Oral Contraception and the HPG Axis

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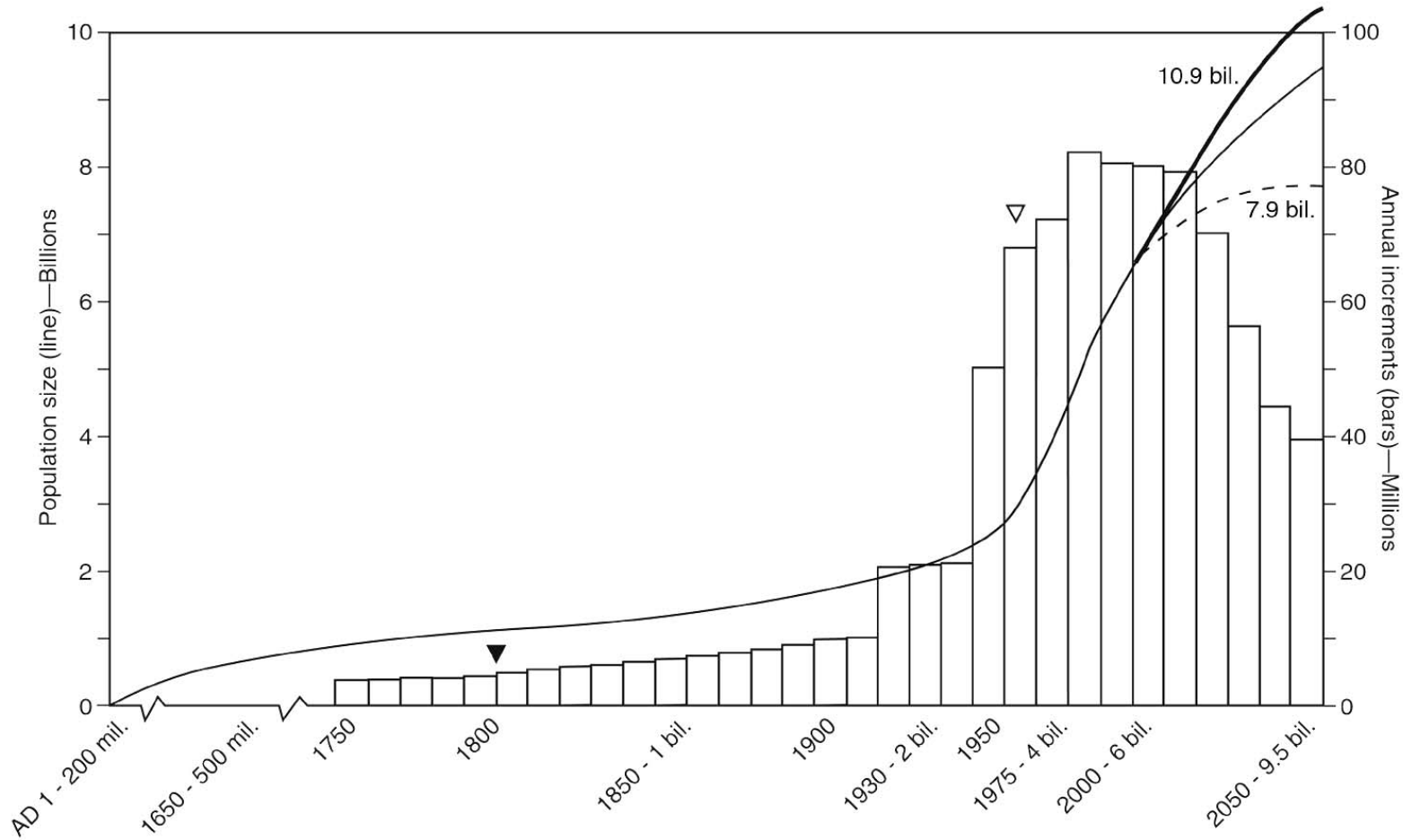
The Growth of the World Population



Raleig, Hum Repro Update 1999

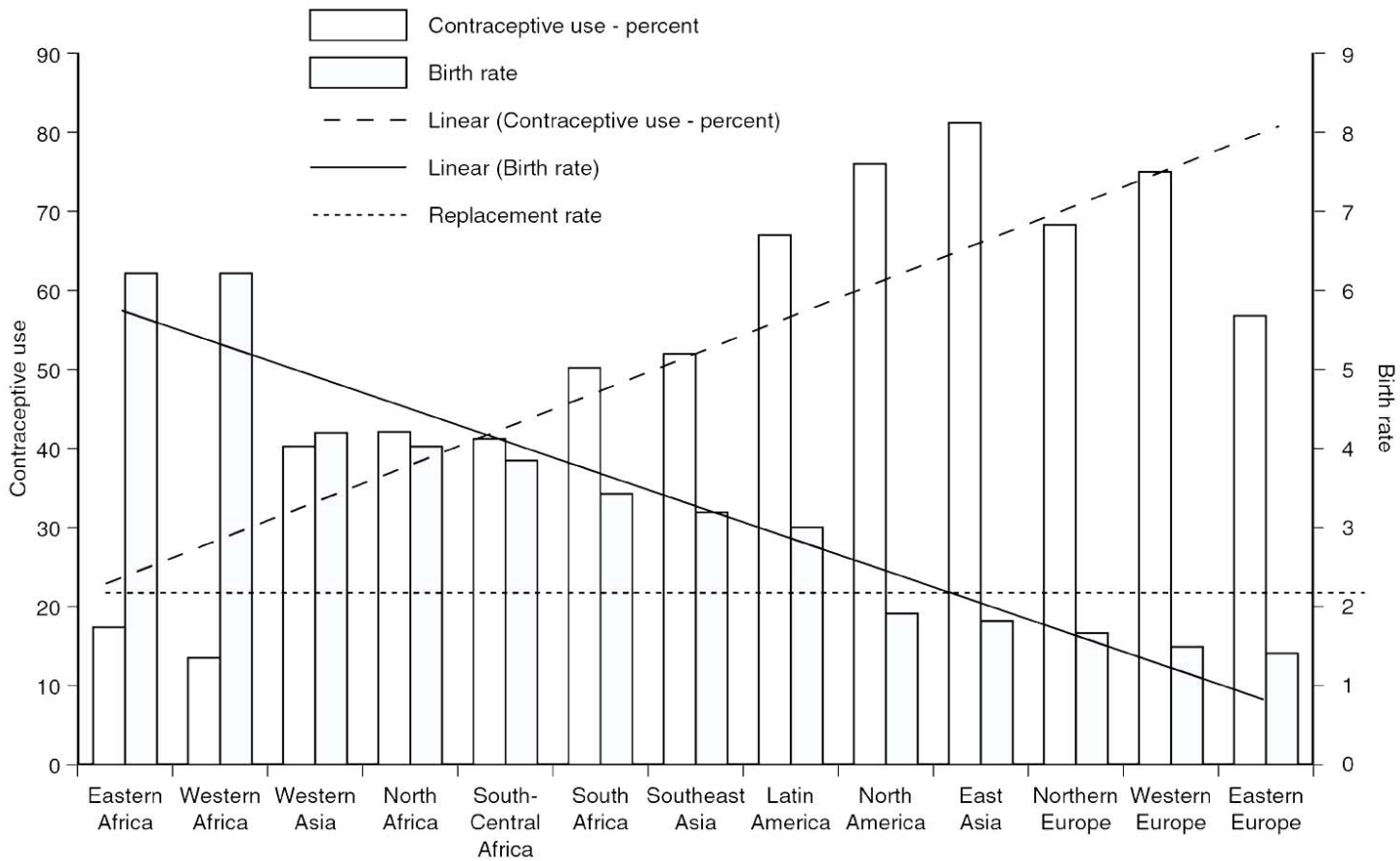


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Table 17–1. Fertility Control Methods: Failure Rates and Continuation of Use (United States Data)

Method	Percent Pregnant during First Year of Use: Estimates 1987 and 1990,* All Methods — Perfect use	Estimates 1987 and 1990,* All Methods — Typical	Estimates 1995,† Reversible Methods	Continuation after First Year of Use* (%)
Chance	85	85	85	?
Sterilization				
Male	0.1	0.2		100
Female	0.2	0.4	ND	100
Surgical				
Chemical (quinacrine)‡				
Women <35 y		13.0		?
Women ≥35 y		7.0		?
Hormonal contraception, emergency contraception, and contragestion				
Combination pill	0.1	5.0	8.0	78
Progestagen-only pill	0.5	5.0		81
Norplant	0.05	0.05	2.0	85
Depo-Provera	0.3	0.3	3.0	70
Emergency contraception—hormonal	0.1	3.0	ND	ND
Contragestion—pharmacologic abortion	1.0–5.0 (up to 7 wk)	9.0 (> 7 wk)	ND	ND
Intrauterine devices (IUDs)				
IUD-progesterone T	1.5	2.0		80
IUD-levonorgestrel 20	0.1	0.1	ND	81
IUD-T 380 (copper)	0.6	0.8		78
Barrier methods				
Condom				
Male	3.0	14.0	14.0	63
Female	5.0	21.0	ND	56
Diaphragm	6.0	20.0	18.0	58
Cervical cap				
Parous women	26.0	40.0	12.0	42
Nulliparous women	9.0	20.0		56
Sponge				
Parous women	20.0	40.0		42
Nulliparous women	9.0	20.0	ND	56
Spermicides	6.0	26.0	26.0	40
Withdrawal	4.0	19.0	24.0	?
Periodic abstinence§				63
Calendar	9.0	?		
Ovulation method	3.0	?	21.0	
Postovulation	1.0	?		
Symptothermal¶	2.0	?		
Lactational amenorrhea provides an effective but temporary method of contraception				

Landmarks in the Development of Oral Contraceptive Methods

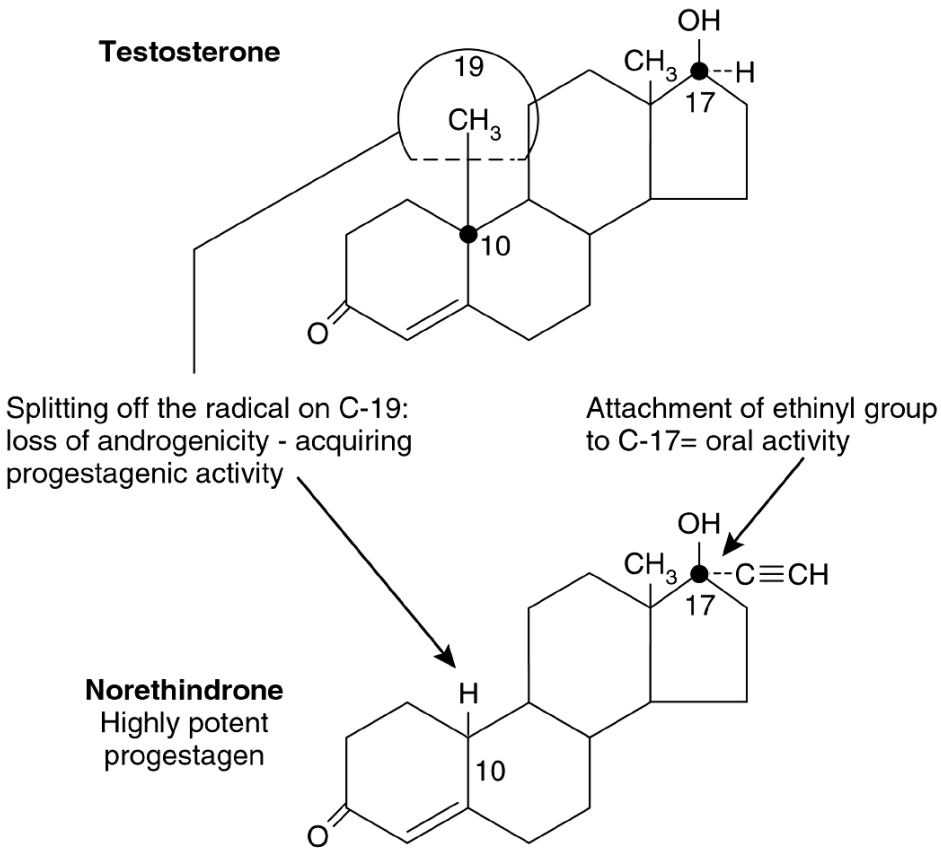
1940: first inhibition of ovulation by estrogens and progestagens

> Sturgis SH and Albright R. Mechanism of estrin therapy in the relief of dysmenorrhea.
> Endocrinology 26:68.

1952: synthesis of norethisterone, orally active progestagen more potent (10x) than natural progesterone

> Djerassi *et al.* 17alpha-Ethynyl-19-nortestosterone.
> American Chemical Society Meeting, abstract18J.

Development of norethindrone from testosterone. Splitting off the C-19 radical from the testosterone molecule changes this androgen to a progestagen. Attachment of the ethinyl group to C-17 enhances the progestagenic activity of the compound and makes it orally active.



Landmarks in the Development of Oral Contraceptive Methods

1953: **John Rock and Gregory Pincus test oral progesterone *(norethynodrel, G.D. Searle)***

Pincus G. The Control of Fertility.
New York, Academic Press.

The Pill was born

Currently Available, « Low Dose » Formulations

Monophasic

EE 35 μg – norgestinate 250 μg	Cilest
EE 30 μg – levonorgestrel 150 μg	Microgynon 30
EE 30 μg – gestodene 75 μg	Minulet
EE 20 μg - -norethisterone acetate 1000 μg	Loestrin 20
EE 20 μg – desogestrel 150 μg	Mercilon

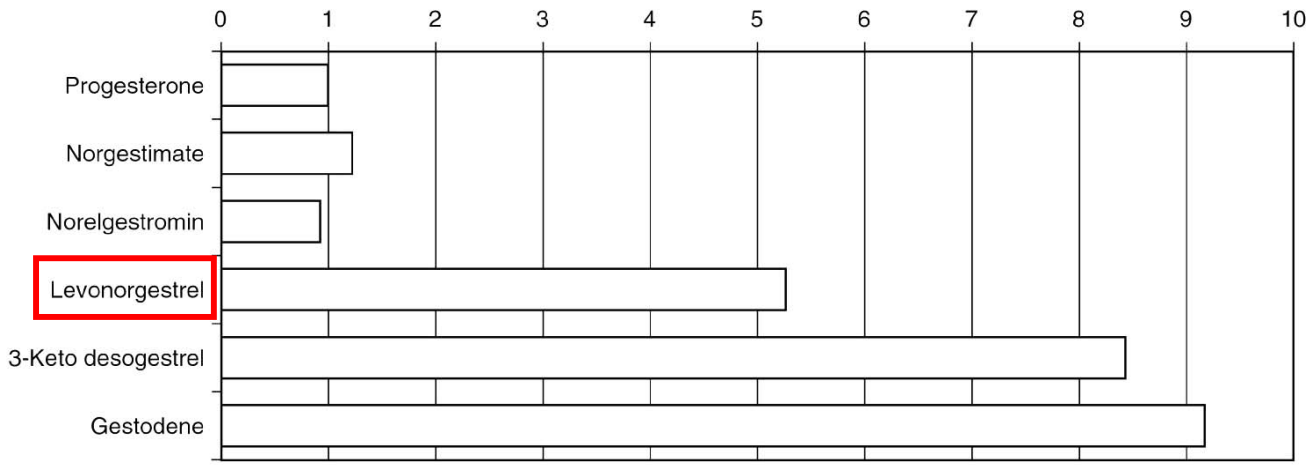
Bi-/Tri-phasic

EE 35 μg – norethisterone 500/750/1000 μg	TriNovum
EE 30/40/30 μg – levonorgestrel 50/75/125 μg	Logynon
EE 30/40/30 μg – gestodene 50/70/100 μg	Tri-Minulet

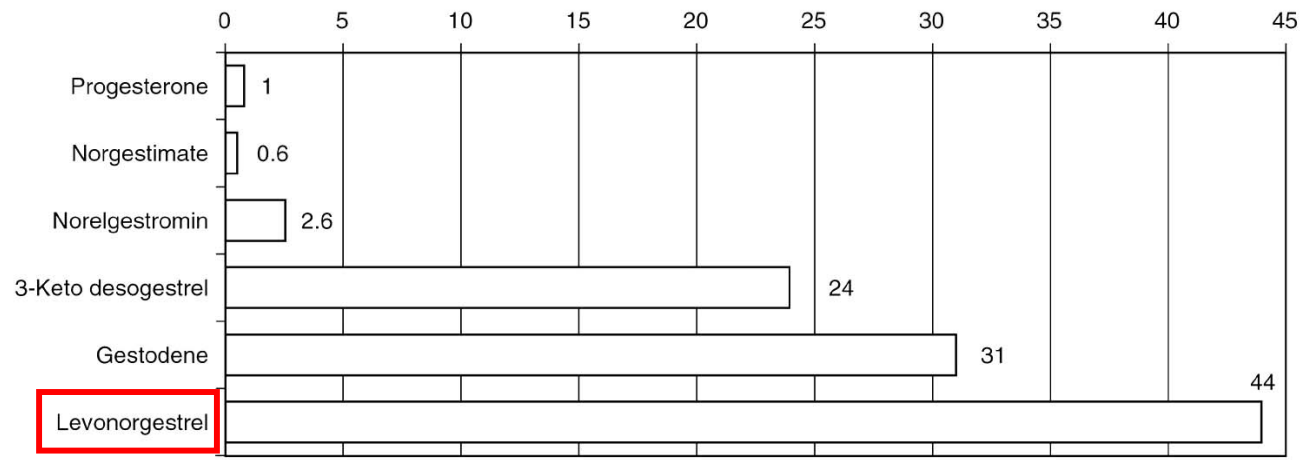
EE: 17α-ethinylestradiol

The multifaceted nature of the steroid molecule is illustrated by its capacity to bind to several different receptors and activate them to various degrees.

Relative binding affinity to progestogen receptors



Relative binding affinity to androgen receptors



Ovarian Function During Hormonal Contraception

Combined oral contraceptives exert a range of effects on the reproductive tract, resulting in the inhibition of ovulation.

- **Estrogens and progestogens inhibit LH secretion**
  - → **no preovulatory LH surge**
- **Estrogens suppress FSH**
  - → **no follicular development**

Ovarian Activity during Regular Oral Contraceptive Use

Follicular-like structures were observed in 9/51 patients

Table 2. Characteristics of the cycles with follicular development

Pill	Pts.	Cycle	No. pill	Follicular diameter (mm)	Endometrial thickness (mm)	Hormonal values			
						E2 (pg/ml)	Prog (ng/ml)	FSH (UI/L)	LH (UI/L)
Triphasic pill*	S.S.	3rd	7	11	6	24	0.2	4.4	3
	F.P.	4th	10	13	9	<5	<0.2	1.0	0.5
	S.S.	6th	7	19	6	<5	<0.2	7.7	7
	M.M.	6th	10	11	3	29	0.3	3.6	1
20 mg EE + 75 mg gestodene	A.G.	3rd	11	12	8	<5	<0.2	0.7	<0.5
	R.S.	4th	12	13	4	12	0.3	2.9	5
	A.G.	8th	11	12	8	<5	<0.2	1.8	2
20 mg EE + 150 mg DSG	M.G.	4th	17	17	4	15	0.5	4.5	4
	S.B.	6th	10	13	7	<5	0.3	3.5	1

*Including 35 mg ethinyl estradiol (EE) and 50 mg desogestrel (DSG) in the first seven tablets; 30 mg EE and 100 mg DSG in tablets 8 to 14, and 30 mg EE and 150 mg DSG in tablets 15 to 21.

Crosignani *et al*, Contraception 1996

Activity of the Pituitary-Ovarian Axis in the Pill-Free Interval During Use of Low-Dose Combined Oral Contraceptives

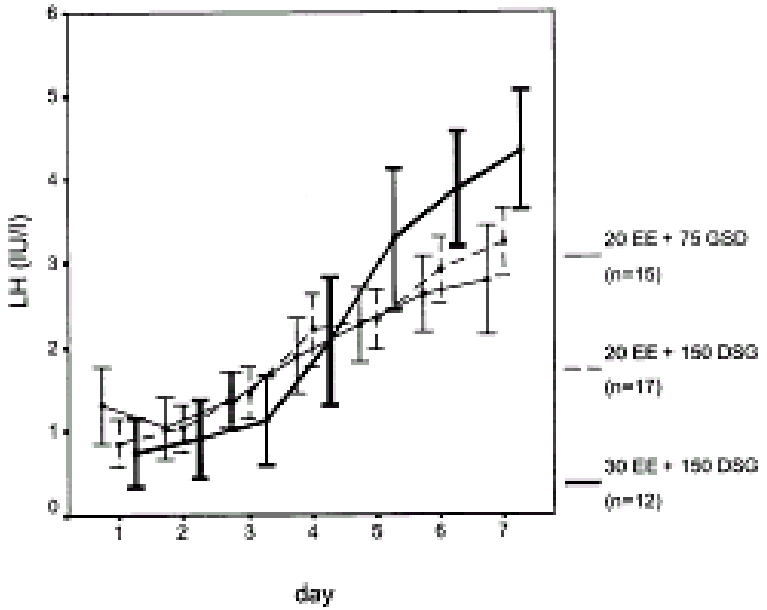
A.M. van Heusden* and B.C.J.M. Fauser*

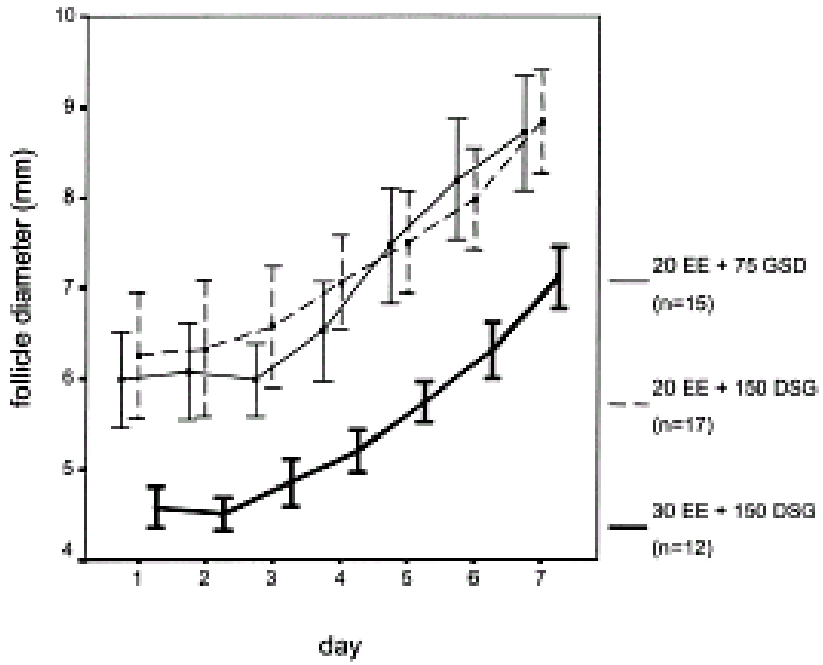
Aim: to evaluate pituitary-ovarian recovery in the pill-free interval during use of three low-dose combined oral contraceptives

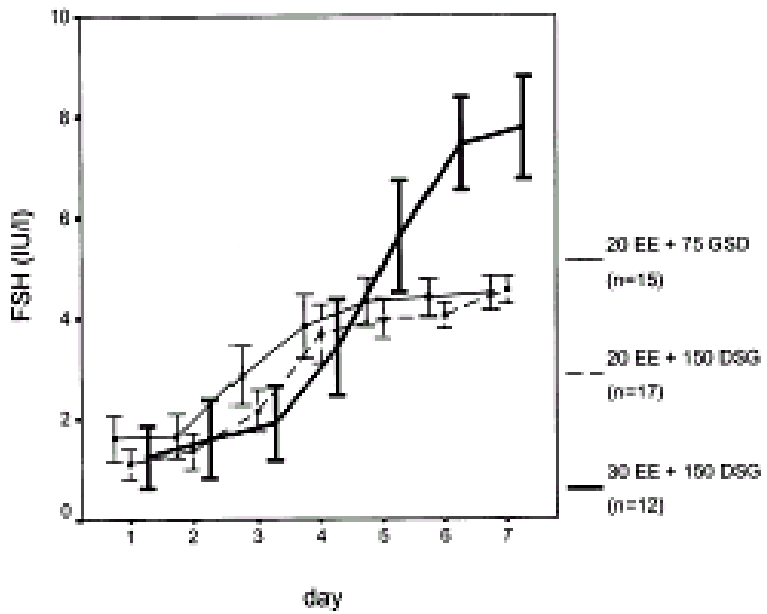
Subjects: 44 healthy volunteers, aged 18-39 years

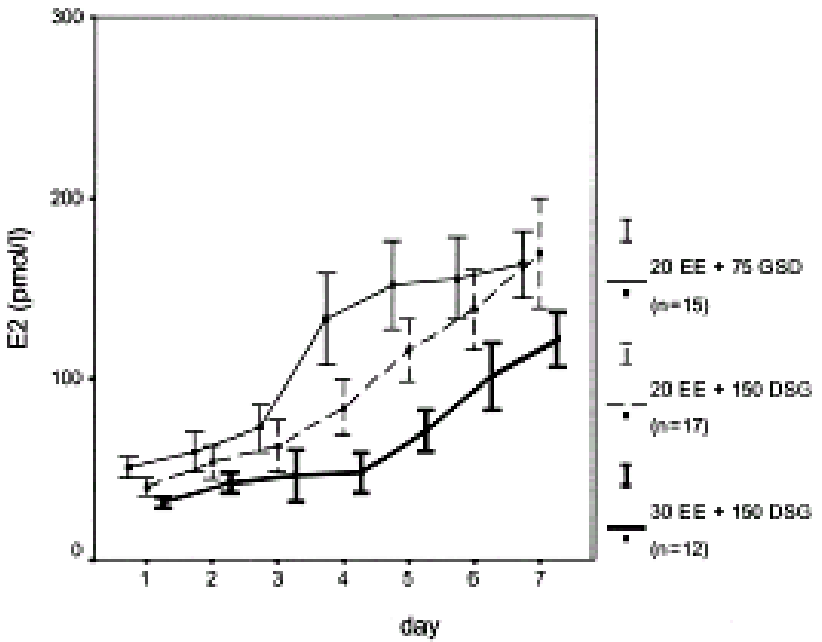
Main outcome: evidence of ovulation and ovarian activity

Contraception 1999


LH (IU/l)
day
20 EE + 75 GSD
(n=15)
20 EE + 150 DSG
(n=17)
30 EE + 150 DSG
(n=12)


follicle diameter (mm)
day
20 EE + 75 GSD
(n=15)
20 EE + 150 DSG
(n=17)
30 EE + 150 DSG
(n=12)


FSH (IU/l)
day
20 EE + 75 GSD
(n=15)
20 EE + 150 DSG
(n=17)
30 EE + 150 DSG
(n=12)


E2 (pmol/l)
day
20 EE + 75 GSD
(n=15)
20 EE + 150 DSG
(n=17)
30 EE + 150 DSG
(n=12)

Results:

- No ovulations were observed
- FSH levels were higher in the 30 μg EE group
- Follicle diameters were significantly smaller in the 30 μg EE group
- Dominant follicles (>10 mm) were observed at the end of the pill-free period in both 20 μg groups, but not in the 30 μg group

Van Heusden and Fauser, Contraception 1999

Conclusion

The EE content, rather than the progestin content, determines the extent of residual ovarian activity at the beginning of the pill-free interval

Van Heusden and Fauser, Contraception 1999

Combined Oral Contraceptive Agents

Two recent studies using pills containing 20 μg EE and 100 mg levonorgestrel:

- **Follicles >10 mm seen in majority of cycles**
- **Spontaneous ovulation in 1.7 – 2.7% of cycles**

Coney and Del Conte, Am J Obst Gynecol 1999

Jain *et al,* Contraception 2000

Combined Oral Contraceptive Agents

Large follicles (>12 mm) can be found during treatment with combined OC.

Because of the low LH concentrations, these follicles secrete very little estradiol.

However, they may continue to produce inhibin and hence can be called *functional*.

Combined Oral Contraceptive Agents

20 μg of EE probably represents the minimum that will reliably suppress folliculogenesis

The ESHRE Capri Workshop Group, 2001

Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 μg) and ethinyl estradiol (15 μg) on ovarian activity

Helen Sullivan, M.D., Hilary Furniss, M.B., Ch.B.,* Jurgen Spona, Ph.D.,† and Max Elstein, M.D.**

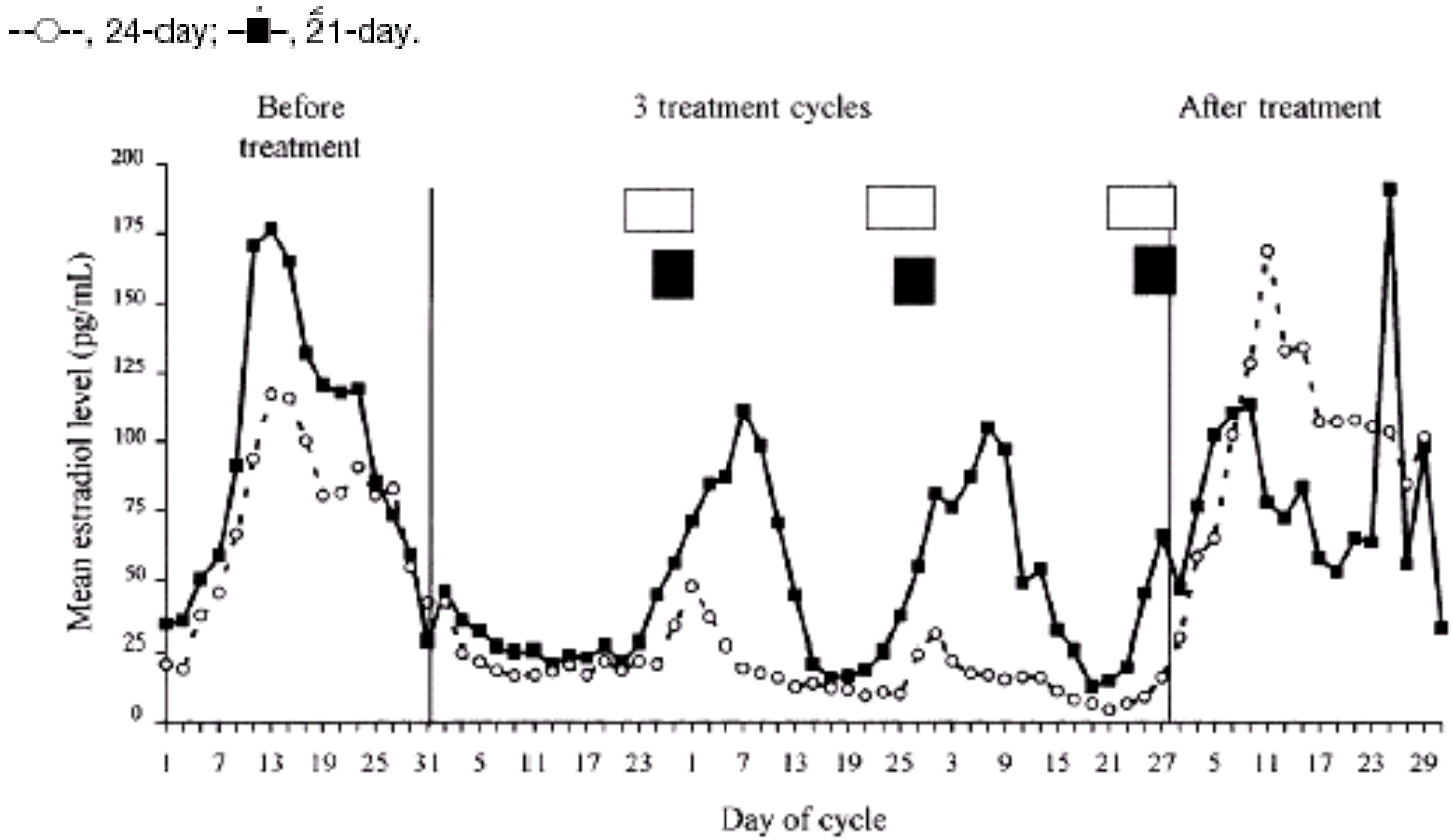
Aim: **to compare ovulation inhibition and ovarian activity with 21-day and 24-day regimen of combined oral low-dose contraceptive *(60 μg gestodene and 15 μg EE)***

Subjects: **58 healthy volunteers, aged 18-35 years**

Main outcome: **evidence of ovulation and ovarian activity**

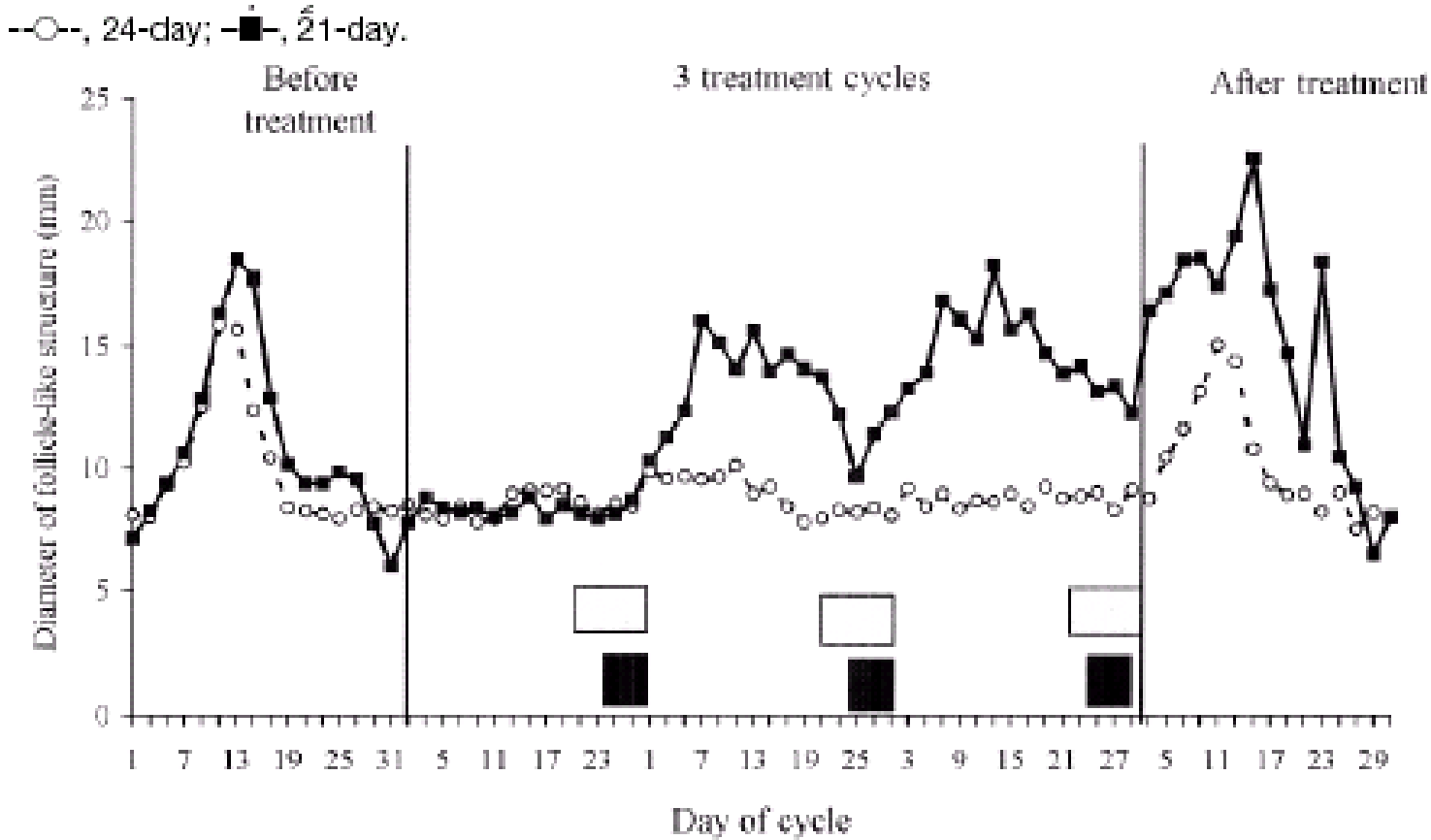
Fertil Steril 1999

Ovarian activity over three consecutive cycles



Sullivan *et al,* Fertil Steril 1999

Follicular growth over three consecutive cycles



Sullivan *et al,* Fertil Steril 1999

Results:

- No ovulation in the 24-d regimen *vs* 1/75 cycles in the 21-d regimen
- No luteinized, unruptured follicle in the 24-d regimen *vs* 6/75 cycles (8%) in the 21-d regimen

The 24-d cycle strategy may be useful for maintaining effective ovulation inhibition at ultra-low doses of contraceptive steroids

Sullivan *et al*, Fertil Steril 1999

Progestogen-Only Pills

FSH secretion is very little or not affected by progestagens

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FSH secretion is very little or not affected by progestagens

Follicular development continues during administration of progestogen-only pills and in some *(0.3 mg norethisterone, 0.075 mg levonorgestrel)*, ovulation can occur.

Progestogen-Only Pills

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Follicular development continues during administration of progestogen-only pills and in some *(0.3 mg norethisterone, 0.075 mg levonorgestrel)*, ovulation can occur.

The contraceptive effect is probably dependent on the effect of continuous gestogen on cervical mucous and endometrium

Oral Contraceptive Agents

Non-Reproductive Benefits

Decreased incidence of endometrial and ovarian carcinomas

Condition	Relative Risk (Risk for Nonusers = 1)
A. Reduced Risk of Morbidity	
Endometrial carcinoma	
Years of use	
1	0.8
2	0.6
≥4	0.4
Overall	0.5
Ovarian carcinoma*	
Years of use	
>3	0.5
≥7	0.2–0.4
Overall	0.3
Ovarian cysts	0.4
Pelvic inflammatory disease	0.1
Ectopic pregnancy	0.1
Benign breast tumors	0.5
B. Reduced Risk and Improvement of Quality of Life	
Dysmenorrhea	0.4
Menorrhagia	0.5
Anemia	0.6
Premenstrual syndrome	0.7
Irregular menses	0.7

*Residual protective effect lasts for 10 to 15 years after termination of use.

Oral Contraceptive Agents

Non-Reproductive Benefits

Uterine leiomyomas
Endometriosis
Bone mineral density

Management of hyperandrogenism

Oral Contraceptive Agents

Adverse Events

Most common adverse events:

- Breakthrough bleeding
- Amenorrhea
- Headache, nausea, breast tension, mood change, weight gain

Cardiovascular events:

- Venous thromboembolism
- Stroke *(not increased in non-smokers, with low estrogen pills)*
- Myocardial infarcts

Oral Contraceptive Agents

Polycystic Ovary Syndrome

Two considerations:

- **Effect on the ovaries and ovarian hormone secretion**
- **Effect on accompanying metabolic conditions**

Polycystic Ovary Syndrome: Ovarian Effects of OC

In PCOS, ovaries are enlarged and full of small, immature follicles 2 – 8 mm (cycsts).

Upon treatement with OC, cysts become smaller and ovarian volume decreases

→ **reduction in ovarian testosterone secretion**

→ **increase in SHBG**

Additional advantage of cyproterone acetate