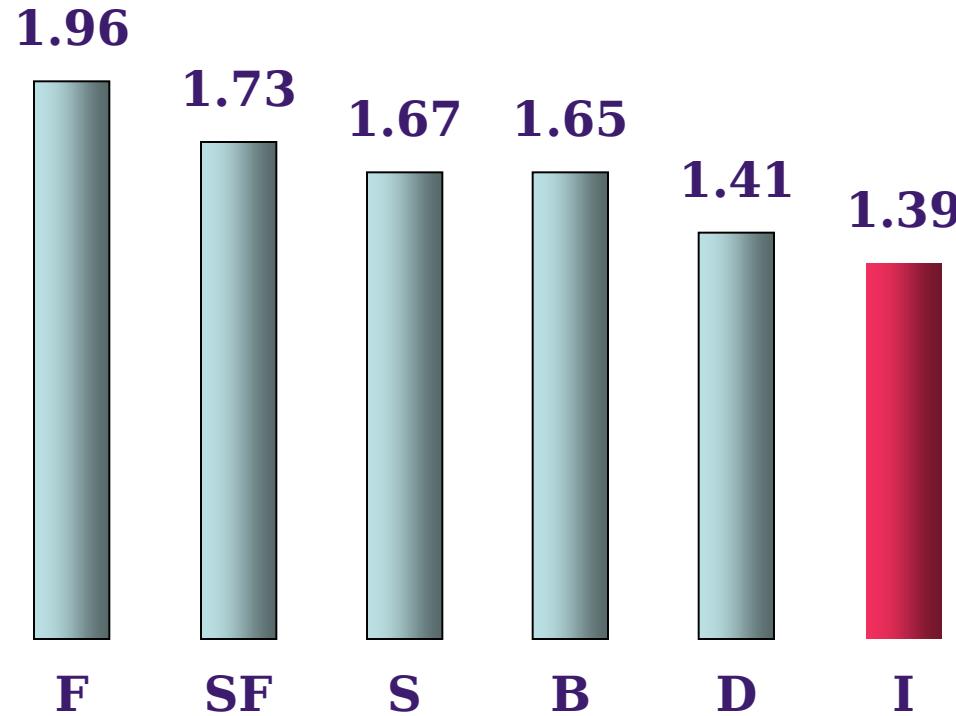
## **Diffusione della contraccezione ormonale nelle diverse regioni italiane**



## Diffusione della contraccezione ormonale in Italia e nei principali paesi europei



## Indice di fecondità in Italia e in alcuni paesi europei



## Tasso di abortività volontaria in Italia e in alcuni paesi europei



## **Diffusione della contraccezione ormonale, tasso di natalità e tasso di abortività volontaria nelle diverse macro-regioni italiane**

