

BENEFITS OF IMPROVEMENT OF ORAL CONTRACEPTIVE PILL COURSE

Master, MD LE QUANG THANH
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Situation of contraceptive method use in Vietnam and in the world

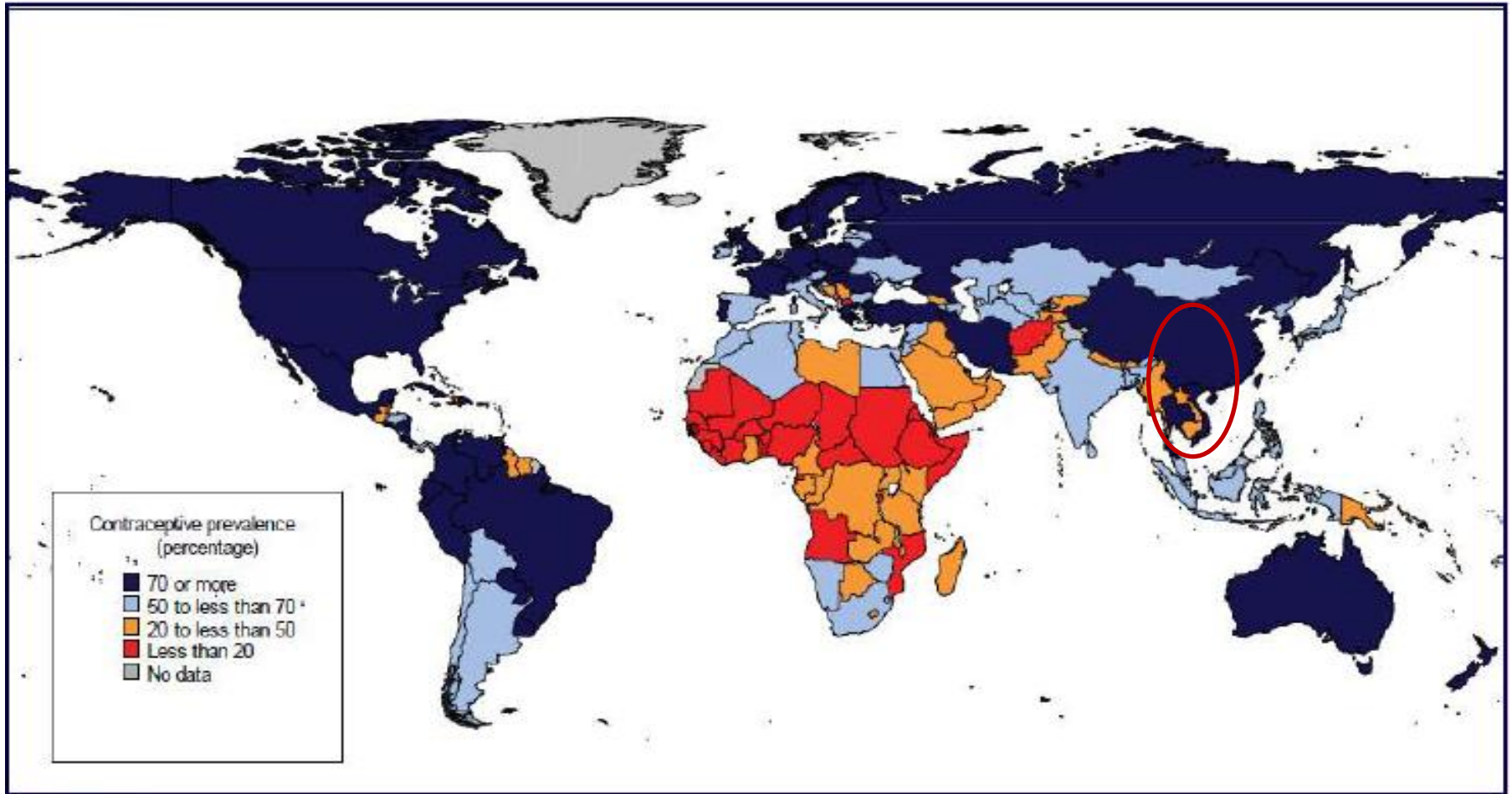
History of oral contraceptive pill development

Benefits of improvement of oral contraceptive pill course

Conclusion

SITUATION OF CONTRACEPTIVE METHOD USE IN THE WORLD

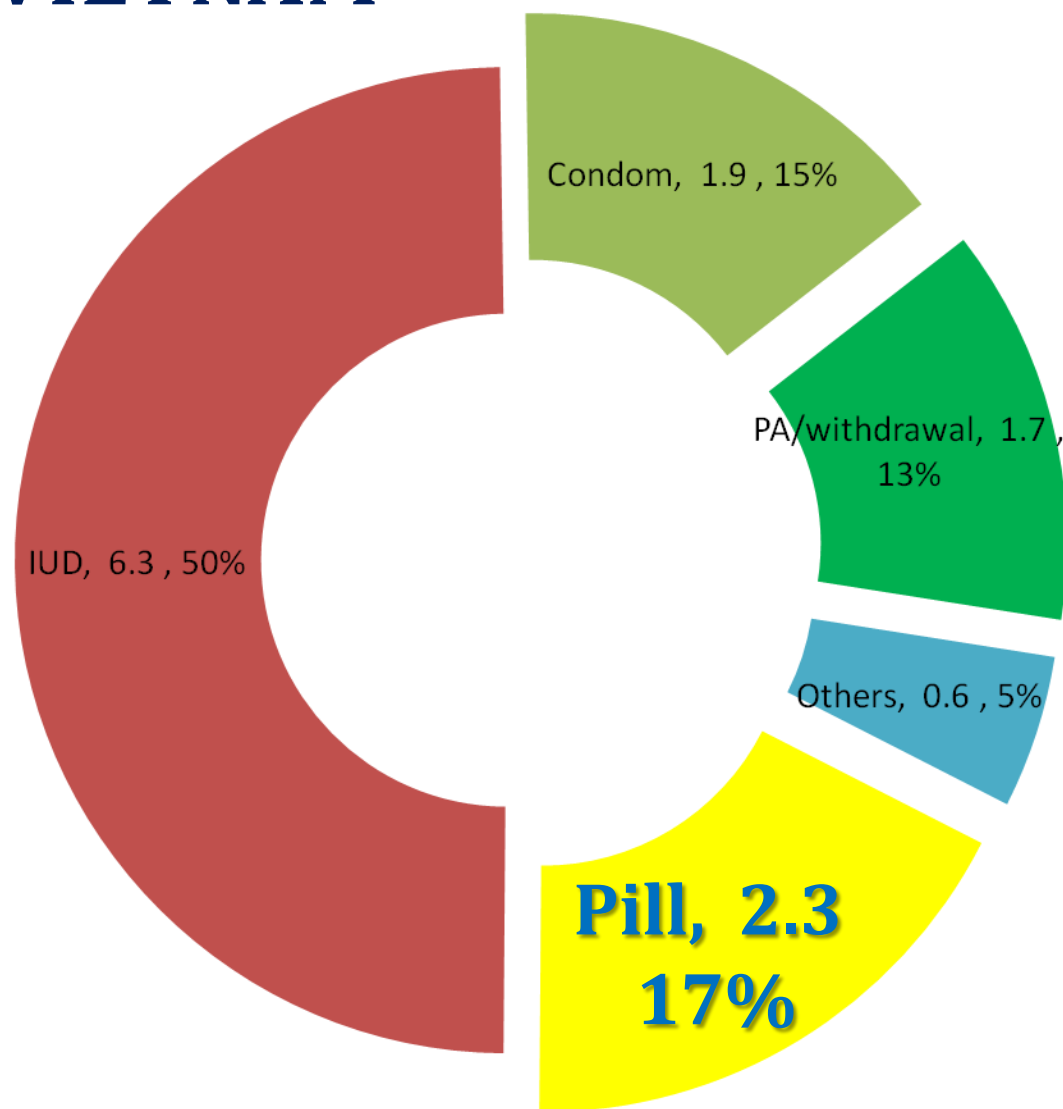
% of women aged 15-49 using contraceptive methods in the world



SITUATION OF CONTRACEPTIVE METHOD USE IN VIETNAM



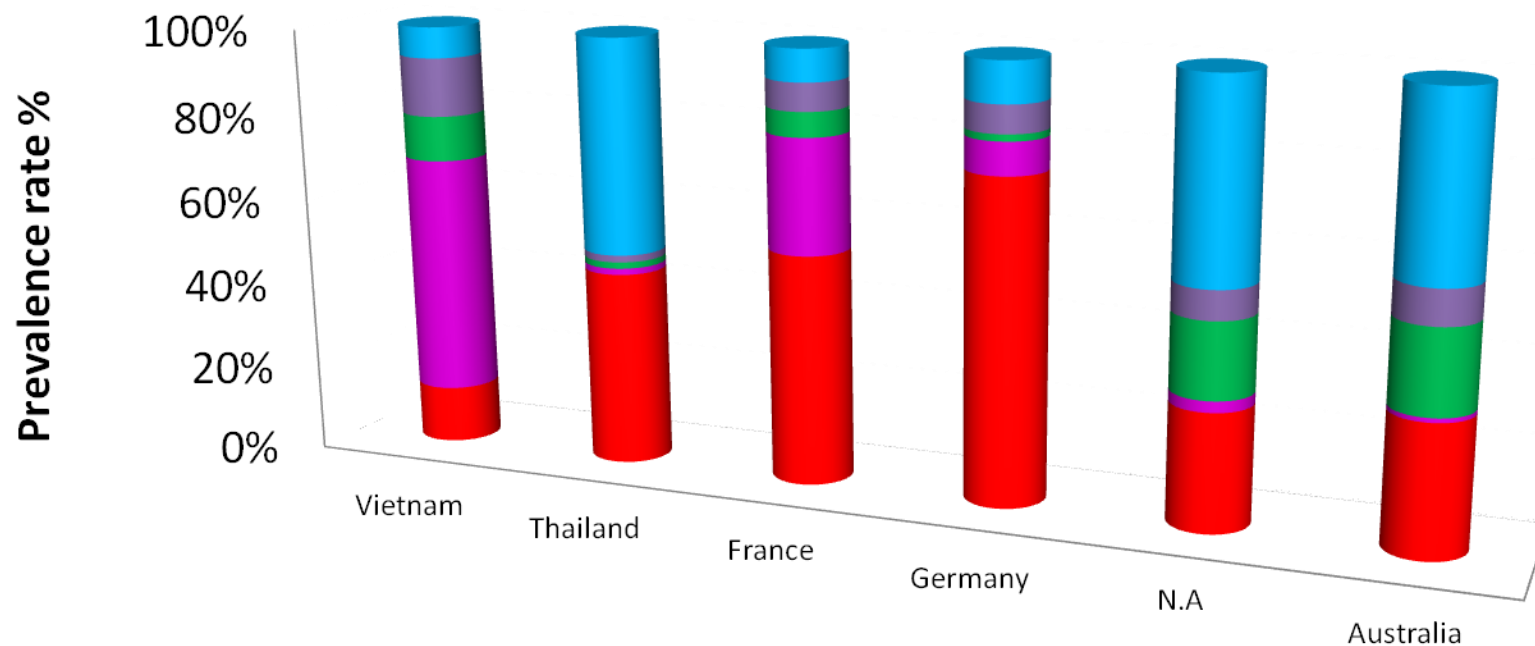
12.8 millions of
Vietnamese women aged
15-49 using contraceptive
methods



(*) 2004-2012: General Statistics Office. "1/4/2012 PCS: Major findings". 12-2012. Table 4.3. Page 38.

Trends of contraceptive method choice in Vietnam compared to other countries in the world

World Contraceptive Use (2009)



	Vietnam	Thailand	France	Germany	N.A	Australia
Others (Implant, injection, foam...)	5.7%	40.7%	6.1%	6.6%	31.8%	32.4%
Withdrawal/periodic abstinence	10.8%	1.3%	5.3%	4.5%	4.7%	6.3%
Comdom	8.3%	1.2%	4.7%	1.1%	12.2%	15.2%
IUD	43.7%	1.2%	21.9%	5.3%	1.8%	0.8%
Pill	10.4%	36.7%	43.8%	52.6%	19.0%	23.8%

CONCEPTS AND INTRODUCTION OF COMBINED ORAL CONTRACEPTIVES (COC)



1927

Adolf Butenand and CS, separated of Estrone from placenta; Nobel prize

1929

Adolf Butenand and Edward Aldlberg Doisy, isolated and identified the molecular structure of estrogens

1938

German scientists, developed ethinyl estradiol

1960

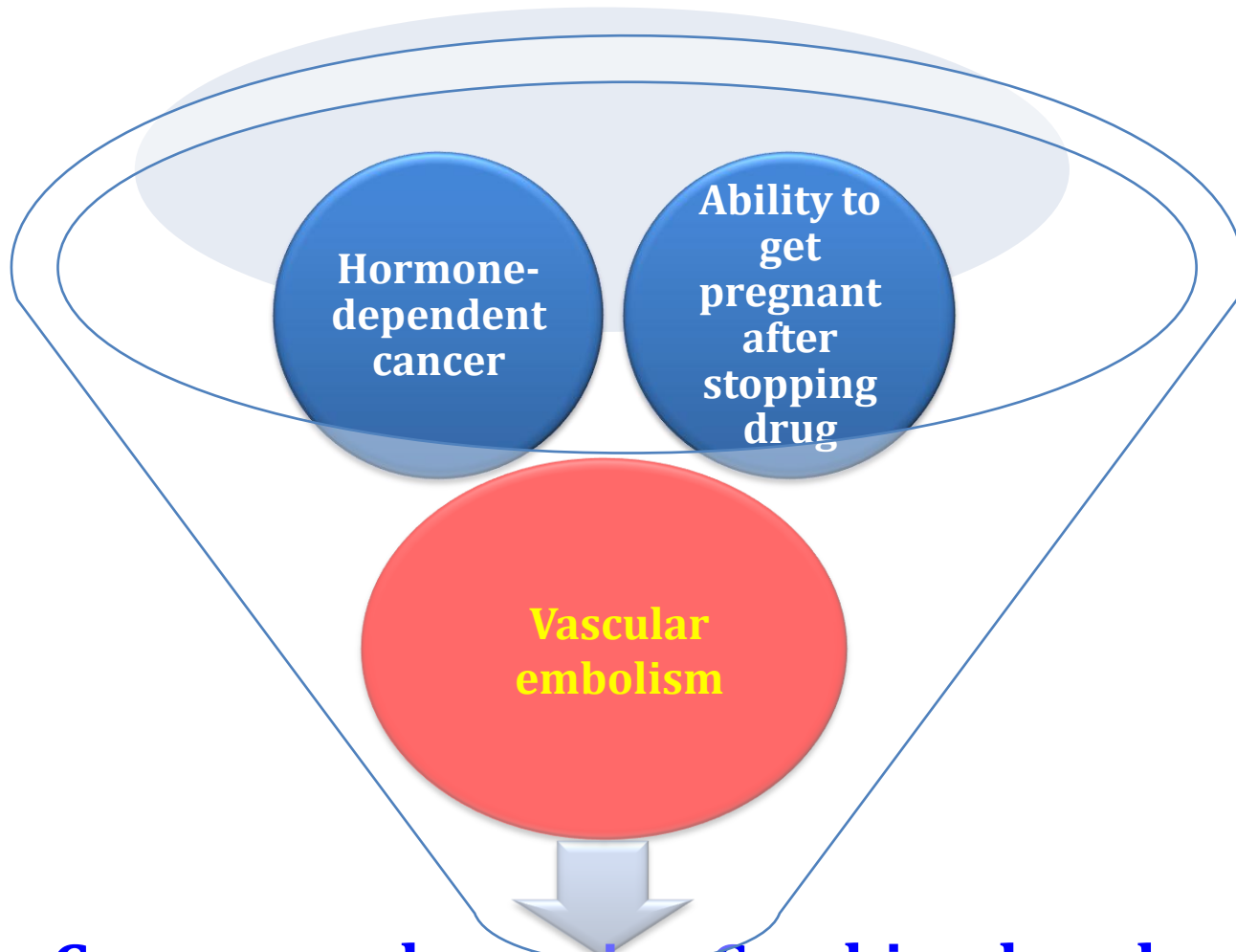
USA, Enovid[®] (norethynodrel + mestranol) were launched in the market

1961

Anovlar[®] (norethindrone acetate + ethinyl estradiol), the first pill of Asia-Pacific was introduced

CURRENT

- Combined hormonal contraceptive pills: Estrogens + Progestins
- Trend:
 - ▶ Reduce estrogen contents, use estrogens closing to natural estrogen.
 - ▶ Improve and find out new progestins
 - ▶ Change course



Concerns when using Combined oral contraceptives (COCs)

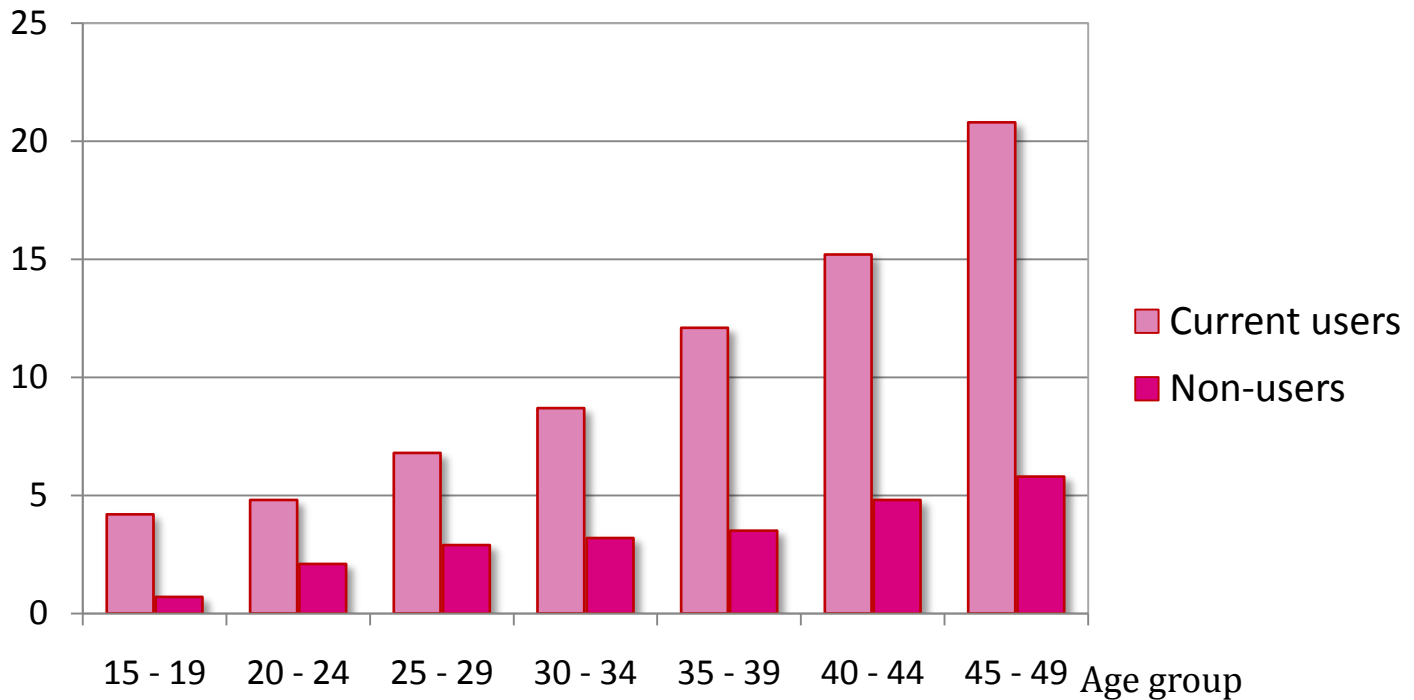
RISK OF THROMBOSIS



- COCs cause VTE (Venous thromboembolism): low
- Usually occurs in women with available risk factors
 - Hypertension, diabetes
 - Obesity
 - Smoking
 - Less movement
- Pregnant women: the risk of VTE is **many times higher** than women taking COCs.
- Usually occurs in the first year of use
- The risk of VTE decreased after several weeks of drug discontinuation which is **equivalent** to those who did not use COCs

Risk of VTE increases with age

Rate per 10,000 women-years



RISK OF VTE

USE AND DO NOT USE COC

- Women of reproductive age
 - ✓ 4–5/10,000 woman-years : Do not use COC
 - ✓ 9-10/10,000 woman-years : Use COC (the average number of studies)
 - ✓ 29/10,000 woman-years : pregnant women
 - ✓ 300–400/10,000 woman-years : women after childbirth
- Risk of VTE in women using COC
 - Highest in the first months of using COC
 - Equivalent to non-users after several weeks of drug discontinuation
 - **This risk is very low and very much lower than in pregnant women**

RISK OF VTE FOR TYPES OF COC

Cochrane 2014: Risk of VTE

- Depending on the types of progestin and doses of ethinyl estradiol (EE)
- Similar for COC having 30-35µg of EE and gestodene, desogestrel, cyproterone acetate and drospirenone, approximately 50-80% higher than the type of levonorgestrel

RISK OF VTE FOR EACH TYPE OF COC

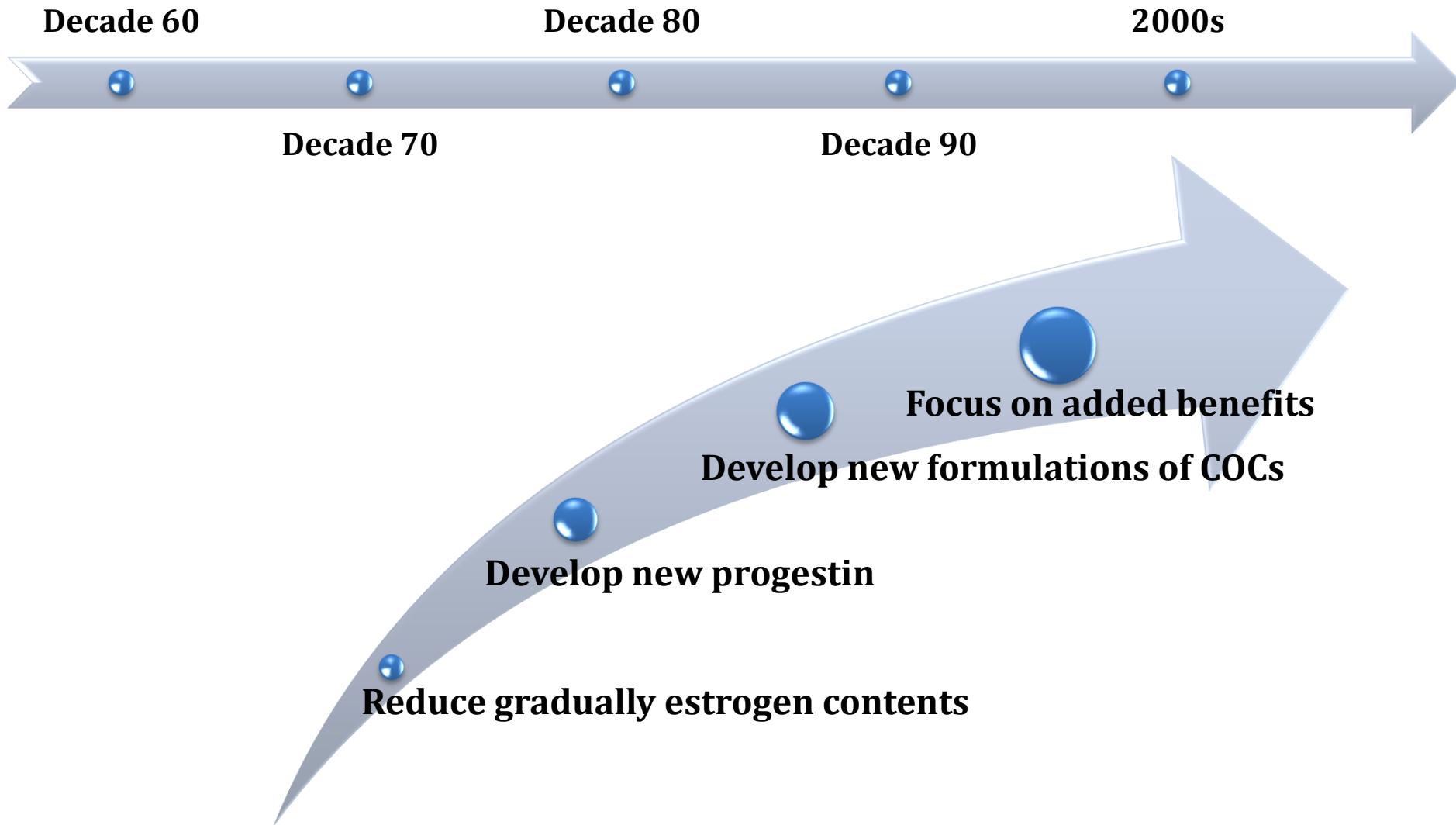
Groups of women	Risk of VTE /year
Not using COC and not pregnant	2/10,000
Levonorgestrel, norethisterone or norgestimate	5-7/10,000
Etonogestrel or norelgestromin	6-12/10,000
Drospirenone, gestodene or desogestrel	9-12/10,000
Chlormadinone, dienogest or nomegestrol	Not yet known ¹

¹ Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products

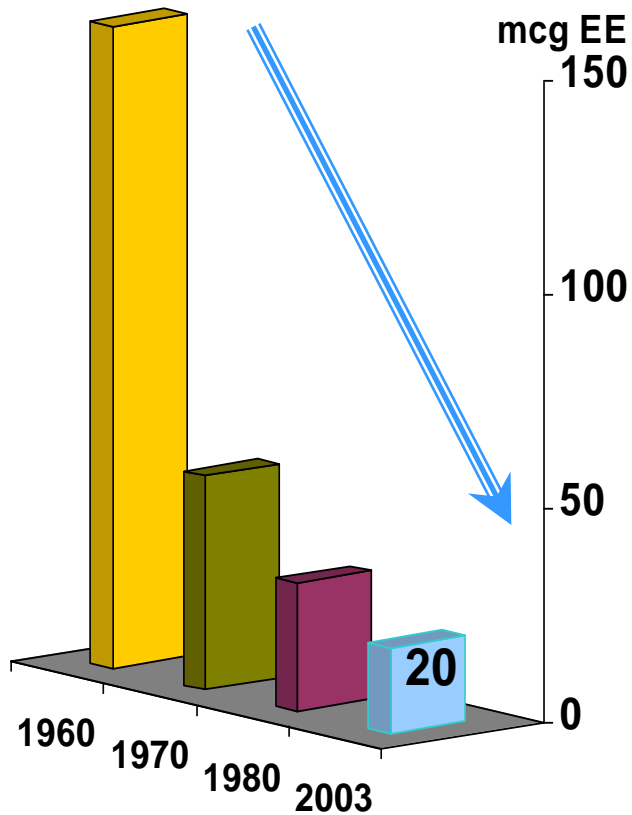
RIGHT UNDERSTANDING ON RISK OF VTE AND COC

- Higher doses of EE, higher risk of VTE
- The rate of VTE is not the same between the types of COC, however the absolute value is not concerned.
- The benefits brought by COC far outweigh the risk of VTE.

RESEARCH AND DEVELOPMENT EFFORTS OF COCs AFTERWARDS



REDUCE ESTROGEN DOSES

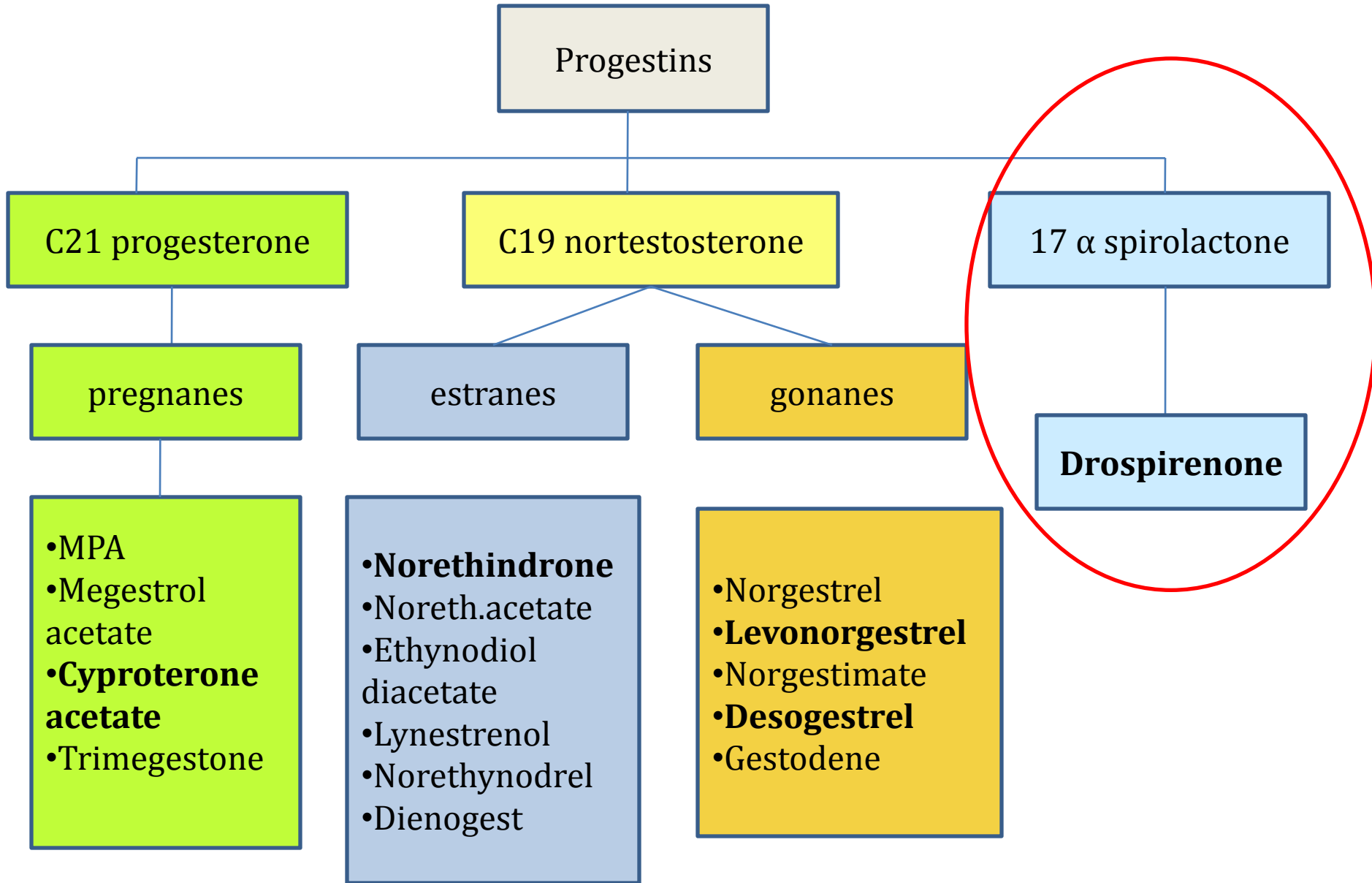


- ❖ Less causing side effects, safety.
- ❖ Highly effective contraception.
- ❖ Added benefits.
- ❖ **Decreased risk of VTE**

DEVELOP NEW PROGESTINS

1 st generation	2 nd generation	3 rd generation	4 th generation
Norethisterone	Levonorgestrel (Rigevidon)	Desogestrel (Estraceptine Regulon, Marvelon, Embevin 28 (POP))	Drospirenone (Drosperin, Drosperin 20, Yasmin, Yaz)
Ethinodiol diacetate (POP)	Norgestrel	Gestodene (Lindynette, Gynera, Ciclomex)	Dienogest (Qlaira with estradiol valerate)
Lynestrenol (Exluton)		Norgestimate (Cilest [®])	
≥ 50 µg EE	30 /35 µg ethinyl estradiol	20 / 30 µg ethinyl estradiol	(20 / 30 µg EE + drospirenone 3 mg)

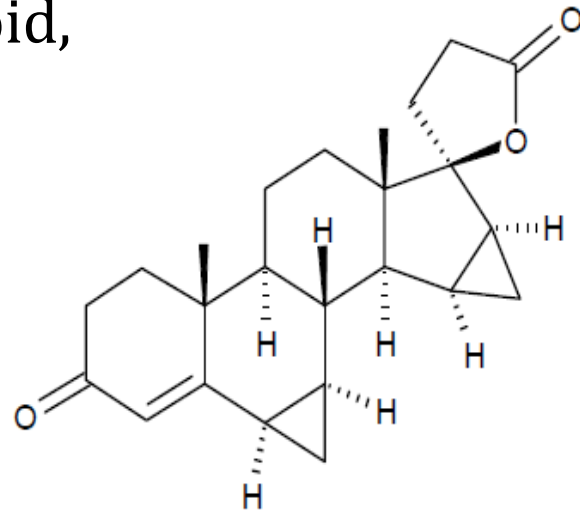
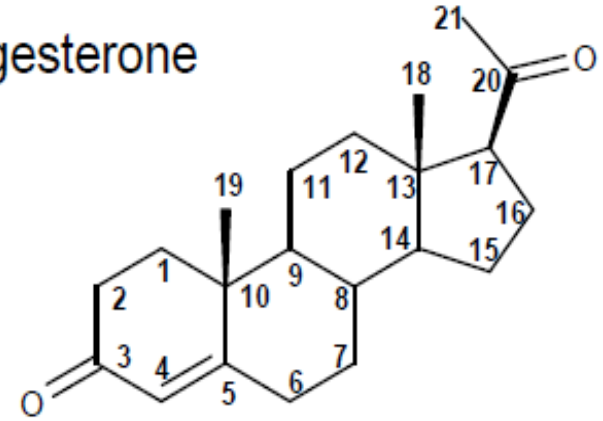
CLASSIFY PROGESTINS ACCORDING TO CHEMICAL STRUCTURE



DROSPIRENONE (DRSP)

1. The chemical formula is very close to natural progesterone
2. Synergy with spironolactone, anti-aldosterone, anti-mineralocorticoid, anti-androgen
3. Average bioavailability
4. Half-life of 30 hours

Natural progesterone



Drospirenone (DRSP)

PHARMACOLOGICAL PROPERTIES OF THE LATEST GENERATION PROGESTOGEN - **DROSPIRENONE**

Progesterones	Pharmacological activity				
	Progesterone	Anti-Mineralocorticoid	Anti-Androgen	Androgen	Glucocorticoid
Progesterone	+	+	(+)	-	-
Cyproterone acetate	+	-	+	-	(+)
Desogestrel	+	-	-	(+)	-
Levonorgestrel	+	-	-	(+)	-
Norgestimate	+	-	-	(+)	-
Drosperinone	+	+	+	-	-

Helps to reduce weight

Treats acne effectively

+ clear effects at therapeutic doses, - no effects, (+) unknown effects

BENEFITS OF DROSPERINONE BESIDES CONTRACEPTION

Drospirenone

```
graph TD; A[Drospirenone] --> B[Anti-mineralocorticoid]; A --> C[Anti-androgen]; B --> D["Similar effects as natural progesterone on the process of salt and water retention:  
Reduce breast turgidity  
Control weight well  
Reduce premenstrual symptoms"]; C --> E["Competes androgen receptor:  
Reduce sebum secretion  
Reduce acne  
Reduce hirsutism"];
```

Anti-mineralocorticoid

Similar effects as natural progesterone on the process of salt and water retention:

- Reduce breast turgidity**
- Control weight well**
- Reduce premenstrual symptoms**

Anti-androgen

Competes androgen receptor:

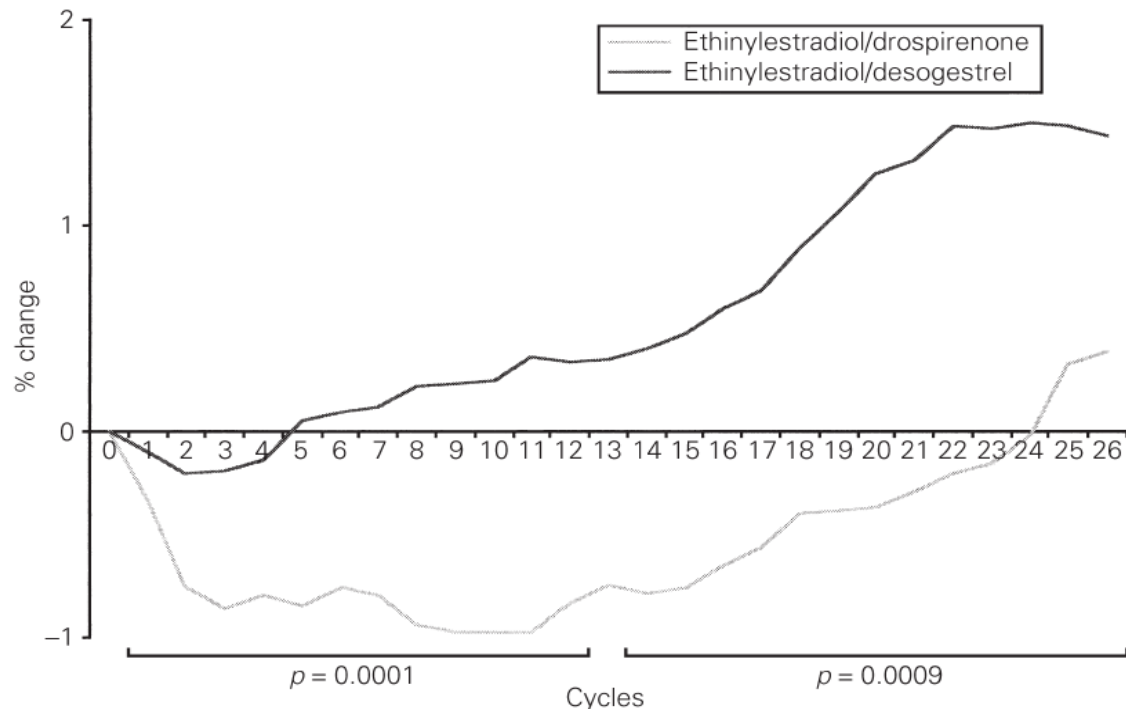
- Reduce sebum secretion**
- Reduce acne**
- Reduce hirsutism**

BENEFITS RELATING TO WEIGHT



Anti-mineralocorticoid: increases water and salt excretion caused by estrogen, helping to reduce body weight.

REDUCE WEIGHT OVER TIME IN THE GROUP TAKING DROSPIRENONE/EE



Randomized, open-label study in the 26 European centers, n = 900 .

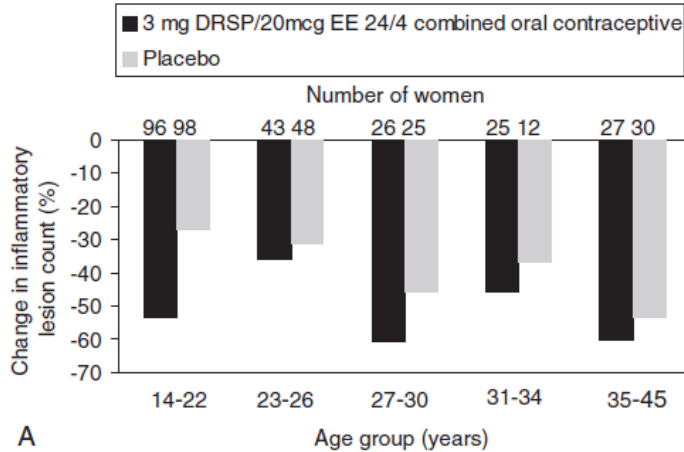
J.-M. Foidart, W. Wuttke*, G. M. Bouw†, C. Gerlinger‡ and R. Heithecker**

The European Journal of Contraception and Reproductive Health Care 2000;5:124-134

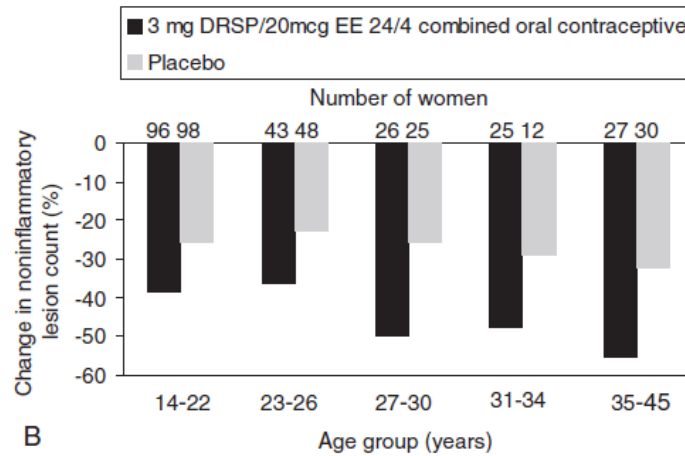
BENEFITS RELATING TO SKIN ISSUES

Anti-androgen: does not cause greasy skin, reduces acne, alopecia, hirsutism, does not cause weight gain.

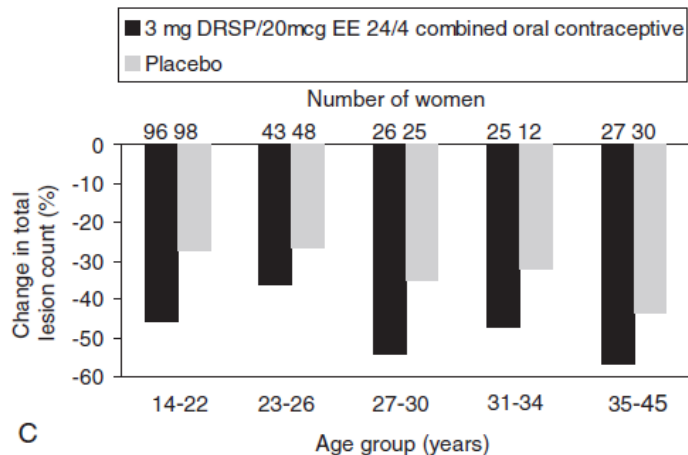
EFFECTIVE TREATMENT OF ACNE



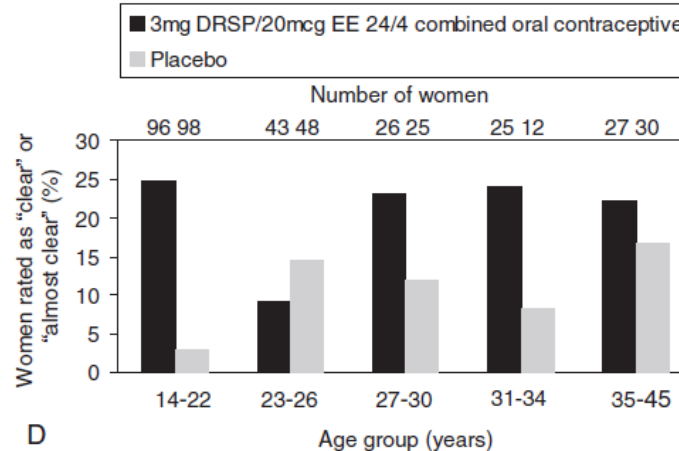
A



B



C



D

Randomised, double-blinded study in 538 health women, in the 28 US centers

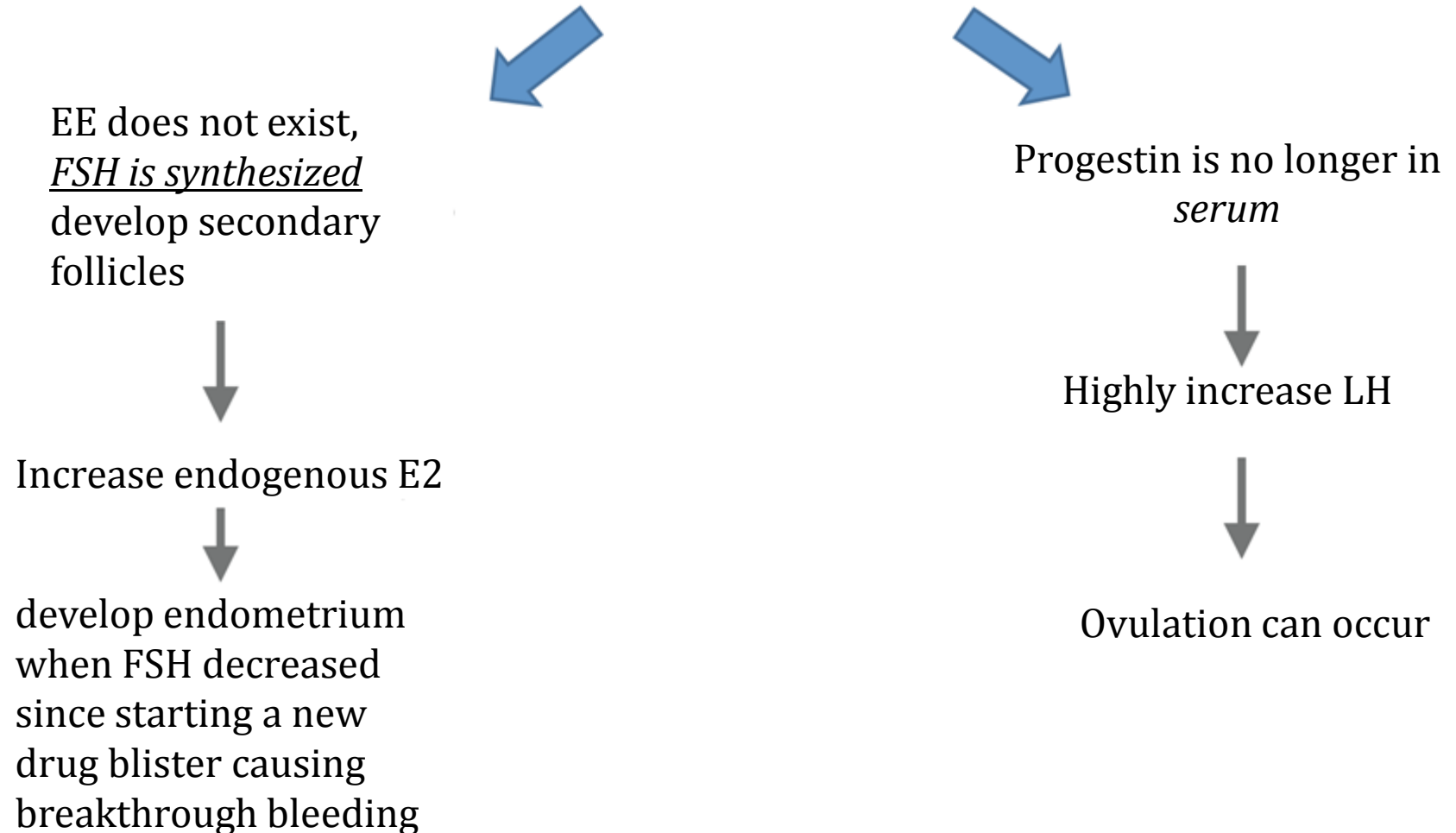
BENEFITS OF HORMONAL CONTRACEPTIVE PILLS WITH EE/DROSPIRENONE BESIDES CONTRACEPTIVE EFFECT

- Regulate menstrual cycle
- Reduce blood loss during menstruation
- Reduce menstrual pain
- Reduce anemia, iron deficiency
- Help the metabolism that leads to cardiovascular benefits
- Improve skin condition
- Improve quality of life

CHANGE COURSE

- According to cycles (11 days taking pills containing only ethinyl estradiol and 10 days taking pills containing both ethinyl estradiol and progestin).
- Combine continuously: (21 day pills with both ethinyl estradiol and progestin) in one phase, two phases, three phases – having change of hormone contents in various phases.
- According to process of 21/7 (21 days taking oral pills with hormone and 7 days taking oral pills without hormone) switched **to 24/4 or 21/2 days with placebo/5 days** with lower hormone level than the first 21 pills, or **84/7**...Explanation for changing the process from 21/7 to 21/2/5 or 21/4 is as follows:

Low EE (20 – 30 mcg) is cleared soon completely in 3-4 days. Using contraceptives according to the process of 21/7, up to 7 days "do not take hormone", the body has many days without EE + Progestin.



IMPROVEMENT OF HORMONE COURSE

Shorten hormone-free interval (HFI)

- **Add** low dose hormone in HFI
- **Increase interval** of taking hormonal drugs

The common formulations of improvement of hormone course

Progestin	Ethinyl Estradiol	Days of taking drugs	Days of discontinuing drugs (remaining days after shortening HFI)
Levonorgestrel 150 mcg	84 days: 30 mcg 7 days: 10 mcg	84+7	0
Norethindrone acetate 1 mg	20 mcg	24	4
Drosperinone 3 mg (**)	20 mcg	24	4
Desogestrel 150 mcg (*)	21 days: 20 mcg 5 days: 10 mcg	21 5	2
Levonorgestrel 150 mcg	30 mcg	84	7

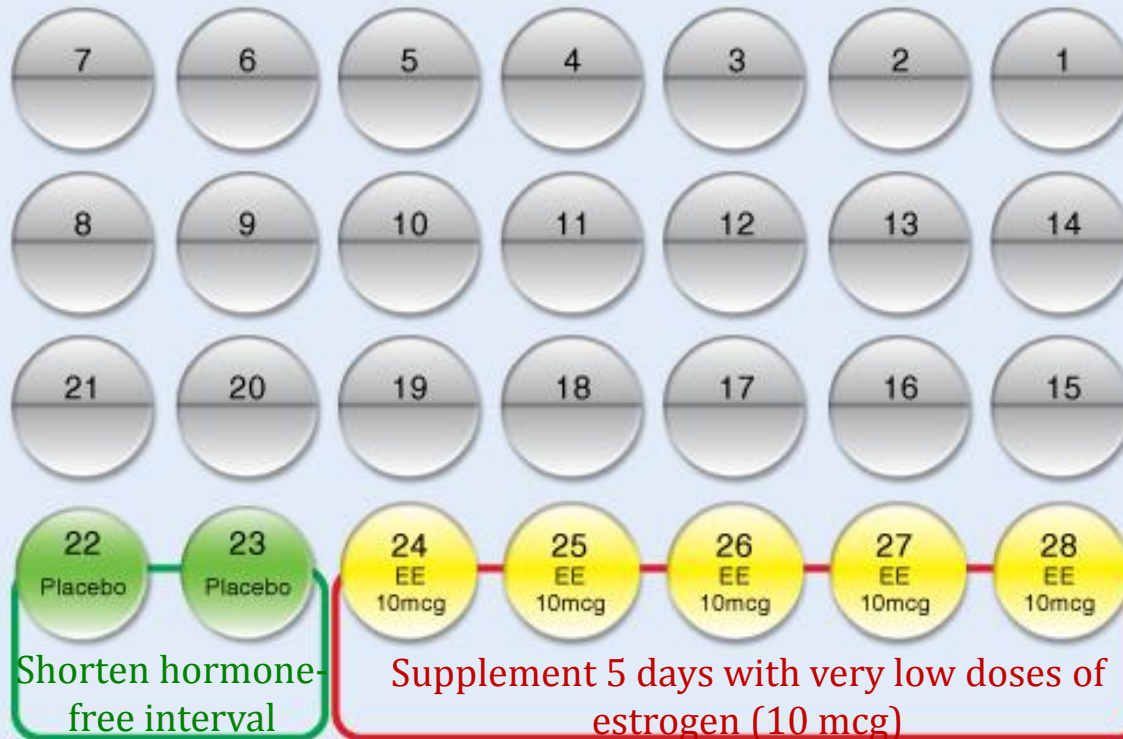
* Course of Estraceptin

** Course of Drosperin 20

SUPPLEMENT VERY LOW DOSES OF ESTROGEN TO HORMONE-FREE INTERVAL

COURSE

21+2+5



Desogestrel 0,15mg

Ethinyl estradiol (EE) 20mcg

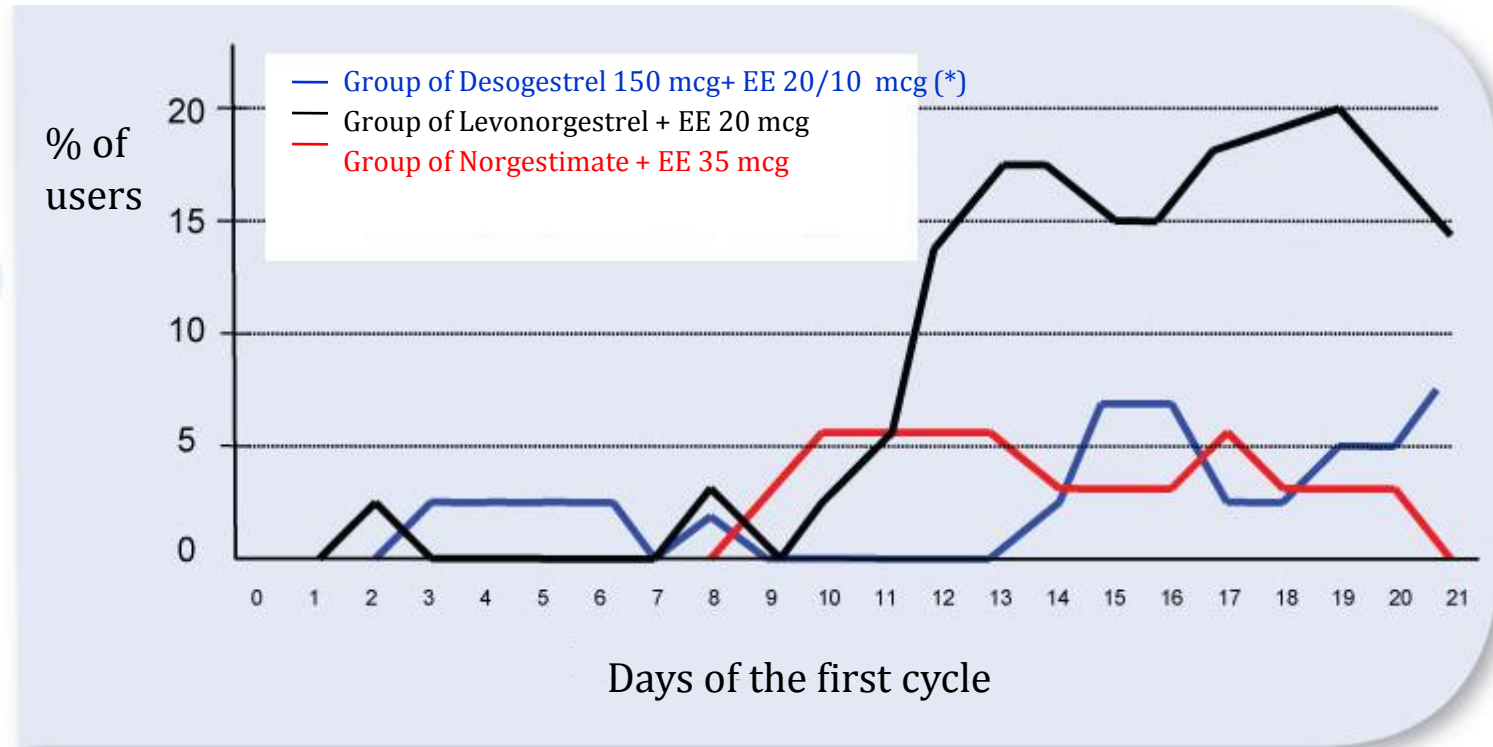
(*) Course of Estraceptin

BENEFITS OF SUPPLEMENTING LOW DOSES OF ESTROGEN TO HORMONE-FREE INTERVAL (HFI)

- Inhibit completely the growth of follicles, reduce ability of ovulation
- Control cycles well
- Reduce premenstrual symptoms, reduce dysmenorrhea
- Still have normal menstruation

Benefits of cycle control

Rate of breakthrough bleeding



Rosenberg MJ., Efficacy, Cycle Control, and Side Effects of Low- and Lower-Dose Oral Contraceptives: A Randomized Trial of 20 mg and 35 mg Estrogen Preparations, *Contraception* 2000; 60:321–329

(*) Composition of Estraceptin

Benefits of cycle control

- Control cycles well: in the first 2 cycles in the group of users taking hormones first time:

Group of desogestrel + EE 20/10 mcg:

- Equivalent to the group of norgestimate + EE 35 mcg
- Better than the group of levonorgestrel + EE 20 mcg

Rosenberg MJ., Efficacy, Cycle Control, and Side Effects of Low- and Lower-Dose Oral Contraceptives: A Randomized Trial of 20 mg and 35 mg Estrogen Preparations, *Contraception* 2000; 60:321–329



Benefits of reducing dysmenorrhea

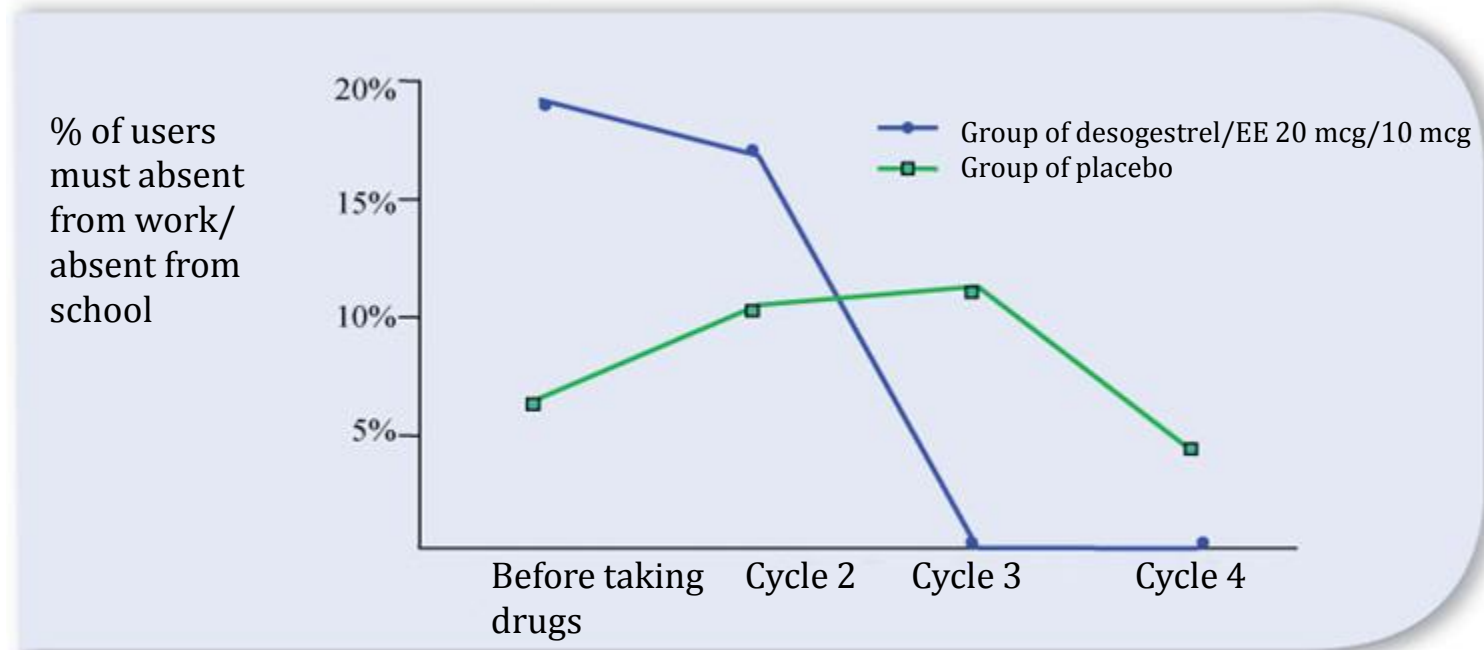
Mean change and treatment effects on the MDQ scale

MDQ Component*	DSG/EE&EE (n = 30)	Placebo (n = 29)	p-value
Cramping symptom score			
Baseline mean	2.6	2.4	0.381
Mean change	-1.4	-0.3	<0.001
Backache symptom score			
Baseline mean	2.0	1.2	0.014
Mean change	-0.6	-0.3	0.257
Menstrual pain scale score			
Baseline mean	1.8	1.5	0.090
Mean change	-0.5	-0.2	0.074
MDQ total score			
Baseline mean	37.1	31.2	0.271
Mean change	-13.7	-6.2	0.095

Hendrix SL et al. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. *Contraception*. 2002 Dec;66(6):393-9.

Improve productivity

Reduce premenstrual symptoms, reduce dysmenorrhea in the group of desogestrel / EE 20 mcg/10 mcg versus placebo helping improvement of work and study



Hendrix SL et al. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. Contraception. 2002 Dec;66(6):393-9.

(*) Composition of Estraceptin

Benefits of shortening hormone-free interval

- There were sufficient studies on supplementing estrogen to hormone-free interval
- The course of desogestrel/EE 20 mcg + 10mcg (Estraceptin) brings many advantages to the users
 - Increase effective contraception.
 - Control cycles well with low dose of 20 mcg/10 mcg estrogen.
 - Reduce premenstrual symptoms, reduce dysmenorrhea.

COURSE

DROSPERINONE/EE 24/4

Drosperinon 3mg
Ethinyl Estradiol 20mcg

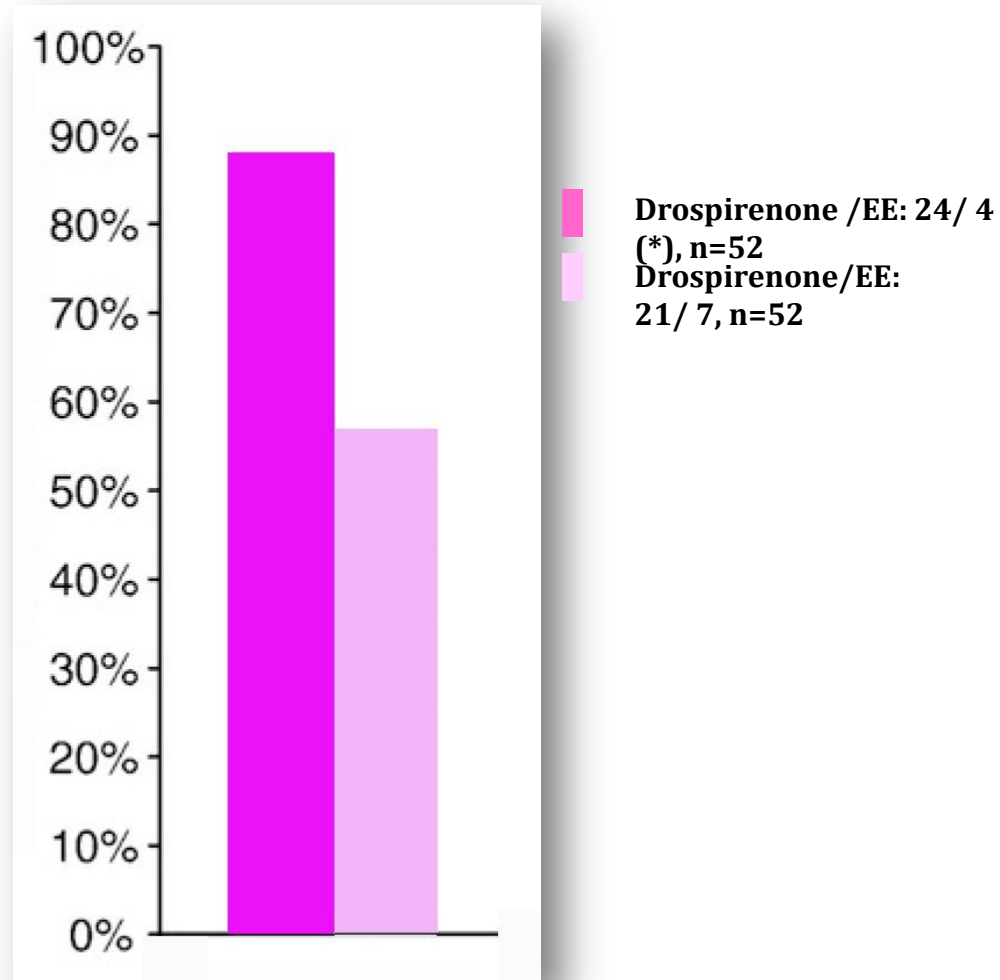
8	7	6	5	4	3	2	1
9	10	11	12	13	14	1 5	16
24	23	22	21	20	19	18	17
25	26	27	28	Placebo			

BENEFITS OF COURSE

DROSPERINONE/EE 24/4

Shorten hormone-free interval (21/ 7 → 24/ 4) helping:

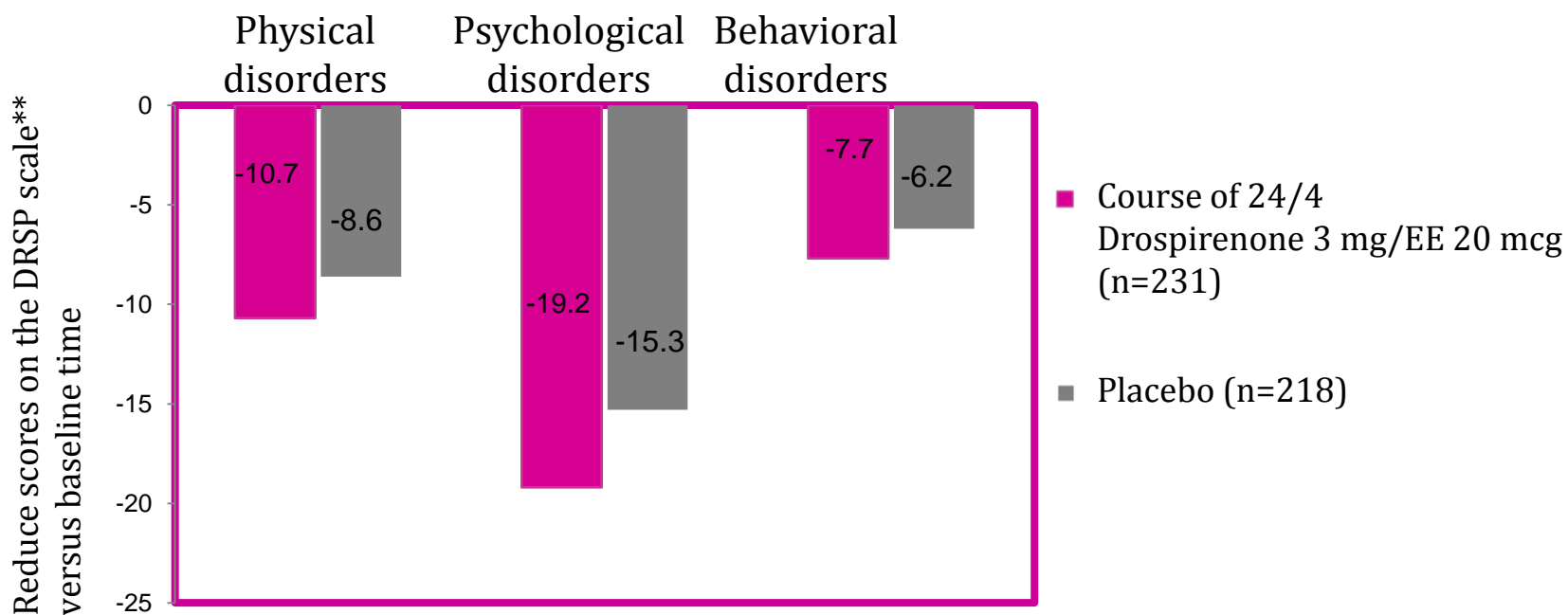
- Stronger inhibition of follicle growth
- More stable hormone concentrations



BENEFITS OF COURSE

DROSPERINONE/EE 24/4

Improve women's quality of life



A multicenter, double-blind, randomized study in 3 cycles in 450 women with symptoms of premenstrual disorder compared to placebo

BENEFITS OF COURSE IMPROVEMENT

SHORTEN HORMONE-FREE INTERVAL (HFI)

- There were sufficient studies on shortening hormone-free interval (HFI) by increasing the time of taking hormone drugs or supplementing low doses of estrogen to HFI
- The course of desogetrel/EE 20 µg+10 µg (21 + 2+ 5) and drospirenone/EE 20 µg (24 + 4) brings many advantages to the users
 - Increase effective contraception.
 - Control cycles well with low dose of 20 mcg estrogen.
 - Reduce premenstrual symptoms, reduce dysmenorrhea.

CONCLUSION

The selection of an appropriate contraceptive method that helps to avoid unintended pregnancy is the top target in reproductive health care programs.

- ✓ Improve reproductive health
- ✓ The woman has time and conditions to take care herself and her family
- ✓ Increase women's quality of life
- ✓ COCs with improvements of combined formulations and course bring many added benefits for women

The Evolution of Birth Control

Contraceptives really changed the
world!
For a better life!



THANK YOU!

