contraccezione d'emergenza

farmaci

IUDs

dopo

rapporto sessuale non protetto nel periodo fertile del ciclo

Fig. 1

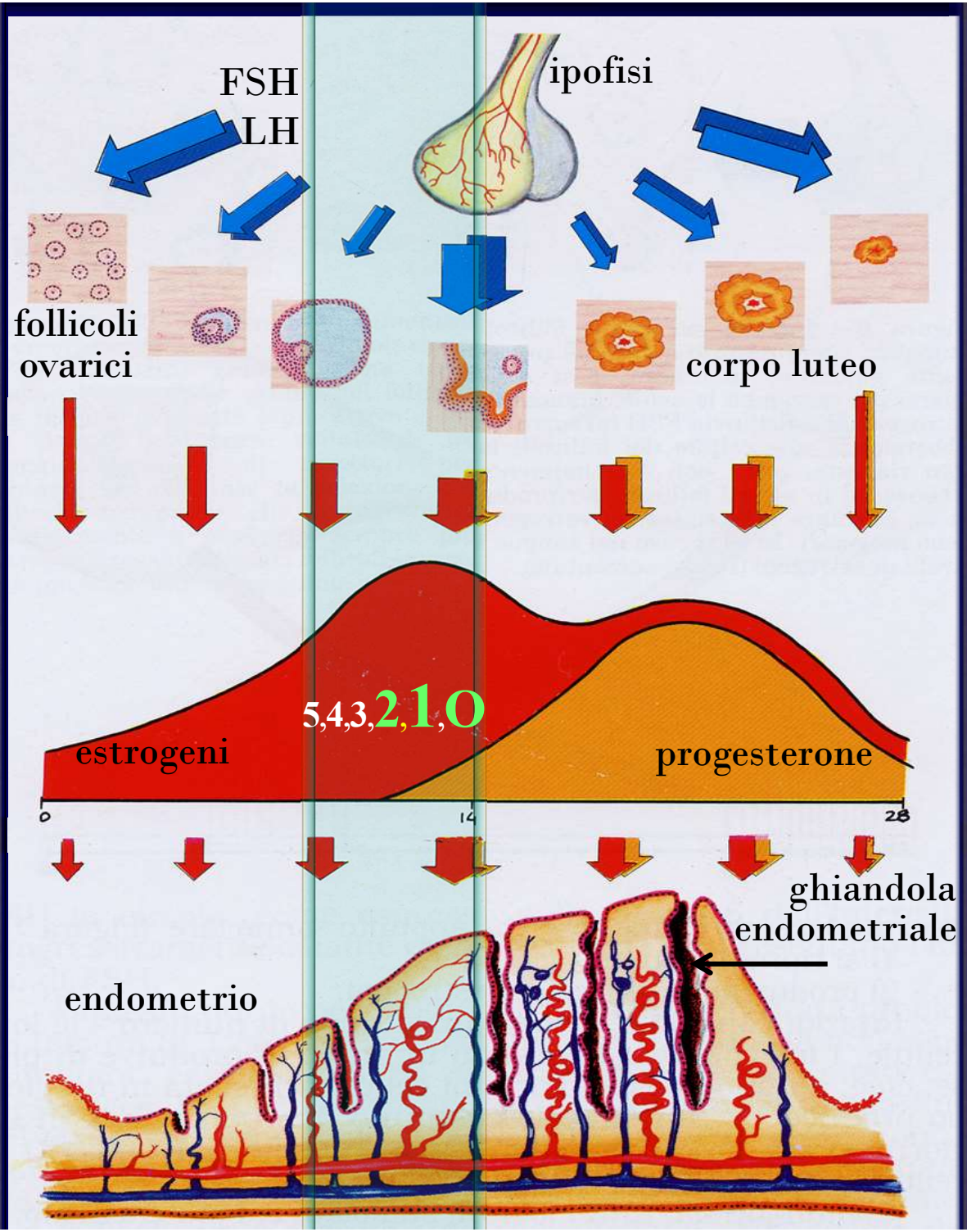

FSH
LH
ipofisi
follicoli
ovarici
corpo luteo
5,4,3,2,1,0
estrogeni
progesterone
0
14
28
ghiandola
endometriale
endometrio

Fig. 2

ella®
ulipristal acetate

FDA Reproductive Health Drugs Advisory Committee
June 17, 2010

HRA Pharma

Fig. 3

CONCEPTION

CM-15

The Fertile Window

David Archer, MD

Probability of conception on specific days near the day of ovulation

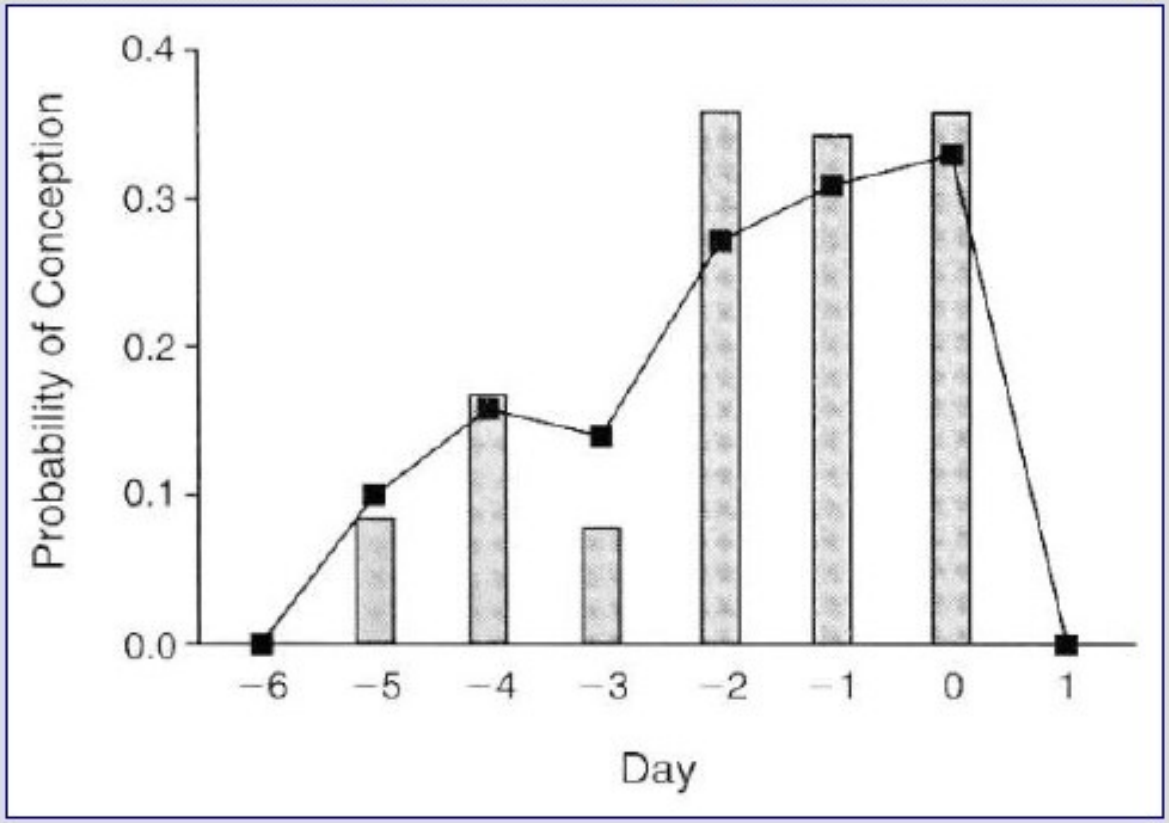


Figure 2 from *Wilcox et al. 1995*

The bars represent probabilities calculated from data on 129 menstrual cycles in which sexual intercourse was recorded to have occurred on only a single day during the 6-day interval ending on the day of ovulation (day 0). The solid line shows daily probabilities based on all 625 cycles, as estimated by the statistical model.

Wilcox, et al. *New Engl J Med.* 1995;33(23):1517-1521.

Fig. 4

INTERCOURSES

CM-16

Frequency of Intercourse

Proportion of contracepting women who have intercourse on a given day of the menstrual cycle, relative to the day of ovulation

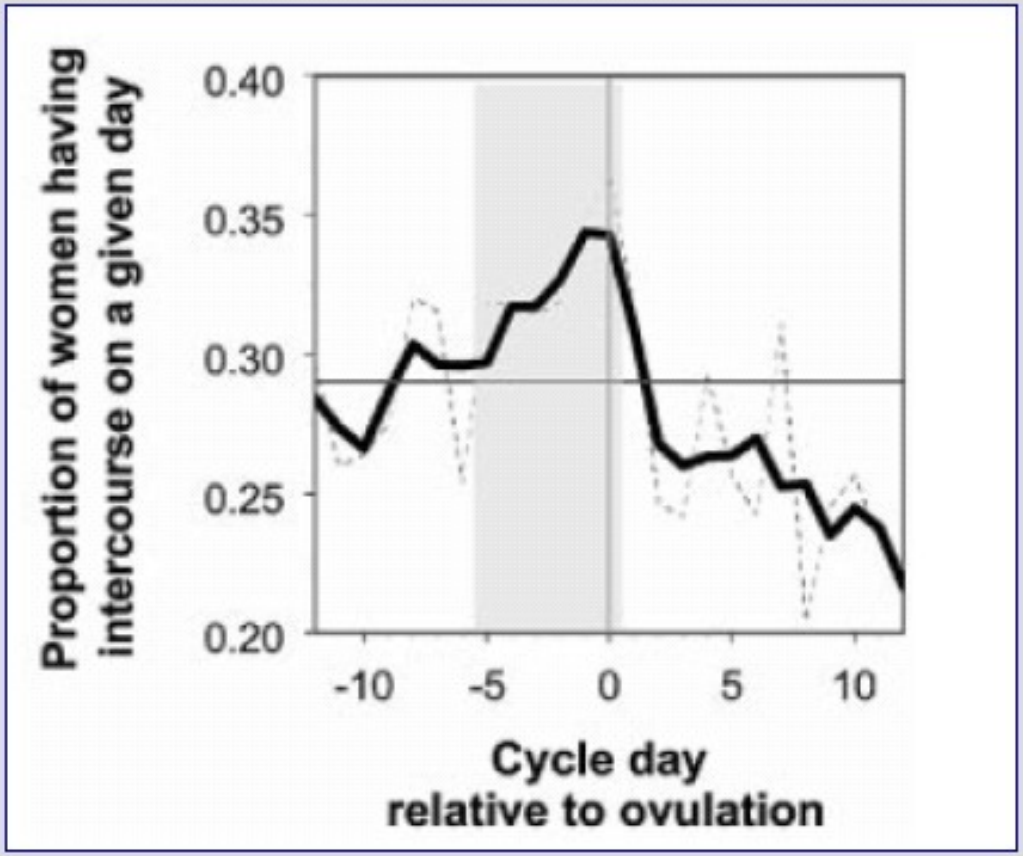


Figure 1 from *Wilcox et al. 2004*

Dashed line shows mean value for each day, while the dark solid line shows the 3-day moving average (each data point representing the mid-point of a 3-day span). The 6 fertile days are shaded, with the day of ovulation (0) marked by the thin vertical line. The intercourse line represents the overall mean frequency of intercourse on non-bleeding days (0.290). n = 68 women, 171 cycles.

Wilcox, et al. *Human Reprod,* 2004;19(7):1539-1543.

Fig. 5

Distribution of UPIs
Study 509 – mITT Population

UNPROTECTED

FIGURE 3.1 - HISTOGRAM OF DAYS FROM FIRST DAY OF LAST MENSTRUAL PERIOD TO THE UNPROTECTED INTERCOURSE (mITT)

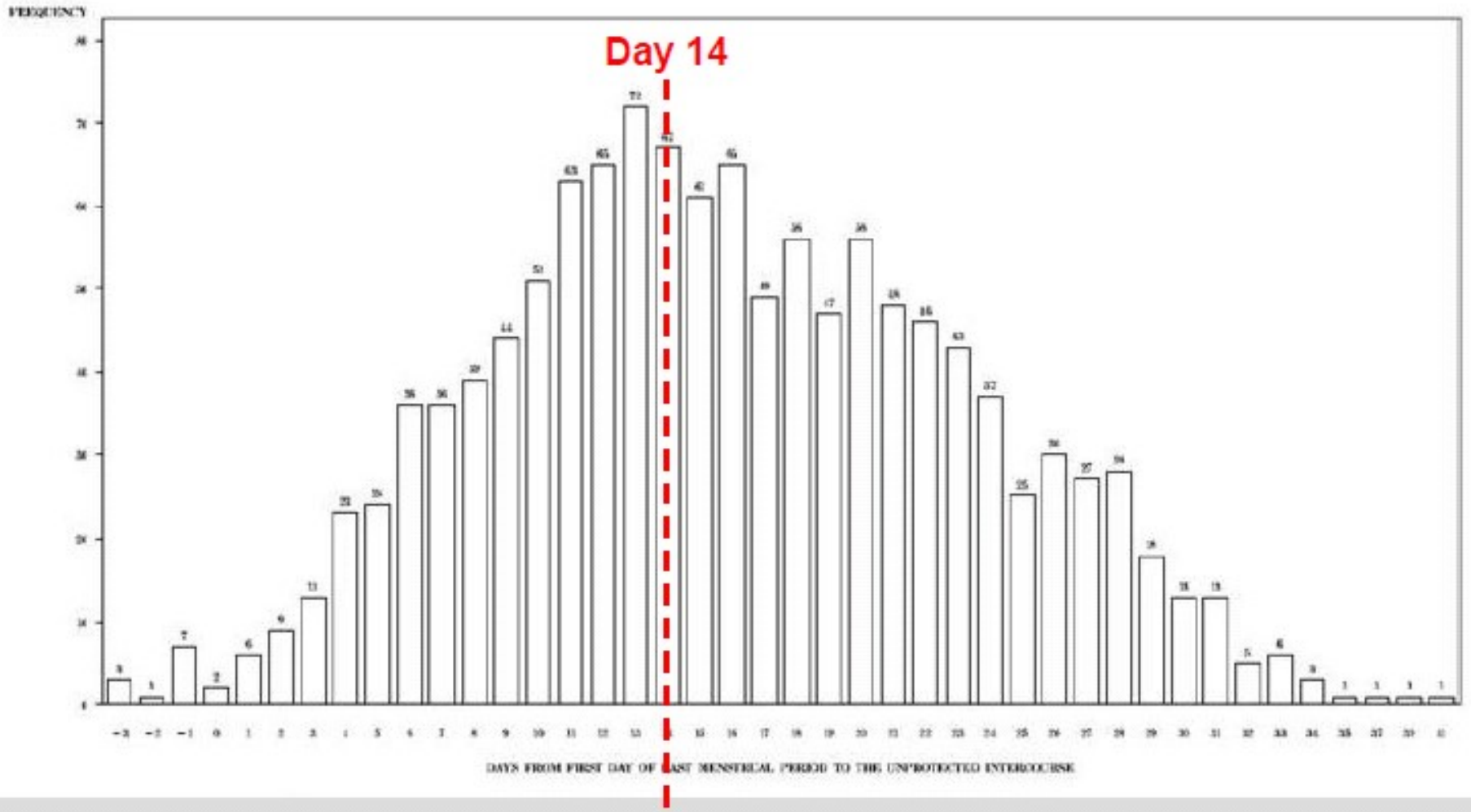
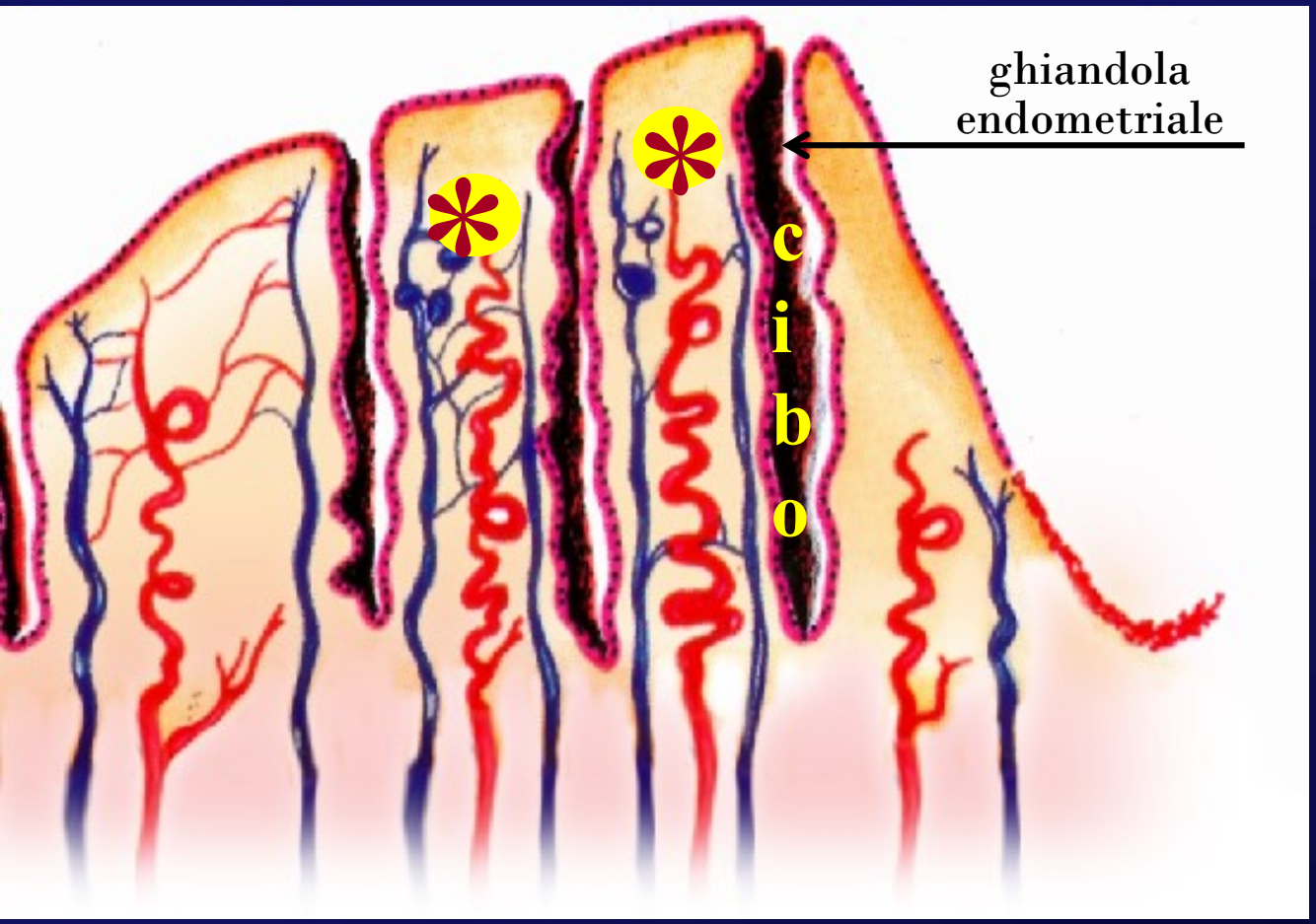


Fig. 6

Progesterone → → Immuno-tolleranza



- Glycodelin
- Th-2>>Th-1
- PIBF → IL-4
- EPF ovarian (Embryo Factor)
- ↓
- I- kβ anti NF-kβ
- p-NKc → u-NKc

hCG embryo

endometrio

END-1

MMP

Endothelin-1 --- Enkefalinase

Fig. 7

PAF Platelet Activating

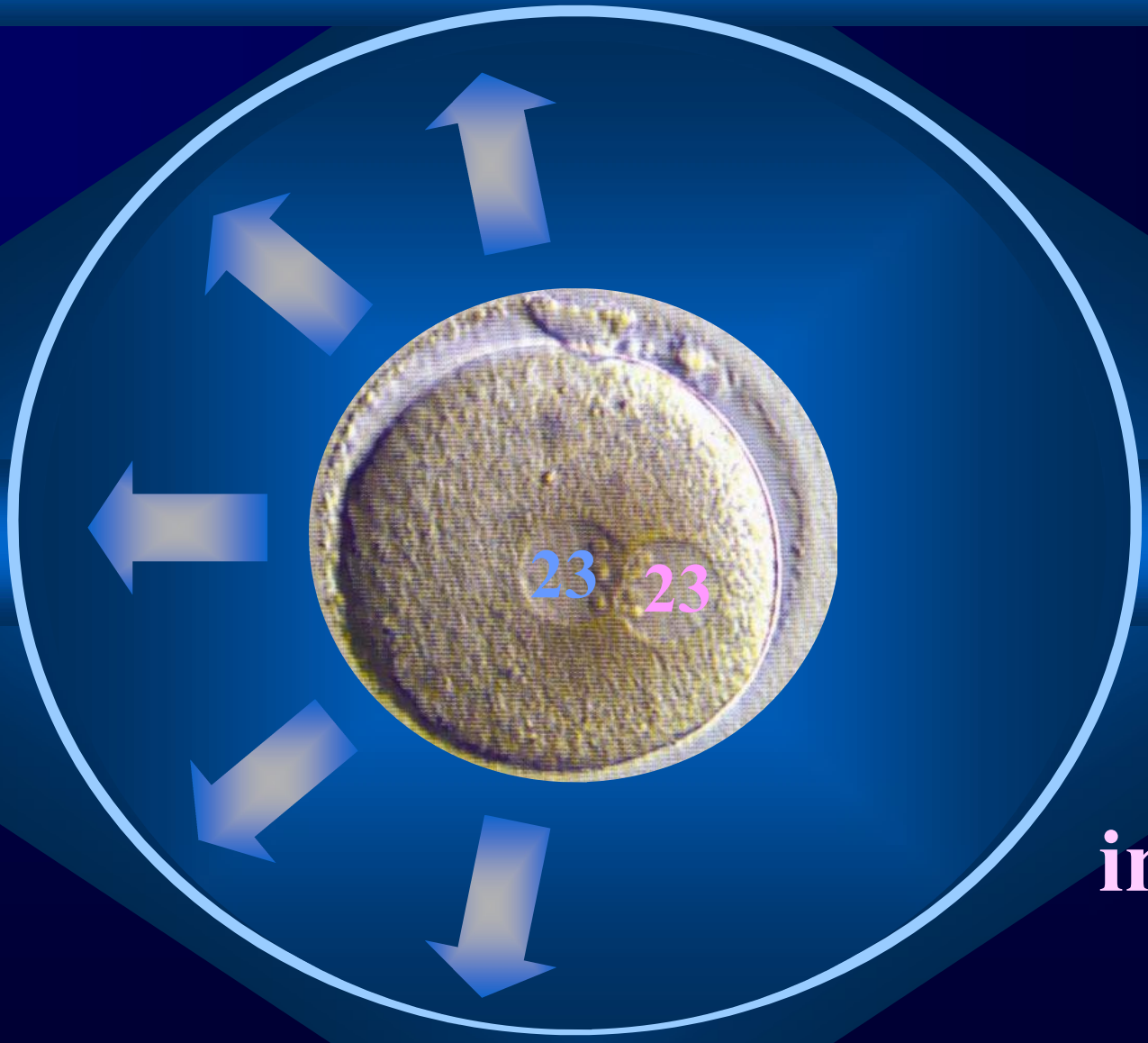
entro 48 h

Fig. 8

Immuno

IF

suppressivo

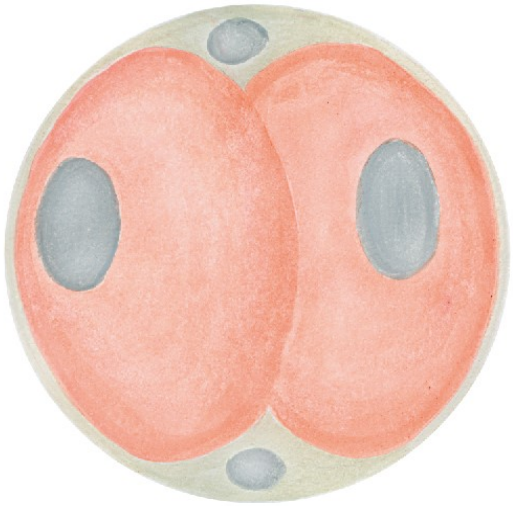


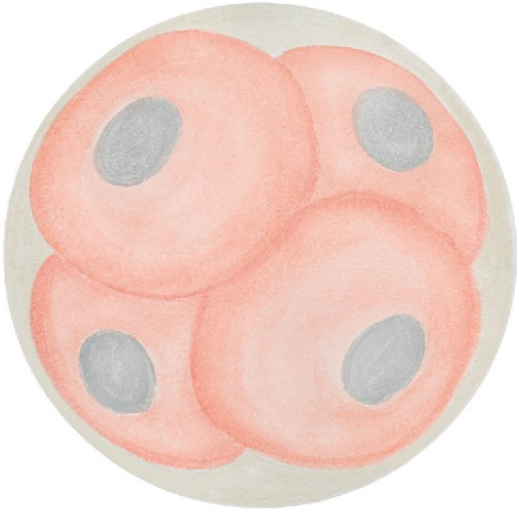
modula

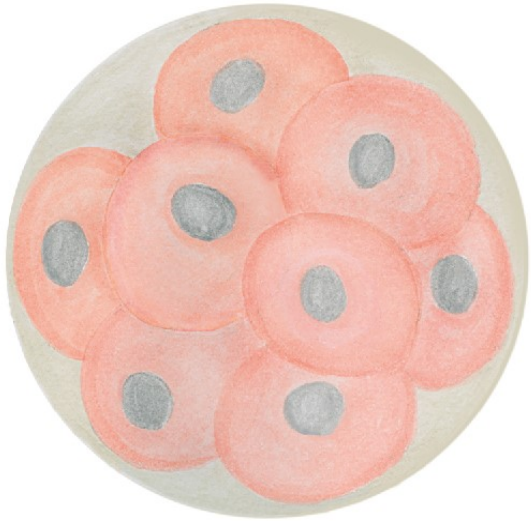
difese immunitarie materne

EPF Early Pregnancy

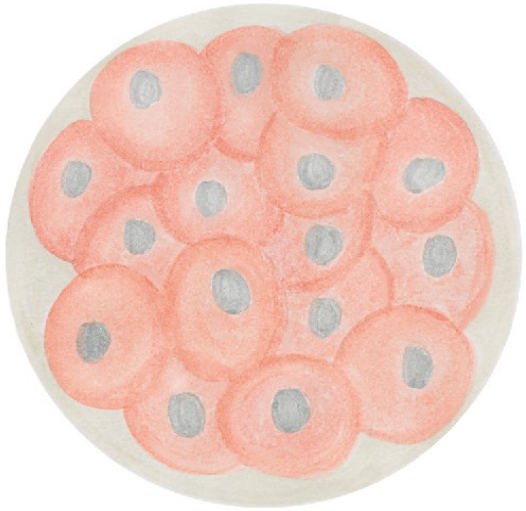
immediatamente



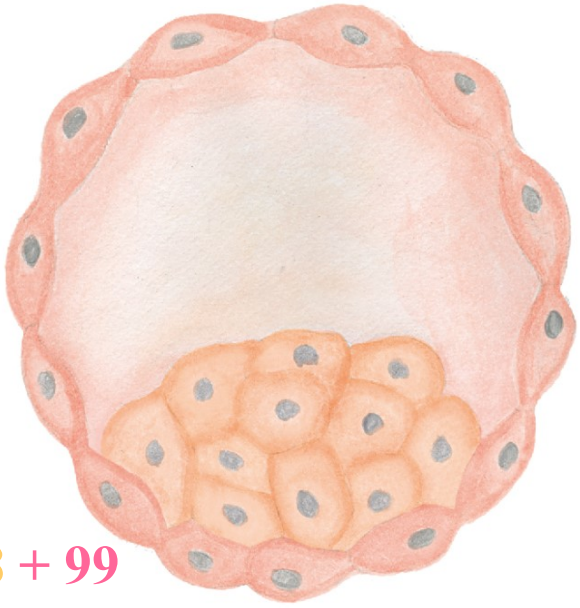




volume costante



5 + 53



8 + 99

Fig. 9

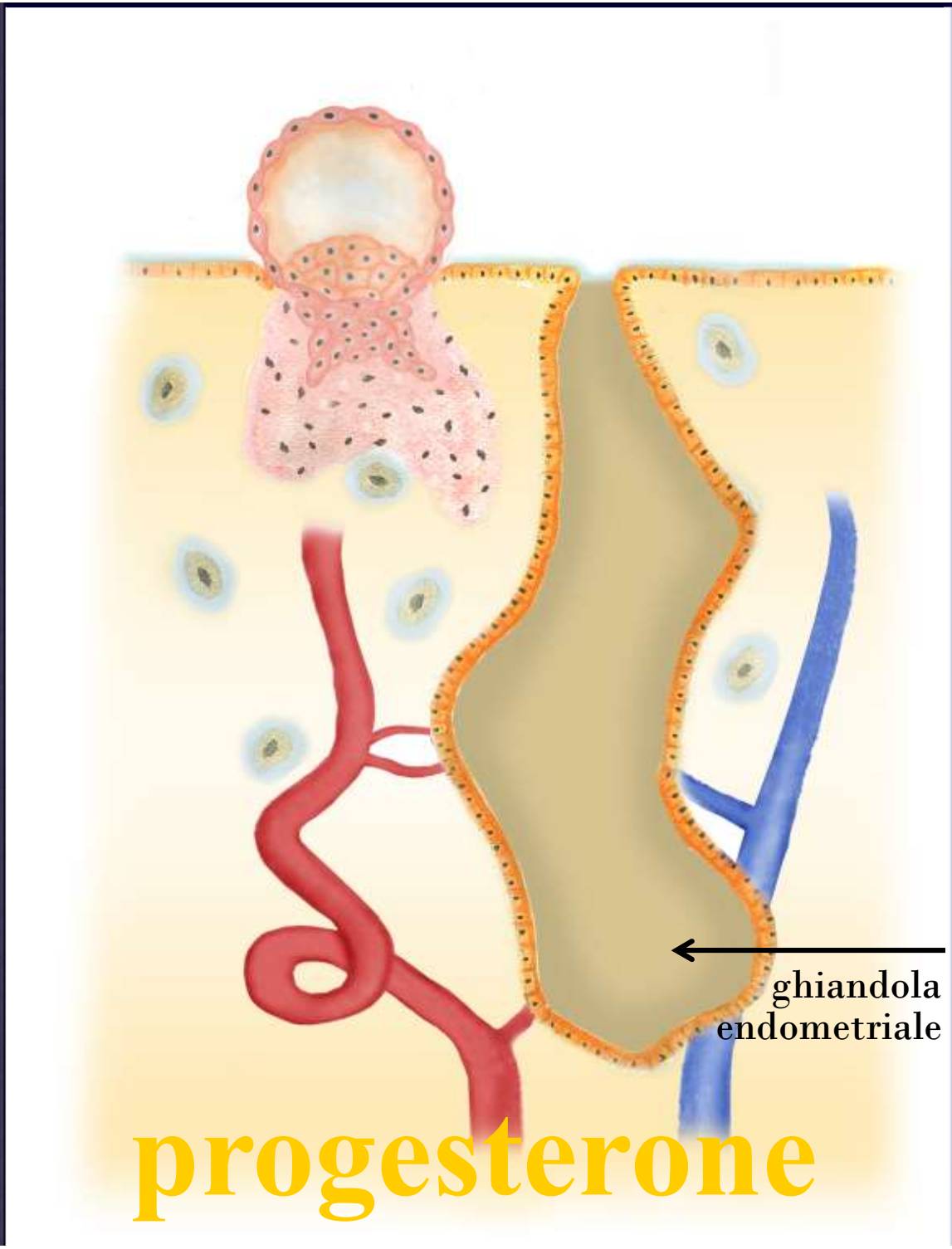
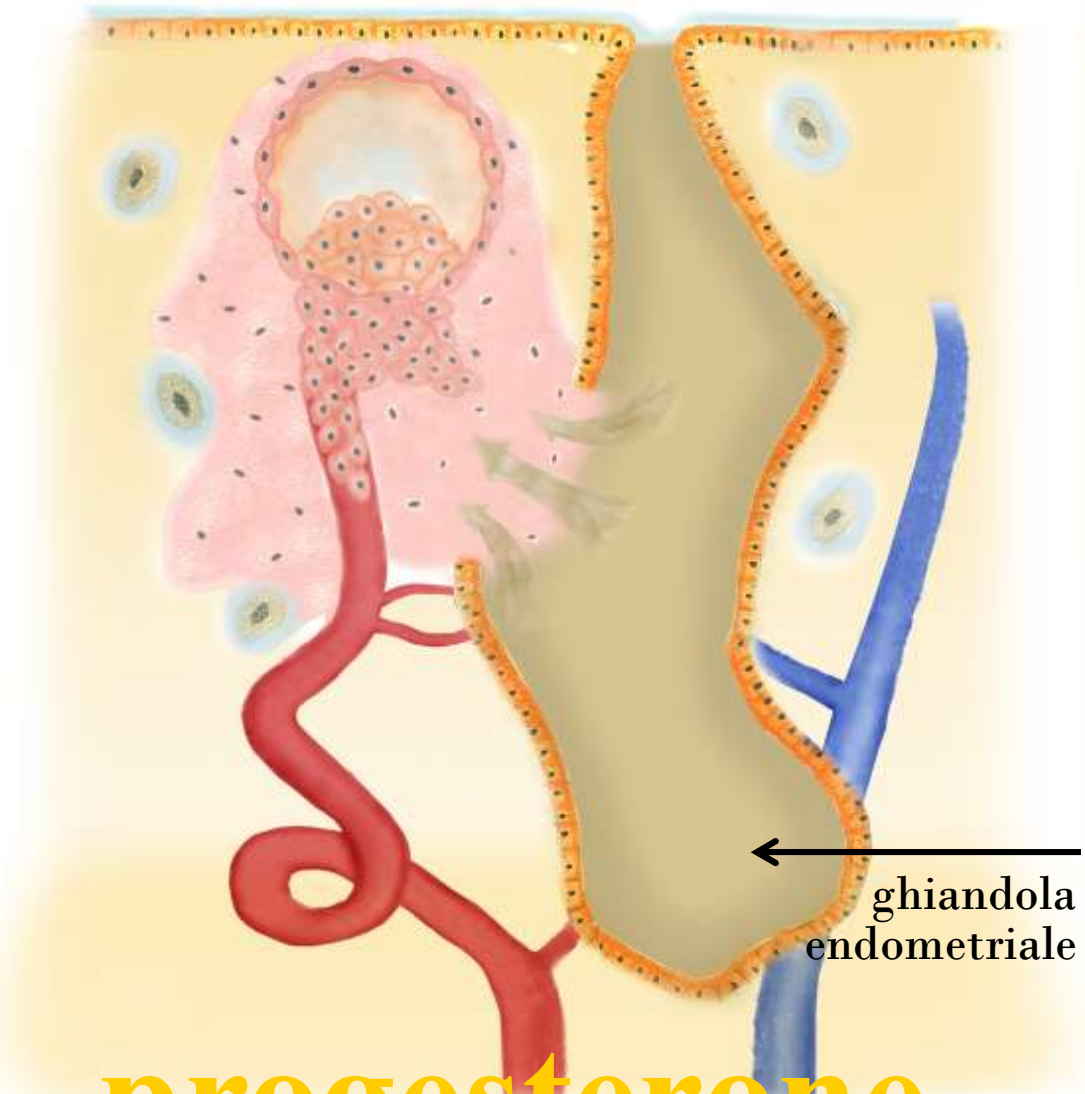


Fig. 10



progesterone

Fig. 11

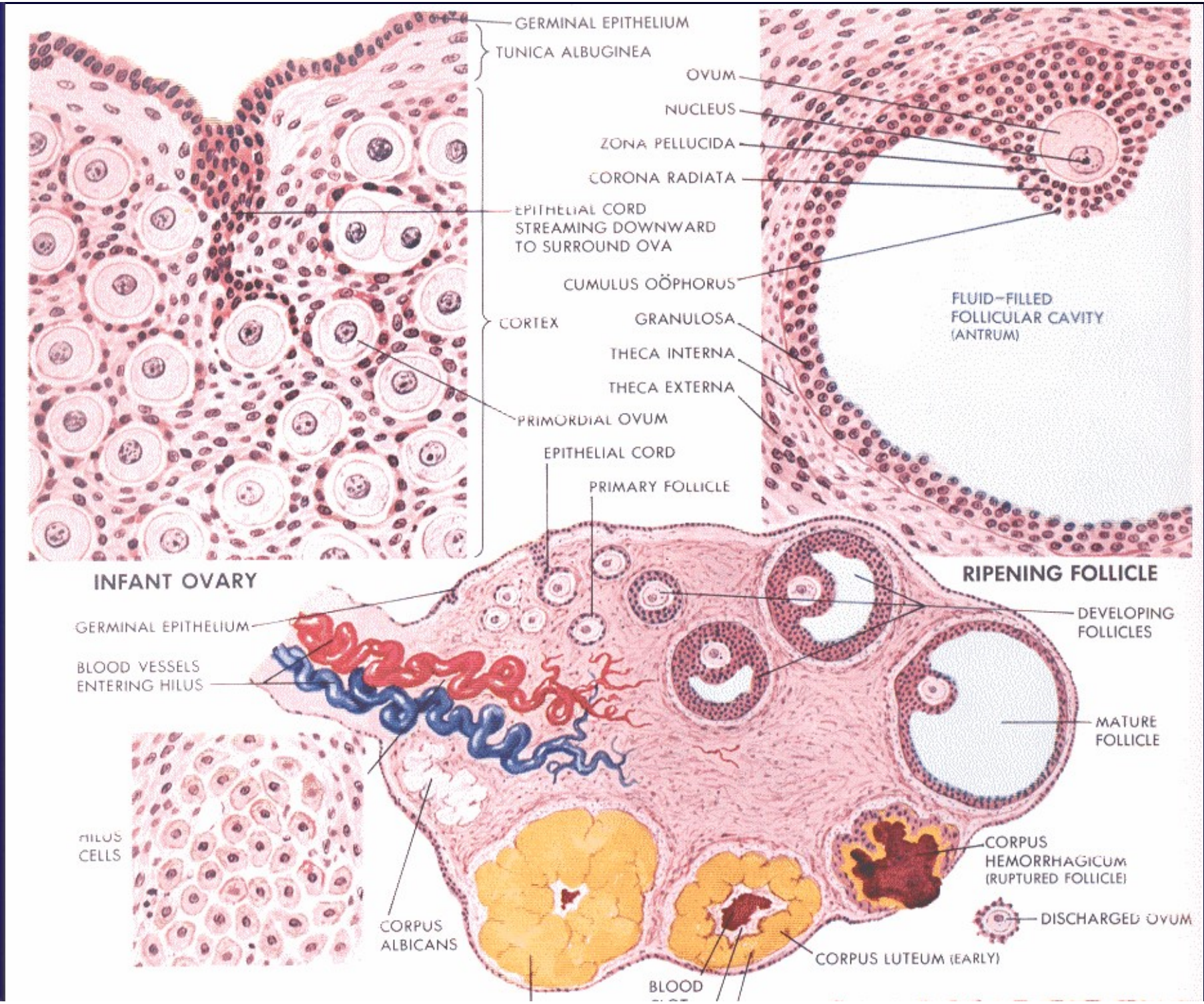

GERMINAL EPITHELIUM
TUNICA ALBUGINEA
EPITHELIAL CORD STREAMING DOWNWARD TO SURROUND OVA
CORTEX
PRIMORDIAL OVUM
INFANT OVARY
OVUM
NUCLEUS
ZONA PELLUCIDA
CORONA RADIATA
CUMULUS OÖPHORUS
GRANULOSA
THECA INTERNA
THECA EXTERNA
FLUID–FILLED FOLLICULAR CAVITY (ANTRUM)
RIPENING FOLLICLE
EPITHELIAL CORD
PRIMARY FOLLICLE
GERMINAL EPITHELIUM
BLOOD VESSELS ENTERING HILUS
DEVELOPING FOLLICLES
MATURE FOLLICLE
HILUS CELLS
CORPUS ALBICANS
CORPUS HEMORRHAGICUM (RUPTURED FOLLICLE)
DISCHARGED OVUM
CORPUS LUTEUM (EARLY)
BLOOD

Fig. 12

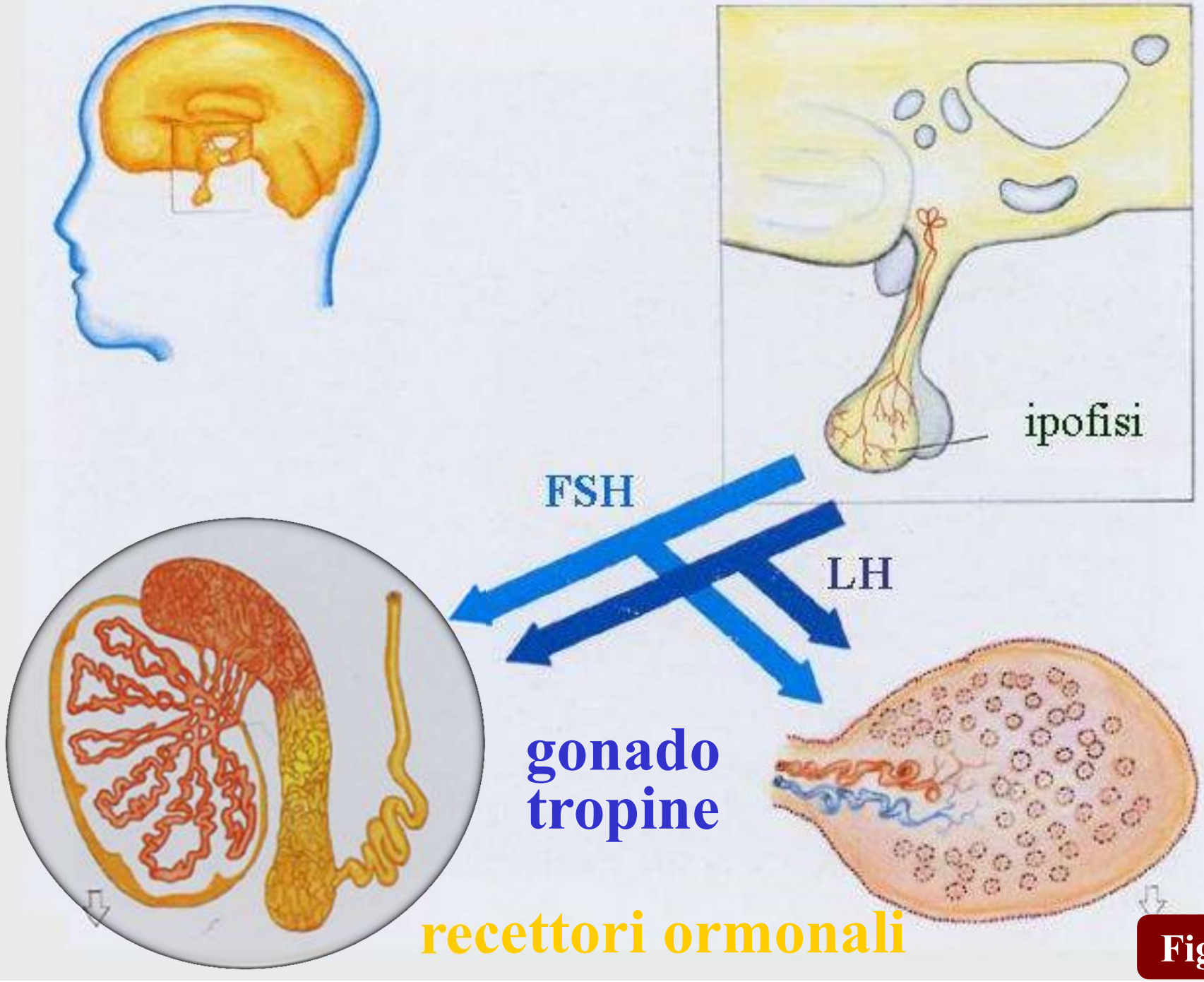


Fig. 13

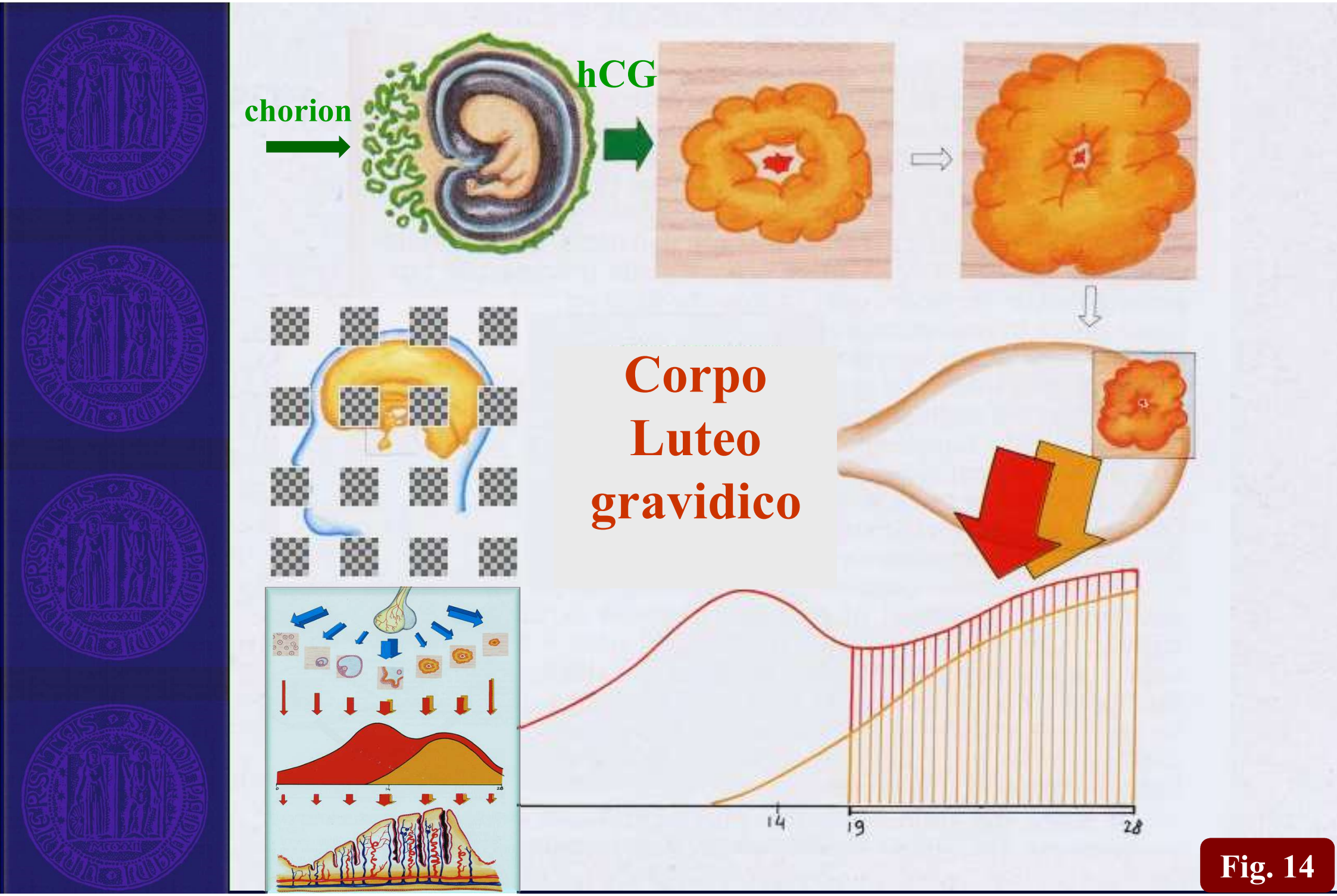
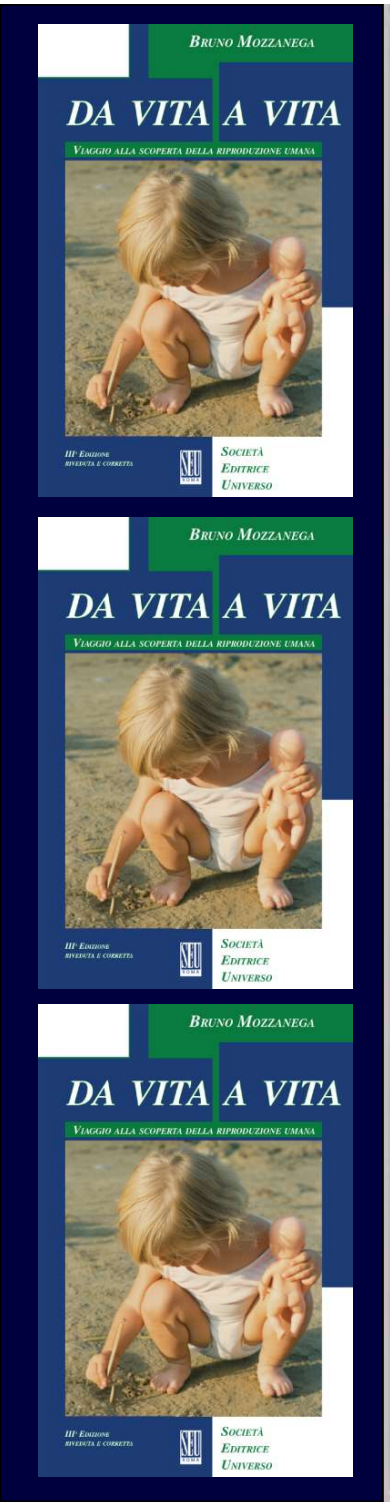


Fig. 14


BRUNO MOZZANEGA
DA VITA A VITA
VIAGGIO ALLA SCOPERTA DELLA RIPRODUZIONE UMANA
IIF EDIZIONE RIVEDUTA E CORRETTA
SEU
SOCIETÀ EDITRICE UNIVERSO
BRUNO MOZZANEGA
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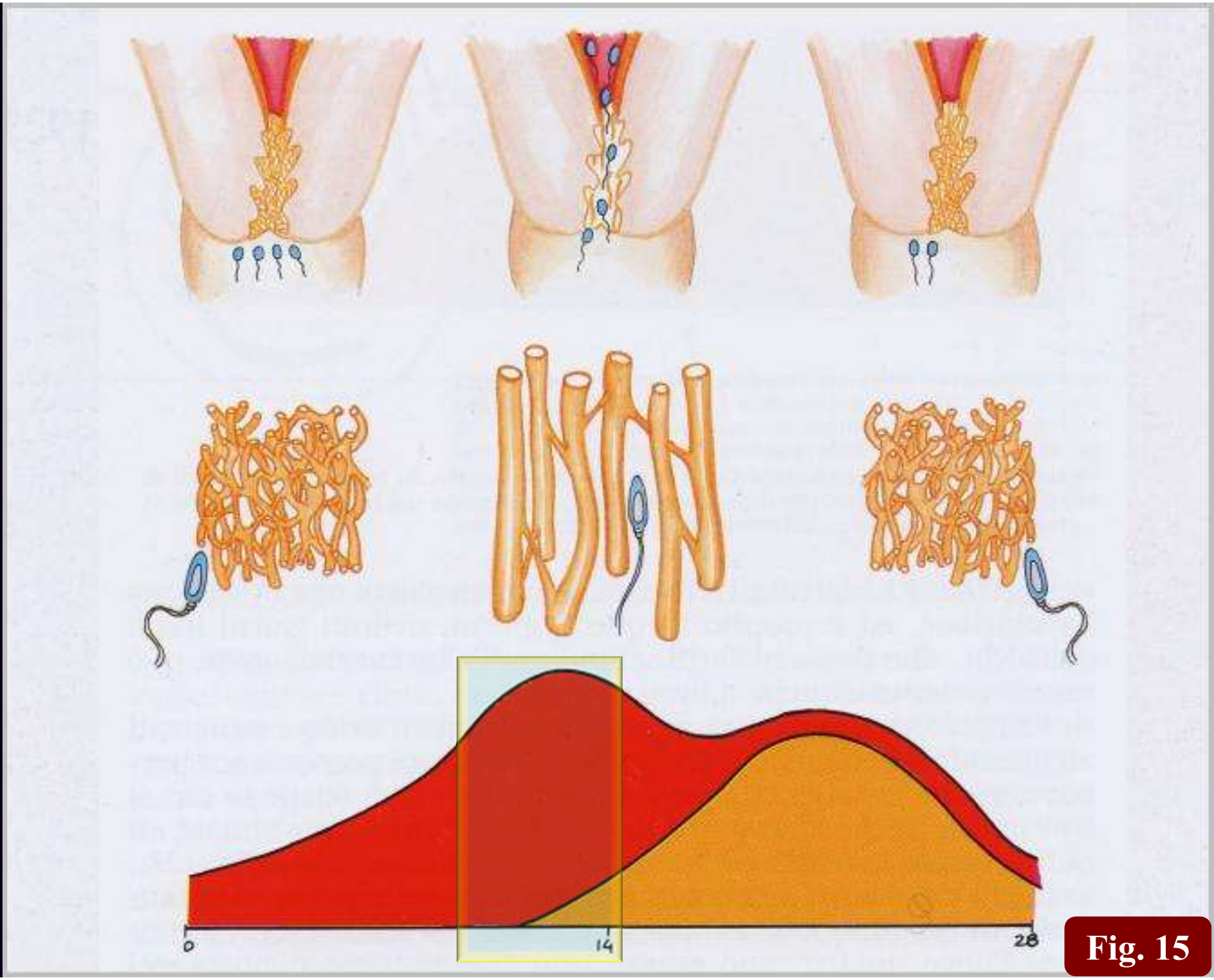
0
14
28

Fig. 15

pillola del giorno dopo

LNG

Fig. 16

Phase 2/3 Efficacy Trials
Study 507*

EFFICACY

	Methods
Time window	within 72 hr of intercourse
Study sites	7 clinical sites (USA)
Design	Randomized & double blind
Treatments	UPA 50 mg + placebo 12 hr later
	LNG 0.75 mg × 2 12 hr apart
Primary efficacy endpoint	Observed pregnancy rate
Hypothesis tested	Non-inferiority UPA to LNG
Sample size for efficacy analysis	770 subjects per group

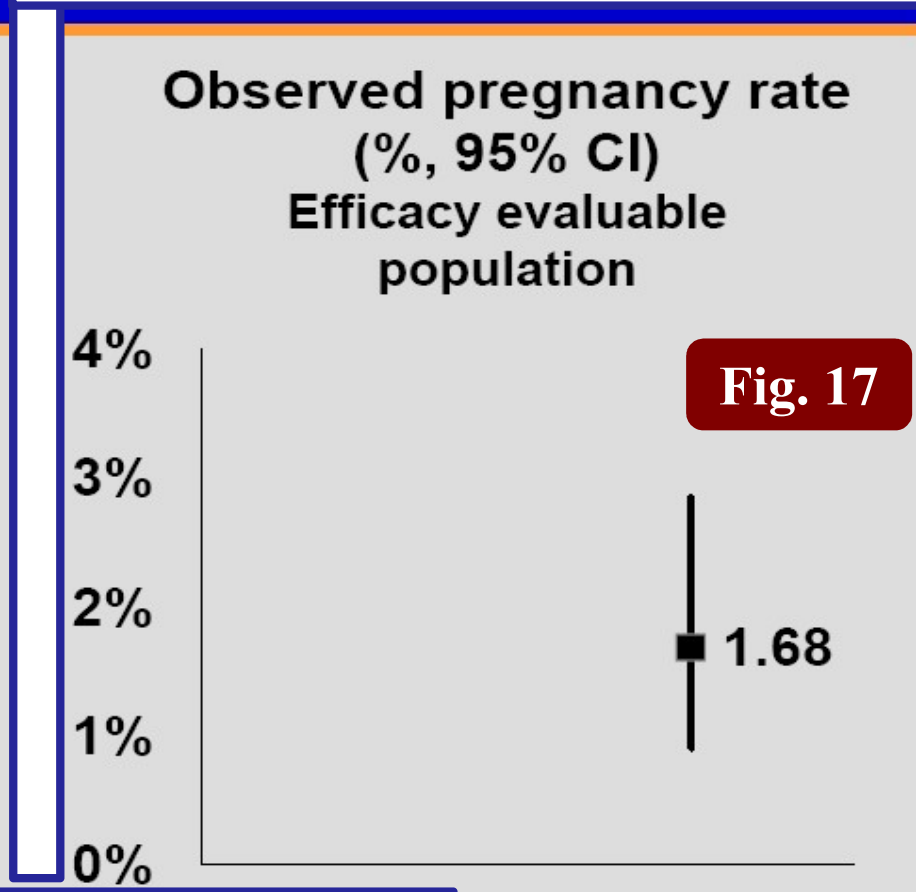

Fig. 17

1.7 vs. 5.8

attese

* Creinin, et al. *Obstet Gynecol*. 2006;108(5):1089-1097.

(ICEC)

International Consortium for Emergency Contraception
International Federation of Gynecology & Obstetrics

*Statement on Mechanism of Action (**2008**, updated **2011** and **2012**)*

(FIGO)

How do levonorgestrel-only emergency contraceptive pills (LNG ECPs) prevent pregnancy?

- Inhibition or delay of ovulation is LNG ECP's primary and possibly the only mechanism of action.
- Review of the evidence suggests that LNG ECPs cannot prevent implantation of a fertilized egg.
- Language on implantation should not be included in LNG ECP product labeling.

Fig. 18

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Fig. 19

Hapangama, Contraception 2001, 63: 123-9
Okewole, Contraception 2007, 75: 372-377
Durand, Contraception 2001, 64: 227-34

LNG

pillola “del giorno dopo”

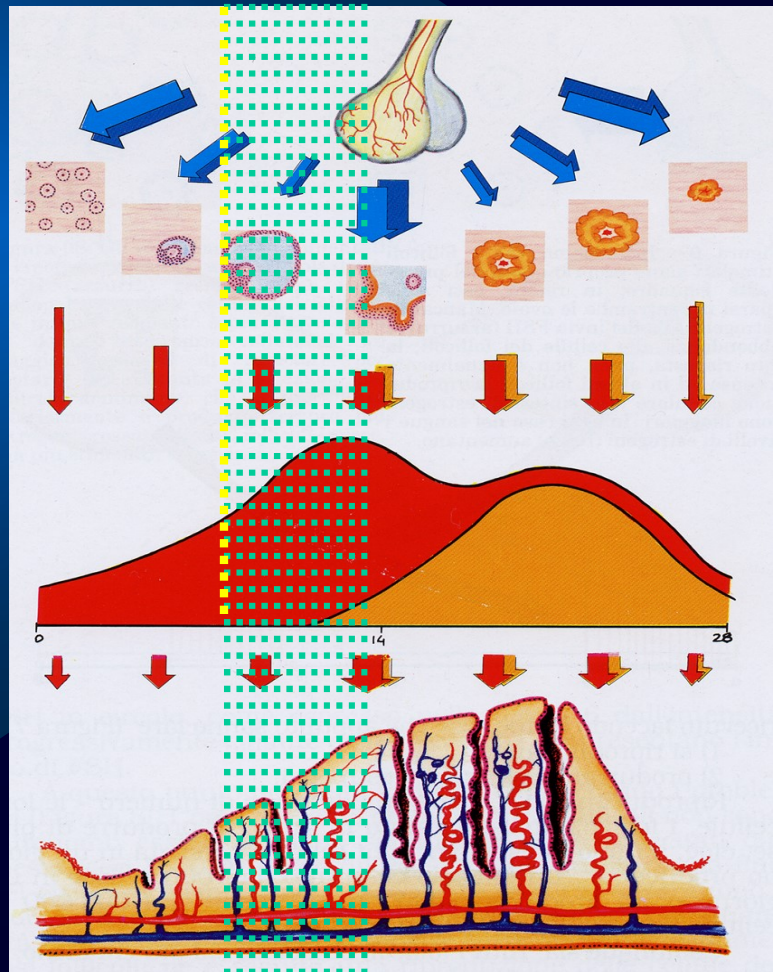
primo giorno fertile

ritardo ovulatorio incostante

il rapporto non protetto nei giorni precedenti è in giorni non fertili

nei cicli ovulatori fase luteale breve

Fig. 20



Hapangama, Contraception 2001, 63: 123-9
Okewole, Contraception 2007, 75: 372-377
Durand, Contraception 2001, 64: 227-34

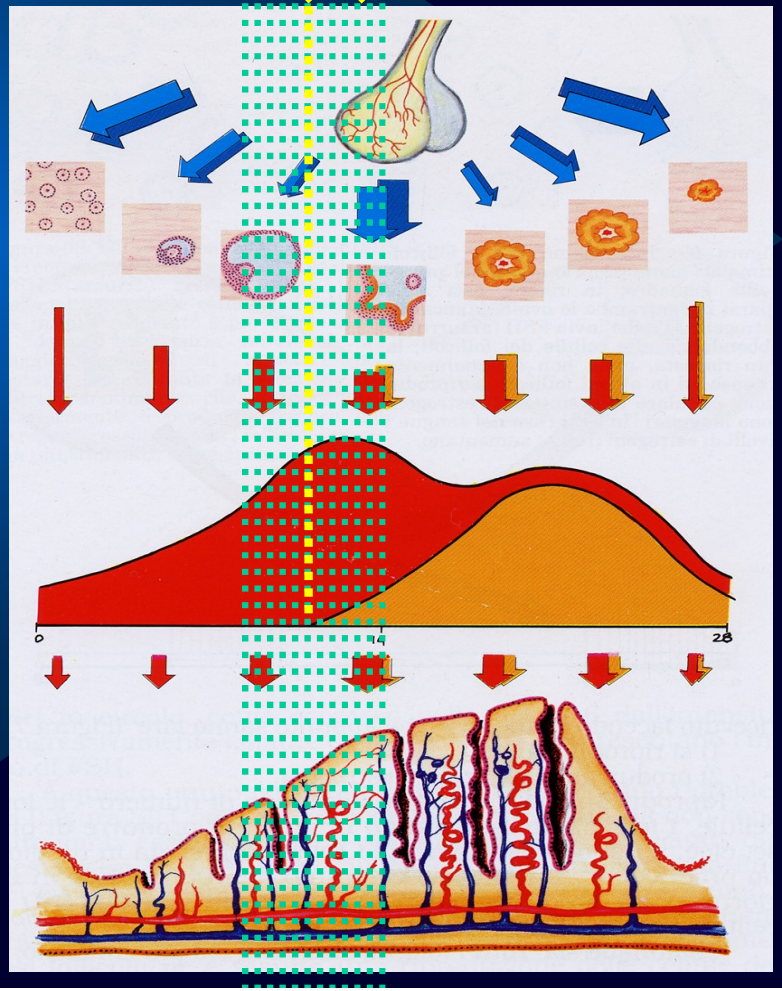
LNG

pillola “del giorno dopo”

giorni più fertili

2-3 giorni preovulatori

Fig. 21



cicli sempre ovulatori

fase luteale breve o inadeguata

ELSEVIER

Contraception

Contraception 63 (2001) 123–129
Original research article

Statement's Reference 3

The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle☆

Dharani Hapangama, Anna F. Glasier, David T. Baird*

Contraceptive Development Network, Department of Reproductive and Development Sciences, The University of Edinburgh, Centre of Reproductive Biology, Edinburgh, EH3 9ET Scotland

Received 22 November 2000; received in revised form 22 January 2001; accepted 30 January 2001

Abstract

Levonorgestrel (LNG) 0.75 mg administered 12 h apart within 72 h of unprotected coitus, is an established method of emergency contraception (EC). The mechanism of action of LNG used in this manner is unknown. We administered LNG 0.75 mg twice immediately before ovulation, to test the hypothesis that LNG acts as an emergency contraceptive by abolishing the pre-ovulatory lutenizing hormone (LH) surge and thereby delaying ovulation. Twelve women took LNG on or before the day of the first significant rise in urinary LH in 12 cycles. In four women, the LH peak and the onset of next menses were significantly delayed (delay of 16.8 days (SD ± 8.7) from the day of mean LH peak in placebo cycles). One woman did not ovulate at all, despite a normal LH peak and cycle length. In the remaining eight women, LNG did not affect ovulation or the cycle length, but the length of the luteal phase and the total luteal phase LH concentrations were significantly reduced. We suggest that LNG acts as an emergency contraceptive by other mechanisms as well as delaying the LH surge and interfering with ovulation.

Keywords: Emergency contraception; Levonorgestrel; Mechanism of action

Fig. 22

Statement's Reference 2

ELSEVIER

Contraception

Contraception 64 (2001) 227–234
Original research article

On the mechanisms of action of short-term levonorgestrel administration in emergency contraception☆

Marta Durand[a], Ma. del Carmen Cravioto[a], Elizabeth G. Raymond[b], Ofelia Durán-Sánchez[a], Ma. De la Luz Cruz-Hinojosa[a], Andrés Castell-Rodríguez[c], Raffaela Schiavon[d], Fernando Larrea[a,*]

[a]*Department of Reproductive Biology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[b]*Family Health International, Research Triangle Park, NC, USA*
[c]*Department of Cellular Biology, School of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico*
[d]*Reproductive Health Service, Instituto Nacional de Pediatría, Mexico City, Mexico*

Abstract

The effects of short-term administration of levonorgestrel (LNG) at different stages of the ovarian cycle on the pituitary-ovarian axis, corpus luteum function, and endometrium were investigated. Forty-five surgically sterilized women were studied during two menstrual cycles. In the second cycle, each women received two doses of 0.75 mg LNG taken 12 h apart on day 10 of the cycle (Group A), at the time of serum luteinizing hormone (LH) surge (Group B), 48 h after positive detection of urinary LH (Group C), or late follicular phase (Group D). In both cycles, transvaginal ultrasound and serum LH were performed from the detection of urinary LH until ovulation. Serum estradiol (E_2) and progesterone (P_4) were measured during the complete luteal phase. In addition, an endometrial biopsy was taken at day LH + 9. Eighty percent of participants in Group A were anovulatory, the remaining (three participants) presented significant shortness of the luteal phase with notably lower luteal P_4 serum concentrations. In Groups B and C, no significant differences on either cycle length or luteal P_4 and E_2 serum concentrations were observed between the untreated and treated cycles. Participants in Group D had normal cycle length but significantly lower luteal P_4 serum concentrations. Endometrial histology was normal in all ovulatory-treated cycles. I suggested that interference of LNG with the mechanisms initiating the LH preovulatory surge depends on the stage of follicle developm

Fig. 23

Statement's Reference 6

ELSEVIER

Contraception

Contraception 75 (2007) 372–377

Original research article

Effect of single administration of levonorgestrel on the menstrual cycle

Idris A. Okewole[a,*], Ayodele O. Arowojolu[b], Okanlawon L. Odusoga[a], Olufemi A. Oloyede[a], Olufemi A. Adeleye[c], Jide Salu[c], Olukayode A. Dada[c]

[a]*Department of Obstetrics and Gynaecology, Olabisi Onabanjo University Teaching Hospital, Sagamu, P.M.B. 2001, Sagamu, Ogun State, Nigeria*
[b]*Department of Obstetrics and Gynaecology, University College Hospital, Ibadan, Nigeria*
[c]*Centre for Research in Reproductive Health, Olabisi Onabanjo University Teaching Hospital, Sagamu, P.M.B. 2001, Sagamu, Ogun State, Nigeria*

Received 7 November 2005; revised 14 December 2006; accepted 10 January 2007

Abstract

Background: Levonorgestrel (LNG) 1.5 mg administered within 72 h of unprotected coitus is an established method of emergency contraception. Currently, there is some, although incomplete, knowledge about the mechanism of action.
Methods: We administered 1.5 mg LNG peri-ovulatory to determine the effects on serum gonadotrophins, estradiol and progesterone levels. Fourteen women were studied in a pretreatment and treatment cycle; eight women (Group A) took LNG 3 days before the expected day of ovulation, while 6 (Group B) took LNG a day before the expected day of ovulation.
Results: The women in Group A had a significant delay in their LH peak and onset of the next menses compared with their pretreatment cycles (26.4 vs. 39.1 days, $p<.05$). Those in Group B had no significant changes in the endocrine parameters but there was a significant shortening of the mean cycle length in comparison with their pretreatment cycles (25.1 vs. 20.2 days).
Conclusion: Levonorgestrel 1.5 mg acts as an emergency contraception by delaying the LH surge and interfering with ovulation. It may also disrupt corpus luteum formation causing premature luteinization of unruptured follicles.

Keywords: Levonorgestrel; Gonadotrophins; Steroid hormones; Emergency contraception; Women

Fig. 24

trattamento pre-ovulatorio dopo UPSI nei giorni fertili

Table 2
Number of cycles in which FRs and luteal P were detected during follow-up after administration of LNG-EC to women who had intercourse during the fertile days

Time of treatment		Preovulatory (n=87)			Pre- and postovulatory (n=122)		
Parameter		Follicular rupture			Progesterone concentration		
Ultrasound finding at LNG-EC intake		Detected	Undetected	Unknown[a]	≥12 nmol/L	<12 nmol/L	Unknown[a]
Follicle diameter, mm	≥18	30	4	9	23	3	19
	≥15 to 17.9	21	8	5	16	4	14
	≥12 to 14.9	6	2	1	4	0	3
	Unknown[b]		1		1		
Corpus luteum		–	–	–	29	2	4

[a] Unknown because there was no follow-up after examination on the day of LNG-EC intake and/or after FR.
[b] Unknown case in which follicular diameter was not measured; had blood sample but not ultrasonography during follow-up.

0% ovulazione (FR) nelle pazienti valutabili (57/71)

Statement's Reference 9

dopo LNG-EC

assunto nei giorni pre-ovulatori

Fig. 25

trattamento pre-ovulatorio dopo rapporto nei giorni fertili

Table 4
Comparison of the number (*n*) of women at risk of pregnancy and the contraceptive efficacy (expected/observed) according to the method used to estimate the day of ovulation in 337 cases analyzed

Method for estimating ovulatory day	Sexual intercourse		Time of LNG-EC administration				Efficacy, %
	Without risk, *n*	With risk, *n*	Preovulatory (Days −5 to −1)		Postovulatory (Day 0 or +)		
			n	Pregnancies expected/observed	*n*	Pregnancies expected/observed	
Hormones and ecography of actual cycle	215	122	87	13.2/0	35	*7.1/6**	70
LMP and length of previous cycles	168[a]	169	91	12.6/*1***	78	*13.6/3****	77

Italicized values are to emphasize the differences between methods.
Fisher's Exact Test: *p=1.00; **p=.0012; ***p=.0085.
[a] Two pregnancies occurred in this group.

nessuna gravidanza su 13 attese

nonostante l'ovulazione nel 66% delle 87 pazienti
e gli spermatozoi già nelle tube

Noè: "… this suggests that other mechanism prevents pregnancy.
We postulate that increased cervical mucus viscosity ……."

Fig. 26

Brache autore del FIGO Statement

Fig. 27

Date:

Mon, 11/04/2011

The International Consortium for Emergency Contraception (ICEC), in collaboration with the International Federation of Gynecology and Obstetrics (FIGO), has updated its statement "How do Levonorgestrel-only emergency contraceptive pills (LNG ECPs) work to prevent pregnancy?"

The revised statement is based on an extensive review of the recent literature, and concludes that inhibition or delay of ovulation is LNG ECPs' principal and possibly only mechanism of action. LNG ECPs cannot prevent implantation of a fertilized egg.

ICEC's statements and literature reviews are undertaken to provide our community with comprehensive, accurate and concise information that can help you in your work.

We thank our expert contributors, Vivian Brache, Anibal Faundes, Ian Fraser and James Trussell, for their incredible attention to detail and persistence in making sure this statement was accurate and fully reflected the most recent studies.

Access the English version of this statement here.

Brache autore del FIGO Statement

28

Fig. 28

human reproduction ORIGINAL ARTICLE *Fertility control*

Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture

V. Brache [1,*], L. Cochon [1], C. Jesam [2], R. Maldonado [2], A.M. Salvatierra [2], D.P. Levy [3], E. Gainer [3], and H.B. Croxatto [4]

[1]PROFAMILIA, Nicolas de Ovando & Calle 16, Santo Domingo 10401, Dominican Republic [2]Instituto Chileno de Medicina Reproductiva, Santiago, Chile [3]HRA Pharma, 75003 Paris, France [4]Laboratorio de Inmunología de la Reproducción, Universidad de Santiago de Chile y Centro para el Desarrollo de Nanociencia y Nanotecnología-CEDENNA, Santiago, Chile

*Correspondence address. Tel: +1-809-681-8357; E-mail: biomedica@codetel.net.do

Submitted on December 9, 2009; resubmitted on May 11, 2010; accepted on May 25, 2010

BACKGROUND: Current methods of hormonal emergency contraception (EC) are ineffective in preventing follicular rupture when administered in the advanced pre-ovulatory phase. This study was designed to determine the capacity of ulipristal acetate (UPA), a selective progesterone receptor modulator developed for EC, to block follicular rupture when administered with a follicle of ≥18 mm.

METHODS: This was a double-blind, crossover, randomized, placebo-controlled study. Thirty-five women contributed with UPA (30 mg. oral) and a placebo cycle. Serial blood sampling for luteinizing hormone (LH), estradiol and progesterone measurements and follicular monitoring by ultrasound were performed before and for 5 days following treatment. Follicular rupture inhibition was assessed in the overall study population and in subgroups of women stratified by when treatment was administered in relation to LH levels (before the onset of the LH surge, after the onset of the surge but before the LH peak or after the LH peak).

RESULTS: Follicular rupture failed to occur for at least 5 days following UPA administration in 20/34 cycles [59%; 95% confidence interval (CI) (40.7–75.4%)], whereas rupture took place in all cycles within 5 days of placebo intake. When UPA was administered before the onset of the LH surge, or after the onset but before the LH peak, follicle rupture had not occurred within 5 days in 8/8 (100%) and 11/14 [78.6%; 95% CI (49.2–95.3)] cycles, respectively. In contrast, when UPA was given after the LH peak, follicle rupture inhibition was only observed in 1/12 [8.3%; 95% CI (0.2–38.5)] cycles.

CONCLUSIONS: This study demonstrates that UPA can significantly delay follicular rupture when given immediately before ovulation. This new generation EC compound could possibly prevent pregnancy when administered in the advanced follicular phase, even if LH levels have already begun to rise, a time when levonorgestrel EC is no longer effective in inhibiting ovulation.

NCT01107093: Comparison of CDB-2914 versus placebo in the prevention of follicular rupture post-LH surge.

Key words: ulipristal acetate / emergency contraception / follicular rupture / LH surge

Fig. 29

trast, in the cycles in which the UPA treatment took place on the day of the LH peak, when a significant rise in *P* had already occurred, follicle rupture followed within 24–48 h with the exception of one woman who exhibited a luteinized unruptured follicle.

The present results indicate that follicular rupture delay is mainly mediated by postponement of LH peak. Nonetheless, UPA may also have a direct effect on the dominant follicle by interfering with progesterone receptor regulated pathways that modulate ovulation, as has been demonstrated in mice (Palanisamy *et al.*, 2006).

Stratton *et al.* (2000) showed that a single mid-follicular dose of 10–100 mg of UPA (CDB-2914) administered with a follicle of 14–16 mm, caused a dose-dependent delay in the time interval from treatment to follicular rupture and suppression of E_2. At higher doses, the initial lead follicle often stopped growing and was replaced by a new lead follicle. This phenomenon was not observed in our study, and it may be related to the fact that we administered UPA later in the cycle, with a pre-ovulatory follicle ≥18 mm, instead of 14–16 mm; another possible difference may be the lower dose used in our study.

Existing hormonal emergency contraceptives based on LNG or estrogen–progestogen combinations administered well before the onset of the LH surge exert inhibitory effects on ovulation via shunting of the LH surge, but they do not significantly delay or inhibit follicular rupture when administered in the advanced pre-ovulatory phase (Croxatto *et al.*, 2001; Gemzell-Danielsson and Marions, 2004; Novikova *et al.*, 2007). In two studies, conducted by the same investigators, using the same design and same conditions of treatment (administration when lead follicle has reached 18 mm in diameter), LNG-EC inhibited dominant follicular rupture for 5 days after treatment in only 2/17 (12%) and 5/31 (16%) women, respectively (Croxatto *et al.*, 2004; Massai *et al.*, 2007). The results from these two trials were very similar and, when combined, this resulted in follicle rupture inhibition in 7/48 women (14.6%) of the LNG studied cycles as compared with 20/34 (58.8%) women with UPA. When comparing the proportions of follicular rupture inhibition at 5 days of treatment using a Fisher exact test, the difference between LNG and UPA is significant ($P < 0.0001$).

In summary, this study provides mechanistic evidence to explain how UPA could be more effective in preventing pregnancy than current reference EC methods. It suggests that UPA is able to inhibit or significantly delay follicular rupture for over 5 days if given immediately before ovulation by postponing the LH peak.

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Brache & Faundes nei FIGO Statements affermano: «l'inibizione o il ritardo nell'ovulazione è il principale e forse unico meccanismo d'azione di LNG-ECPs»

Fig. 31