emergency contraception

drugs

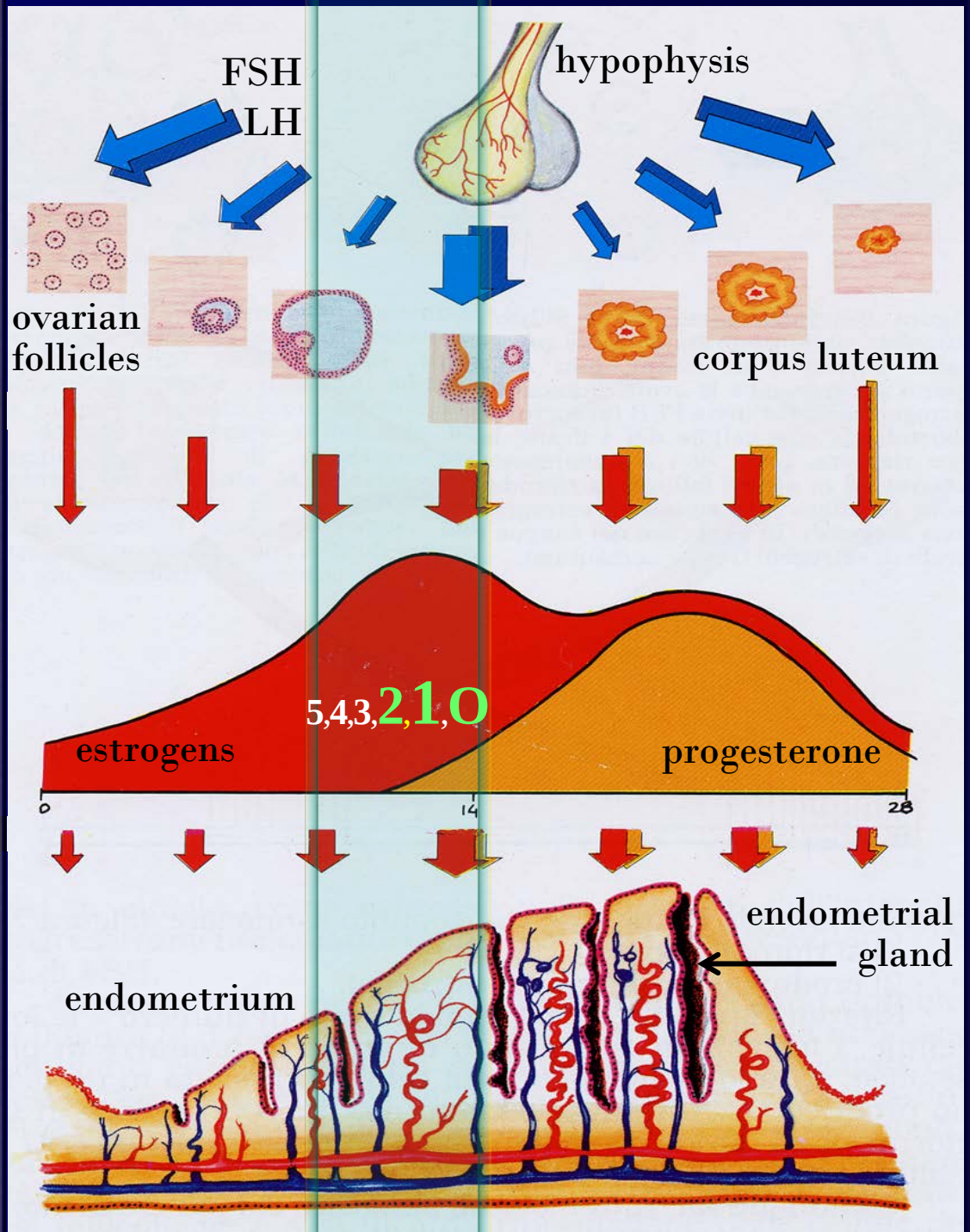
after

UPSI

unprotected sex intercourse

in the fertile period of the cycle

IUDs


FSH
LH
hypophysis
ovarian
follicles
corpus luteum
5,4,3,2,1,0
estrogens
progesterone
0
14
28
endometrial
gland
endometrium

ella®
ulipristal acetate

FDA Reproductive Health Drugs Advisory Committee
June 17, 2010

HRA Pharma

CONCEPTION

The Fertile Window

David Archer, MD

Probability of conception on specific days near the day of ovulation

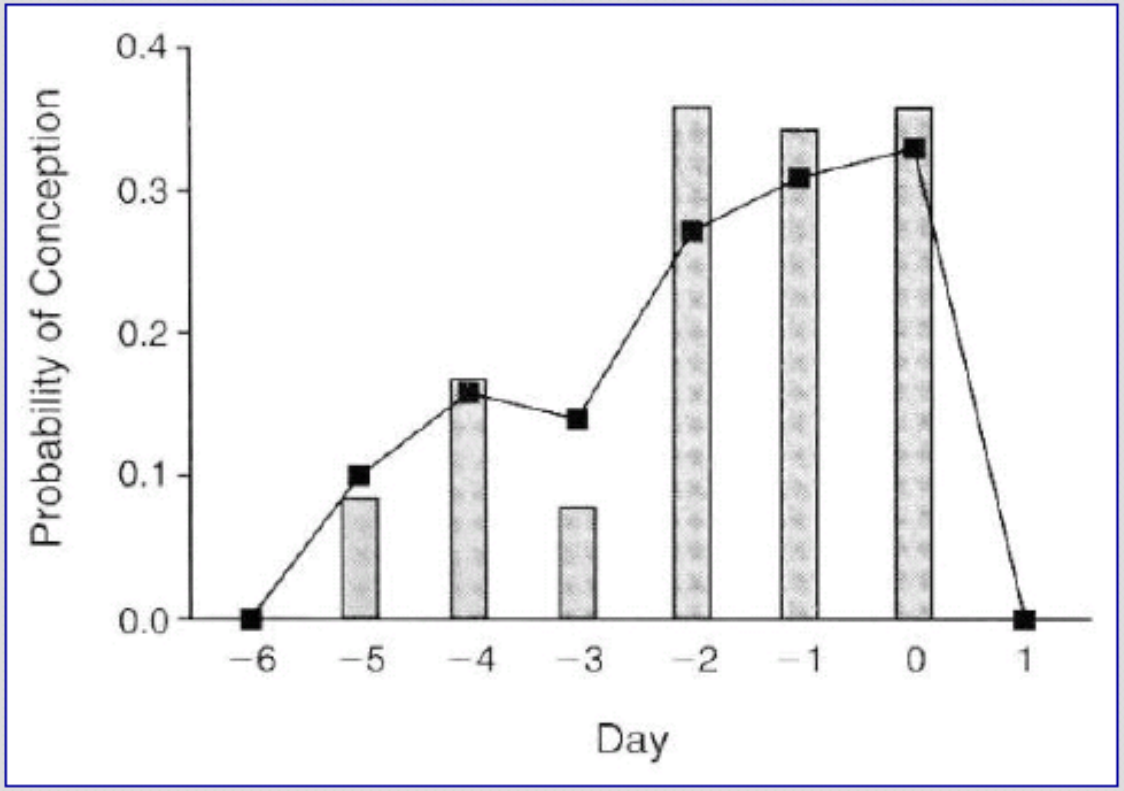


Figure 2 from *Wilcox et al. 1995*

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.

Frequency of Intercourse

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

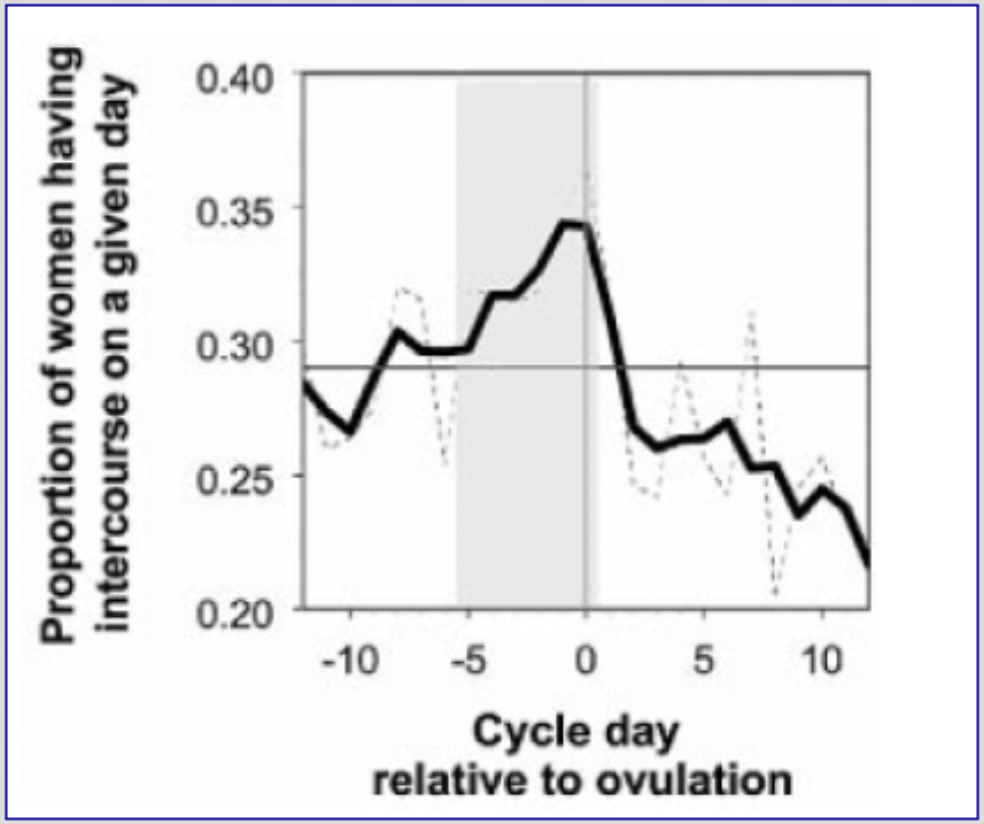


Figure 1 from *Wilcox et al. 2004*

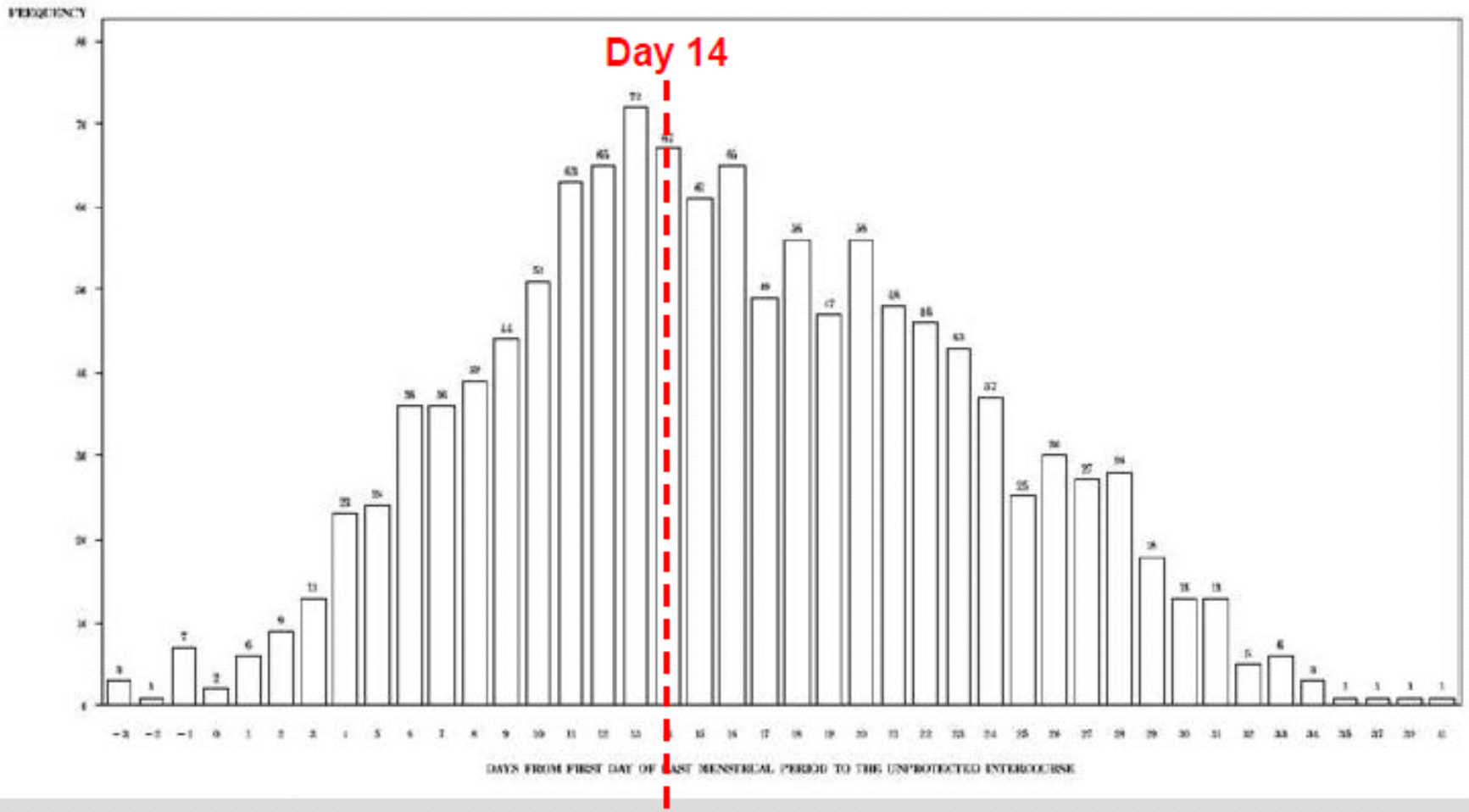
Dashed line shows mean value for each day, while the dark solid line shows the 3-day moving average (each data point representing the mid-point of a 3-day span). The 6 fertile days are shaded, with the day of ovulation (0) marked by the thin vertical line. The intercourse line represents the overall 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.

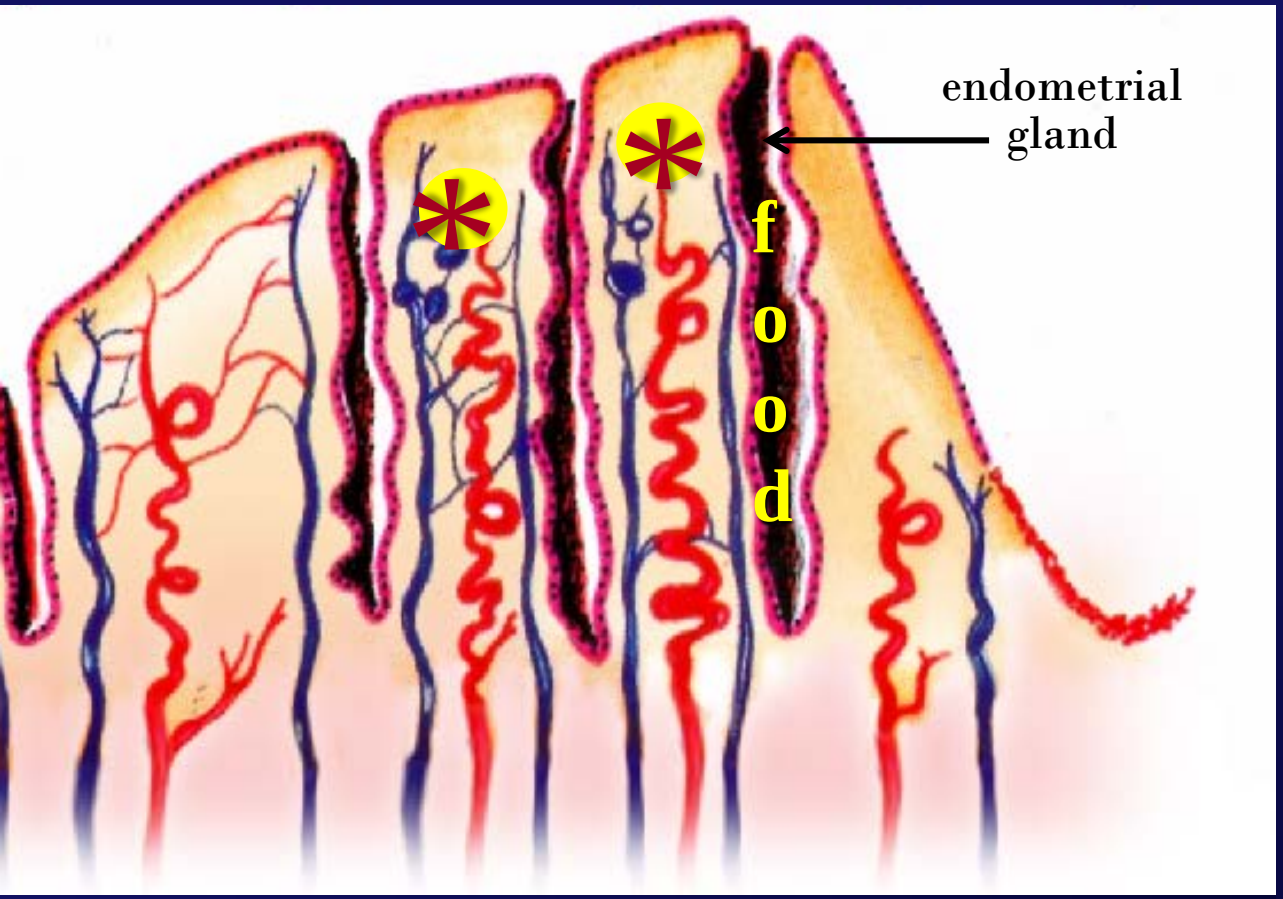
Distribution of UPIs
Study 509 – mITT Population

UNPROTECTED

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



Progesterone → → immune tolerance



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

hCG embryo

endometrium

END-1 ⇓⇓

MMP ⇑⇑

Endothelin-1 --- Enkefalinase

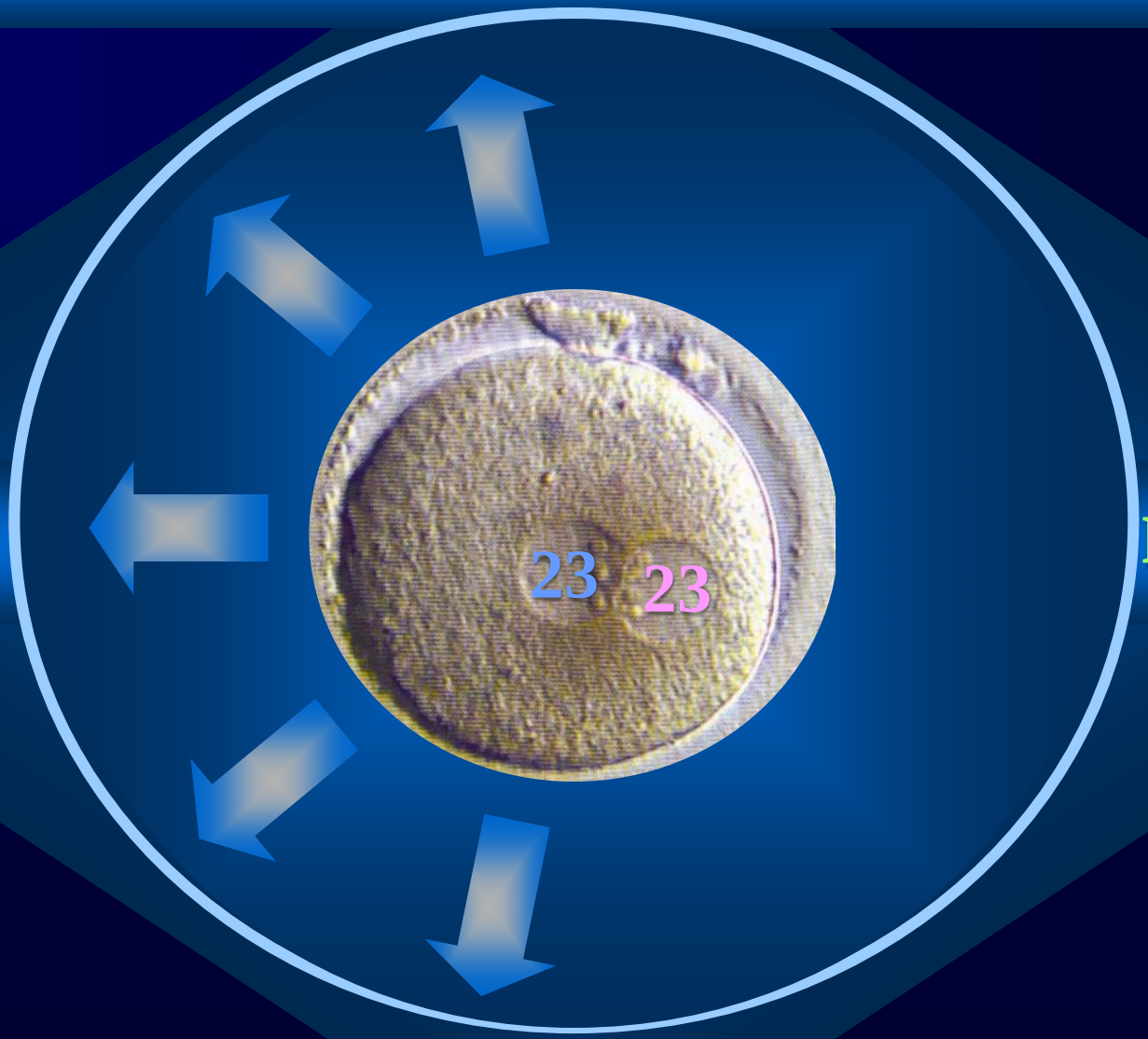
PAF Platelet Activating

within 48 h

Immuno

IF

suppressive

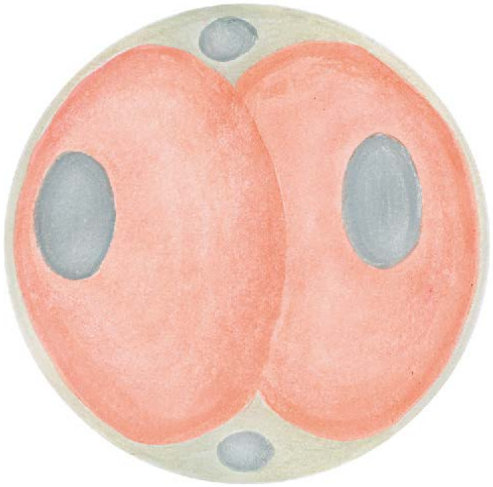


modulates

mother's immune defenses

EPF Early Pregnancy

immediately





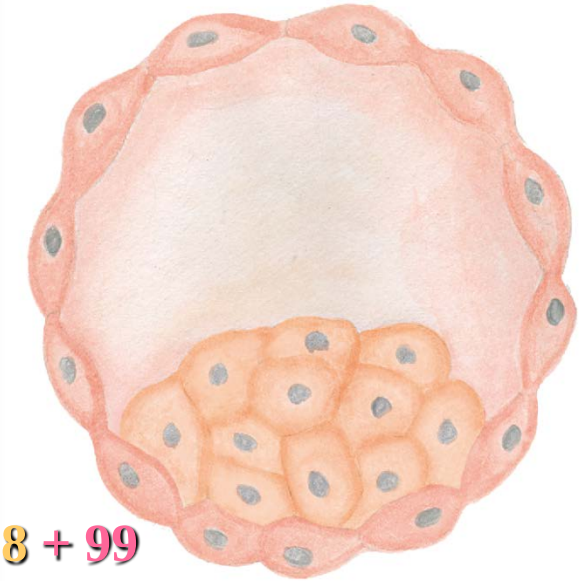


constant volume

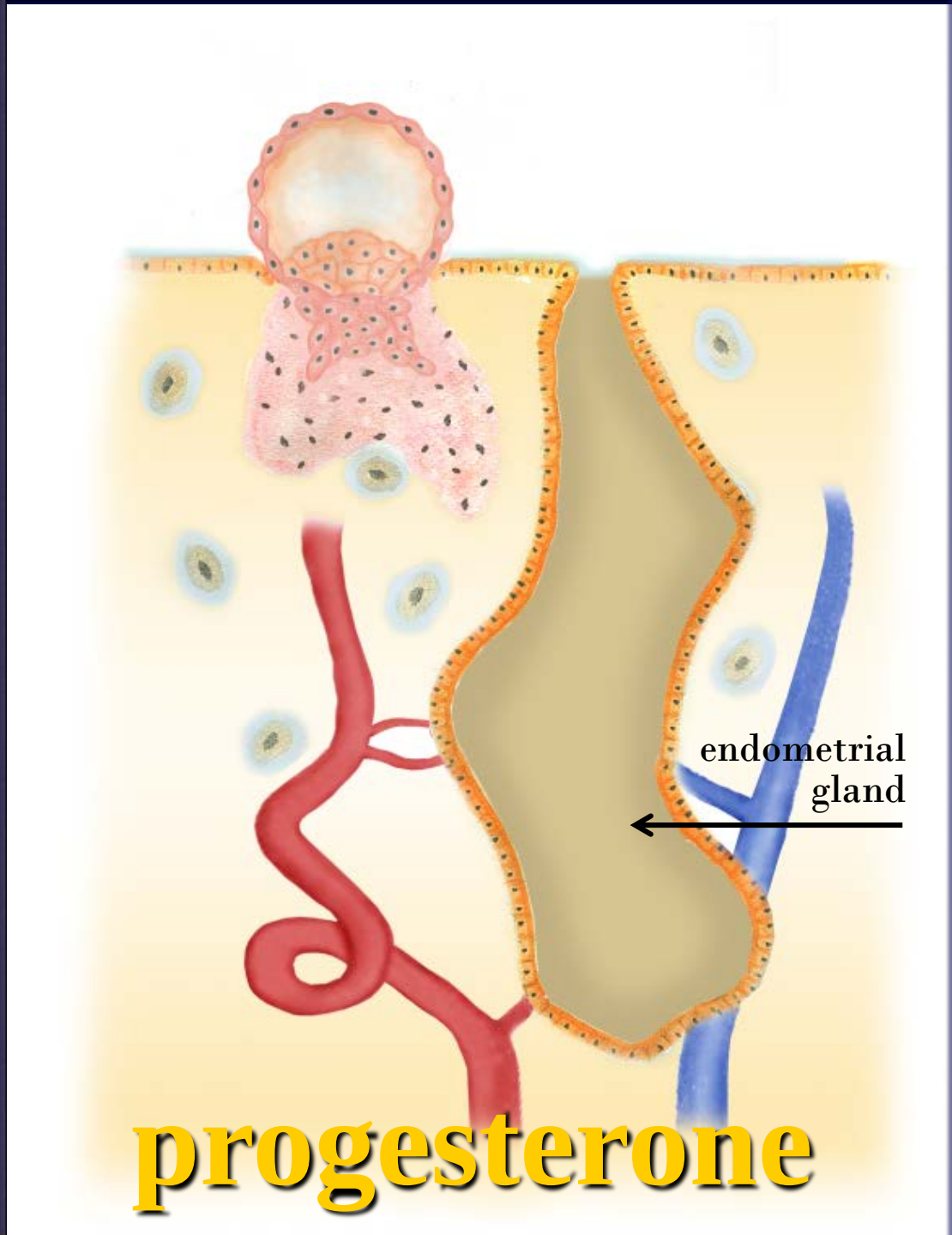




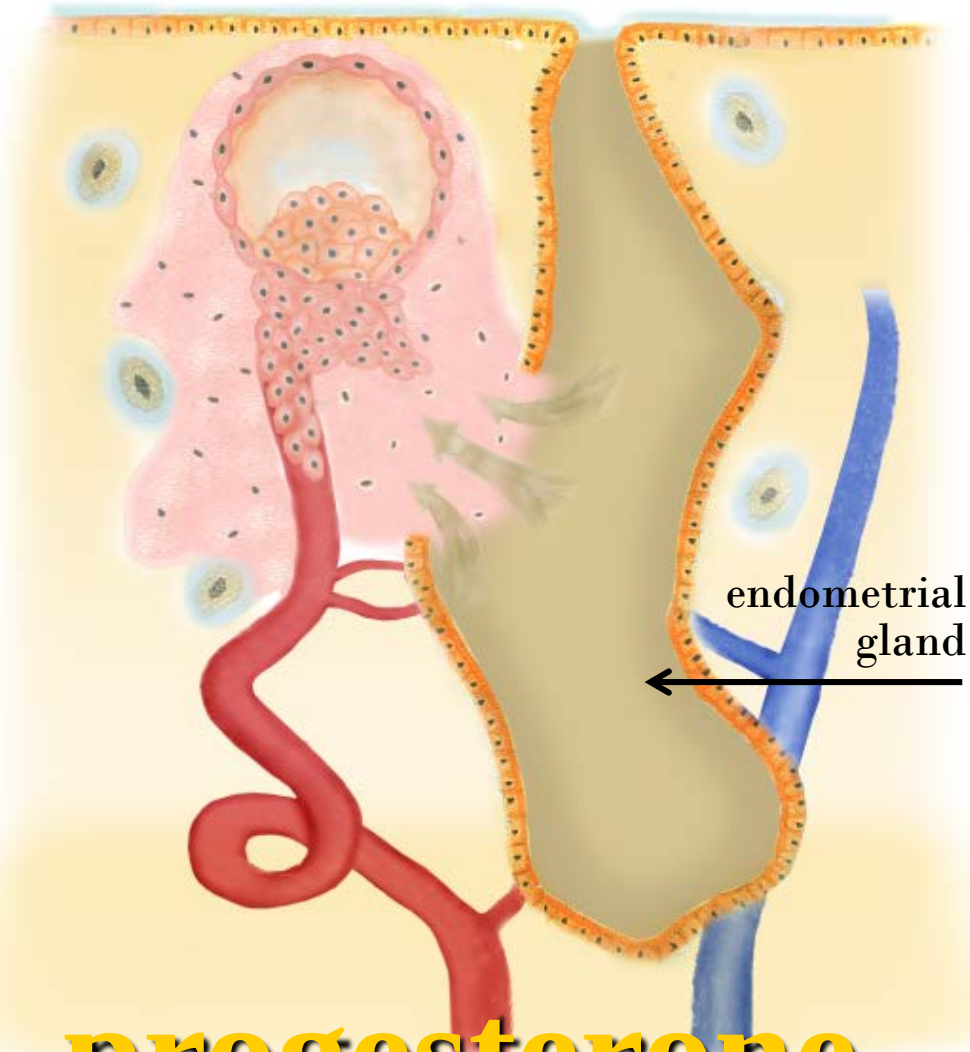
5 + 53



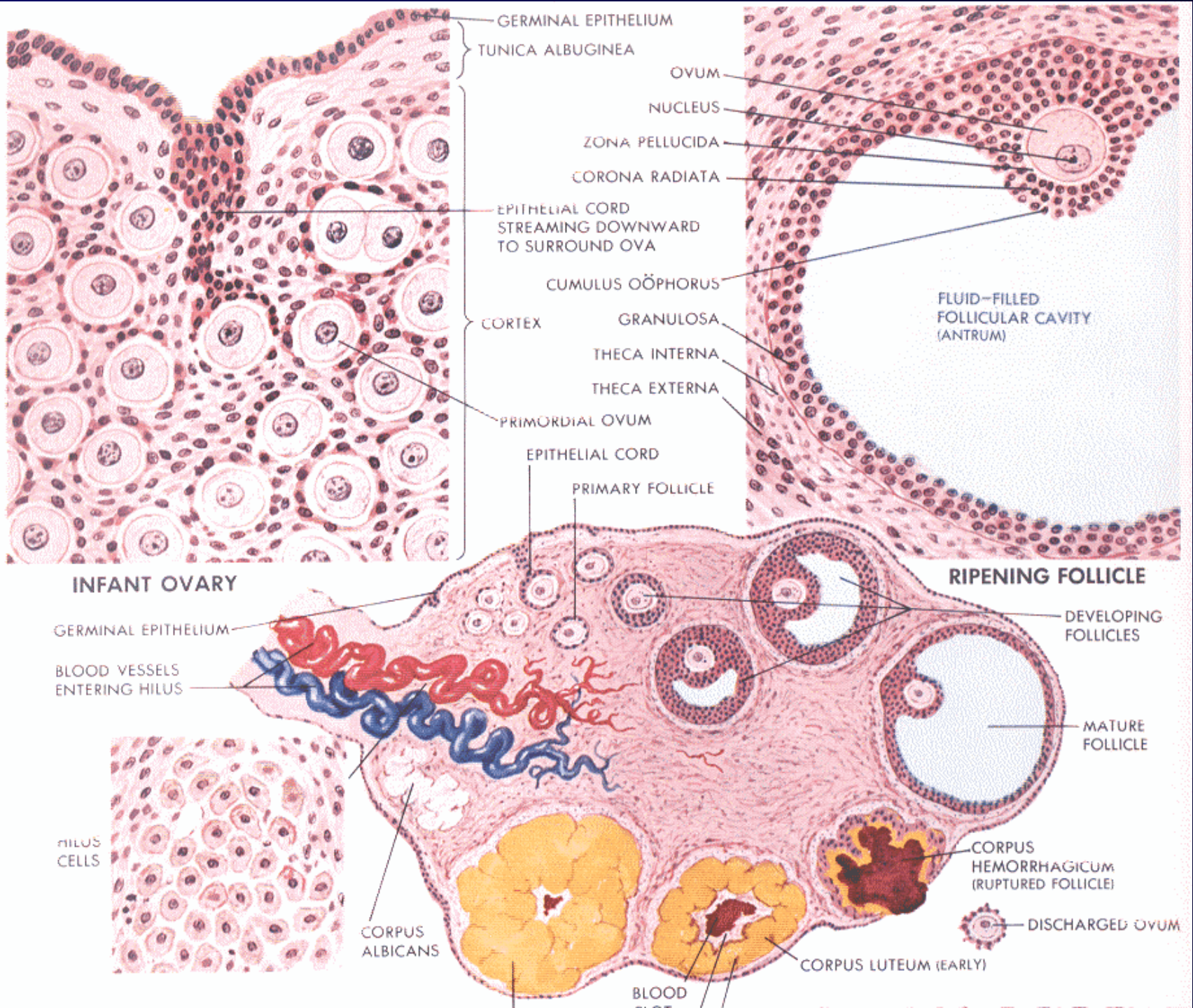
8 + 99



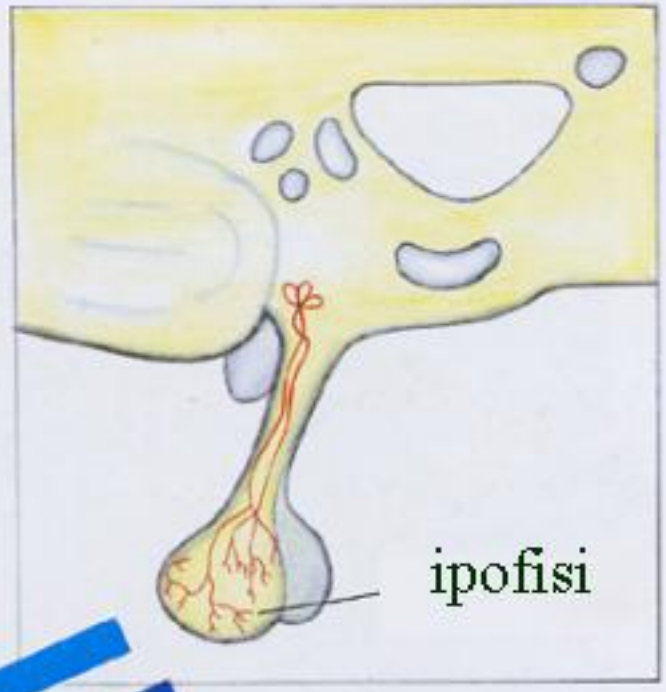
progesterone



progesterone

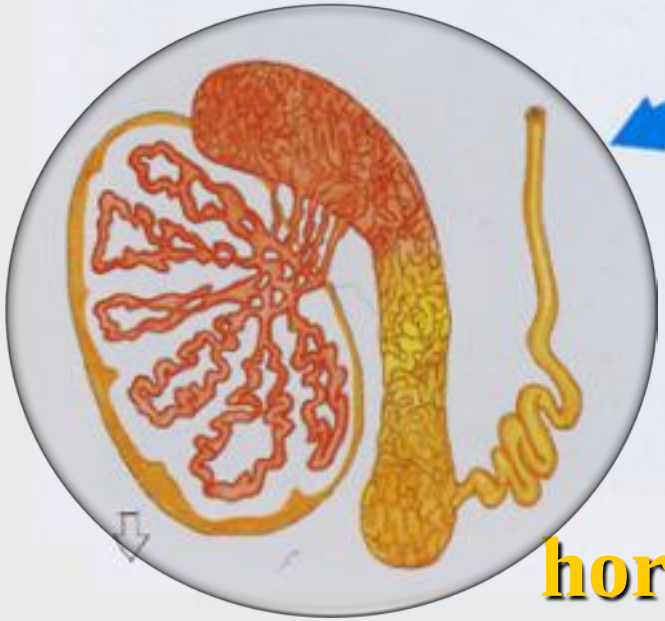

GERMINAL EPITHELIUM
TUNICA ALBUGINEA
OVUM
NUCLEUS
ZONA PELLUCIDA
CORONA RADIATA
EPITHELIAL CORD STREAMING DOWNWARD TO SURROUND OVA
CUMULUS OÖPHORUS
CORTEX
GRANULOSA
THECA INTERNA
THECA EXTERNA
PRIMORDIAL OVUM
EPITHELIAL CORD
PRIMARY FOLLICLE
FLUID-FILLED FOLLICULAR CAVITY (ANTRUM)
INFANT OVARY
RIPENING 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



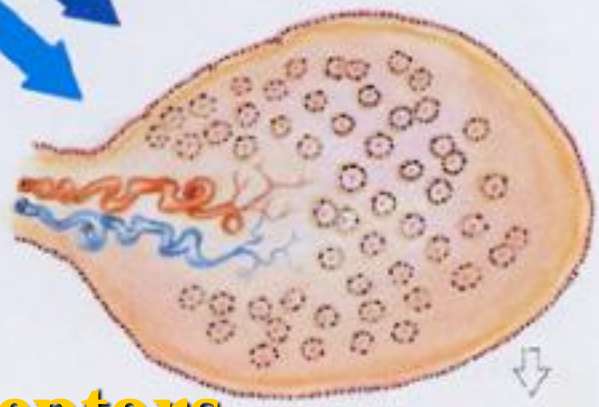


FSH

LH



gonado tropins



hormonal receptors

chorion



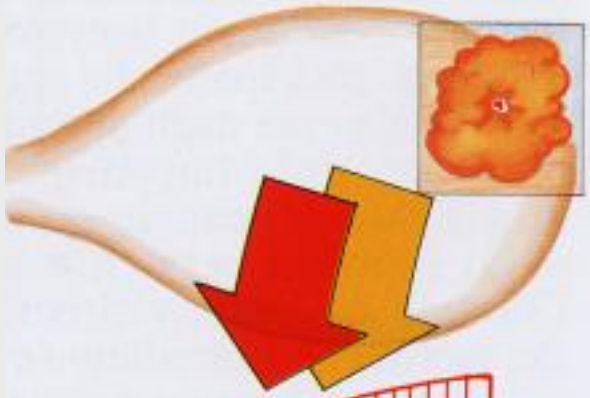
hCG

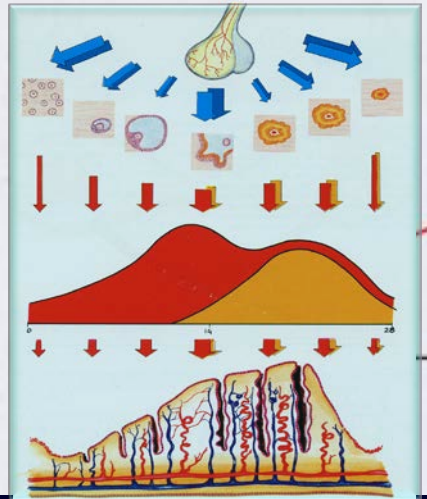


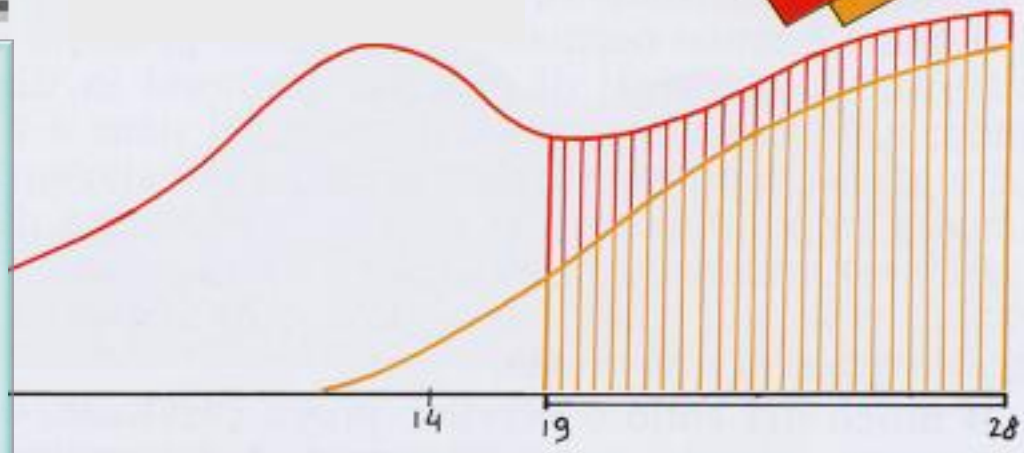




pregnancy corpus luteum





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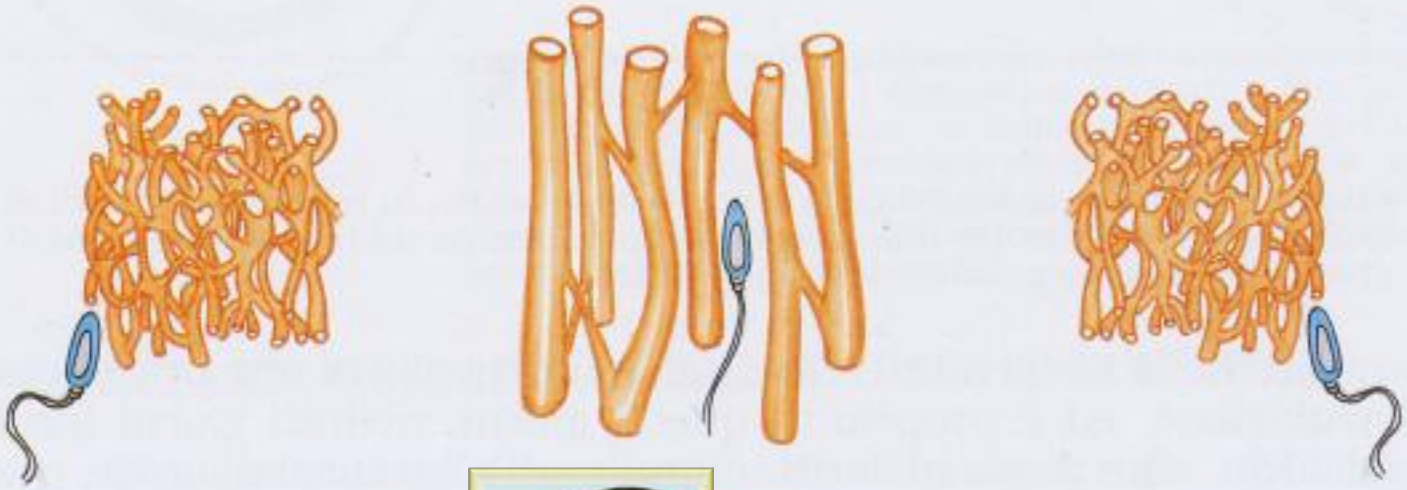
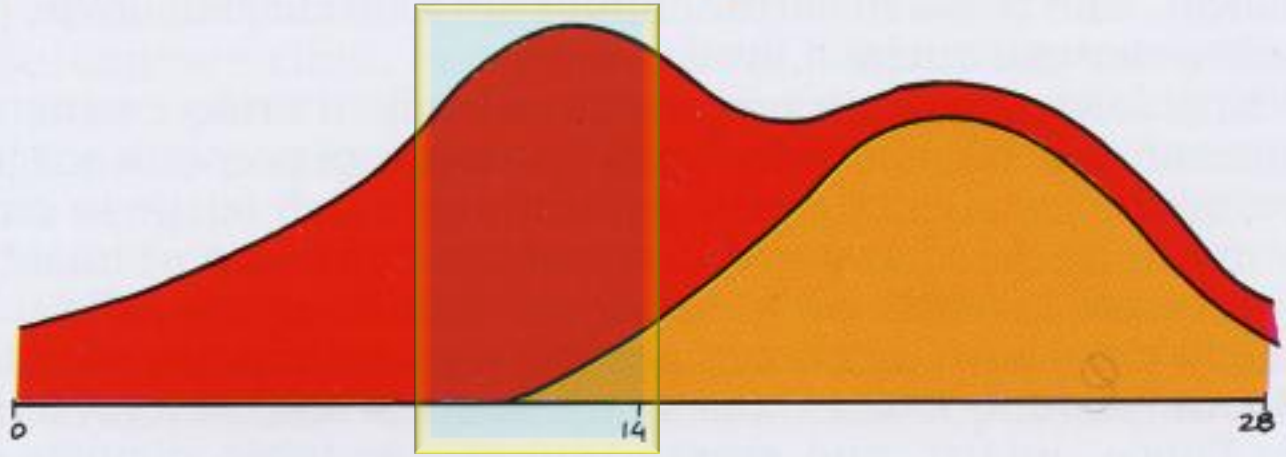



0
14
28

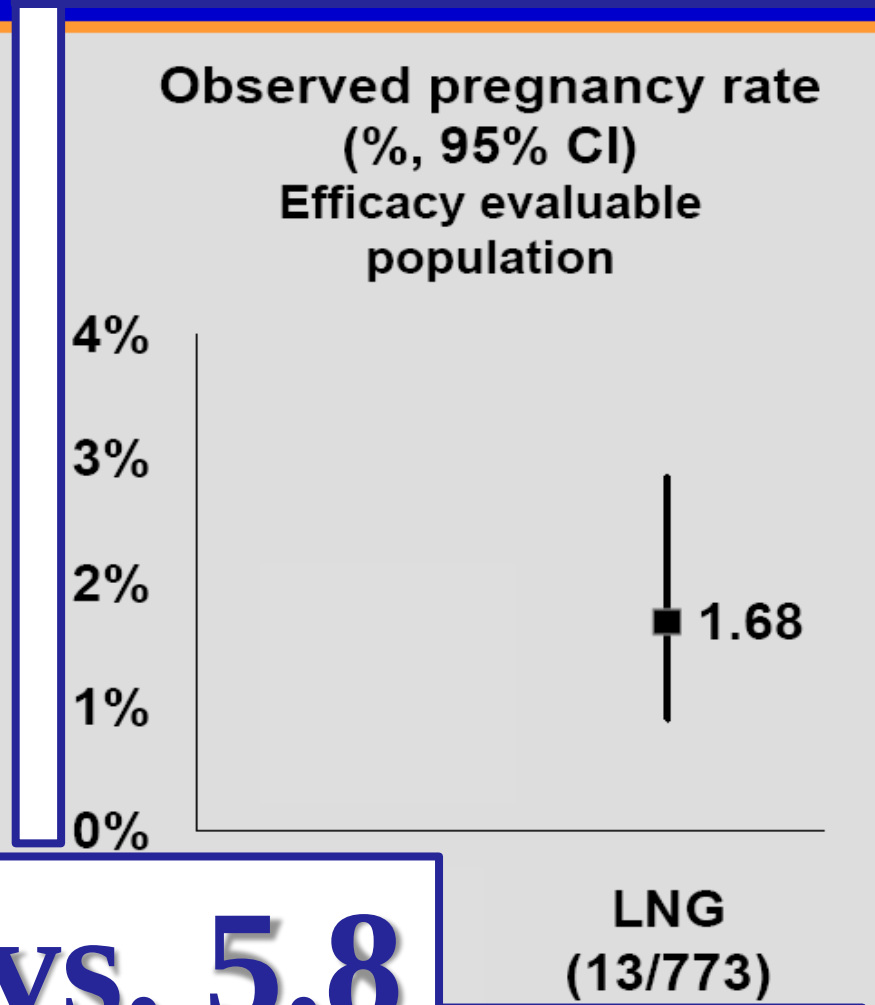
day-after pill

LNG

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



1.7 vs. 5.8

expected

* 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.**

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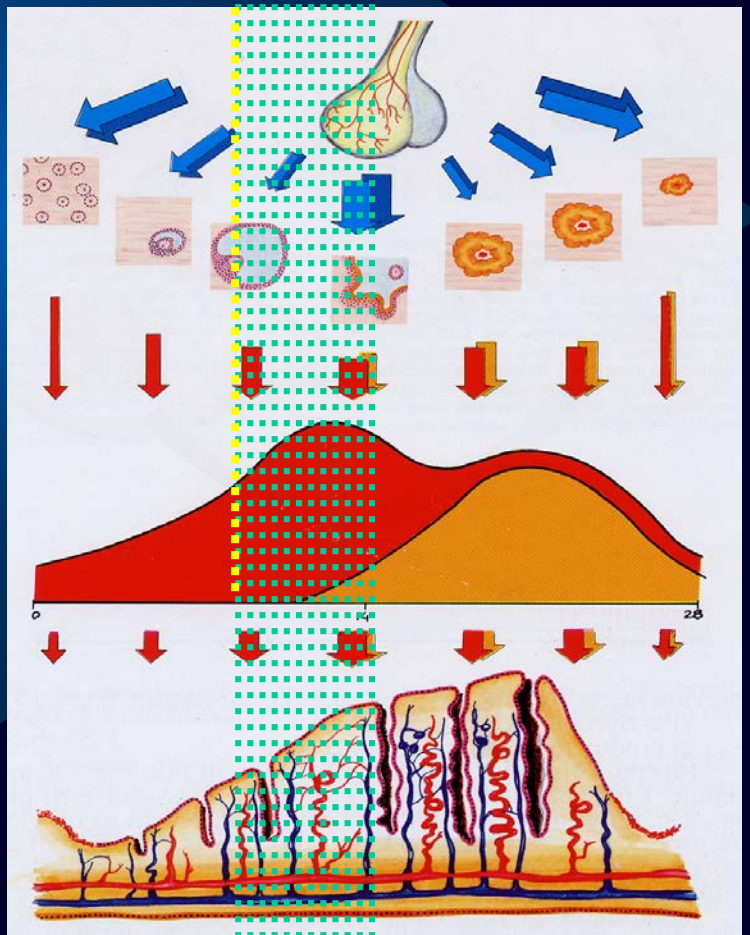
Hapangama, Contraception 2001, 63: 123-9
Okewole, Contraception 2007, 75: 372-377
Durand, Contraception 2001, 64: 227-34

LNG

“day-after” pill

first fertile day



- **ovulation delay (80%)**
- **UPSI in the previous days is in infertile days**

- **20% ovulatory cicles**
- **short luteal phase**

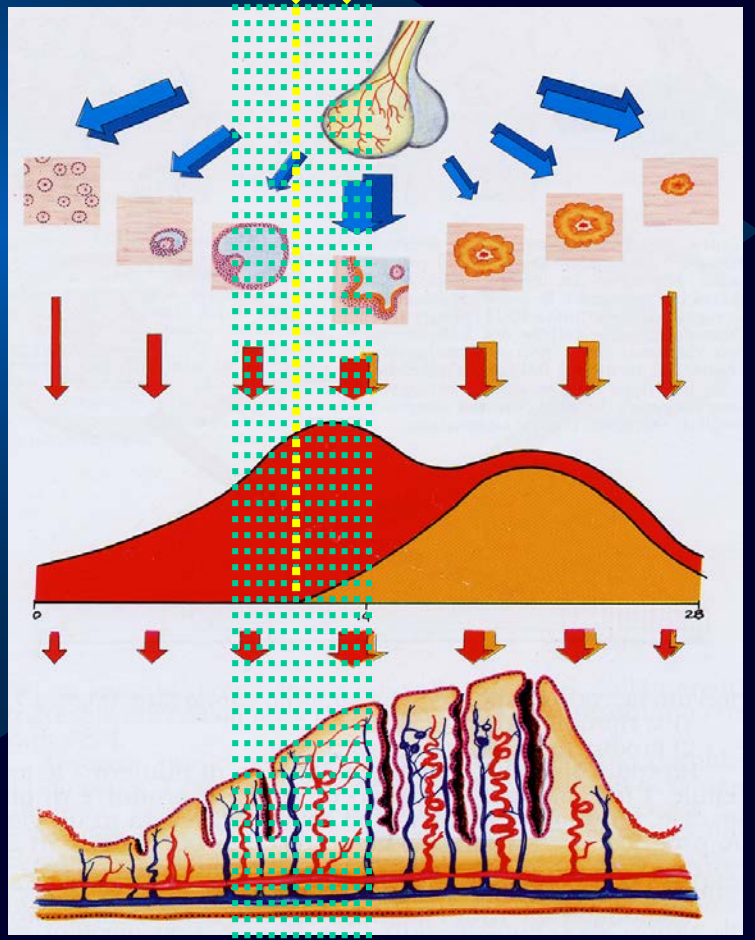
Hapangama, Contraception 2001, 63: 123-9
Okewole, Contraception 2007, 75: 372-377
Durand, Contraception 2001, 64: 227-34

LNG

day after pill

most fertile days

2-3 preovulatory days



- ovulatory cycles
- short/ inadequate luteal phase
- << glicodelin-A endometrial (anti maternal natural-killers)

Statement's Reference 3

ELSEVIER

Contraception

Contraception 63 (2001) 123–129
Original research article

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. © 2001 Elsevier Science Inc. All rights reserved.

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. It is suggested that interference of LNG with the mechanisms initiating the LH preovulatory surge depends on the stage of follicle development.

Statement's Reference 6

ELSEVIER

Contraception 75 (2007) 372–377

Contraception

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.
© 2007 Published by Elsevier Inc.

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

pre-ovulatory treatment after UPSI in the fertile days

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.

66% ovulation (FR) within 5 days after LNG-EC
(in 57 out of 87 patients treated in the preovulatory days)

79% ovulation (FR) without the 15 lost at follow-up

pre-ovulatory treatment after UPSI in the fertile days

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.

no pregnancy out of the 13 expected

in spite of ovulation, sperms entrance and likely fertilization

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

"How do Levonorgestrel-only emergency contraceptive pills (LNG ECPs) work to prevent pregnancy? - Windows Internet Explorer

http://www.escrh.eu/about-esc/news/how-do-levonorgestrel

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"How do Levonorgestrel-only emergency contraceptive pills (LNG ECPs) work to prevent pregnancy?"

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.

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Brache auhtor of the FIGO Statement

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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

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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.

Funding

This study was funded by HRA Pharma.

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Brache & Faundes
Authors of
FIGO Statement

Comments

nts were compared
iii) the timing of the
et was documented.

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ovulation is inhibited in 14.6%

Brache & Faundes in FIGO Statements

state that "inhibition or delay of ovulation is the principal and possibly only LNG-ECPs mechanism of action"

5 days-after pill

UPA

SPRM

Selective
Progesterone
Receptor
Modulator

Ulipristal Acetate

UPA inhibits
Progesterone Receptors

ellaOne ®

within 120 h.s (5 days) after UPSI

(occurred in the fertile period)

Ellaone® : UPA 30 mg micronised

Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis

Anna F Glasier, Sharon T Cameron, Paul M Fine, Susan J S Logan, William Casale, Jennifer Van Horn, Laszlo Sogor, Diana L Blithe, Bruno Scherrer, Henri Mathe, Amelie Jaspart, Andre Ulmann, Erin Gainer

Summary

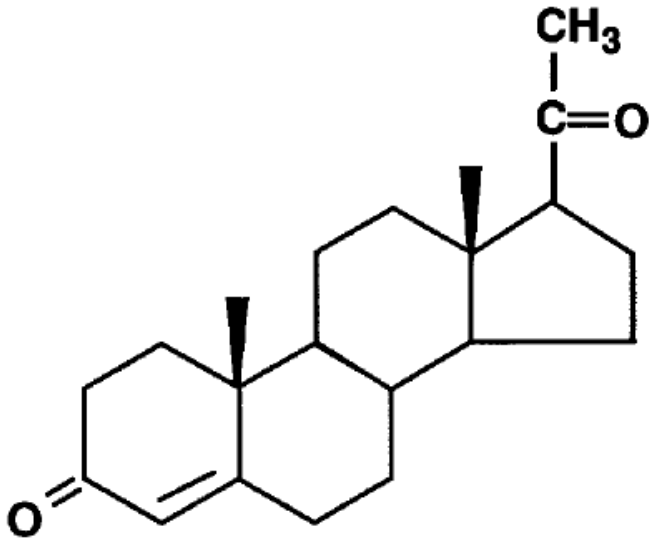
Background Emergency contraception can prevent unintended pregnancies, but current methods are only effective if used as soon as possible after sexual intercourse and before ovulation. We compared the efficacy and safety of ulipristal acetate with levonorgestrel for emergency contraception.

Methods Women with regular menstrual cycles who presented to a participating family planning clinic requesting

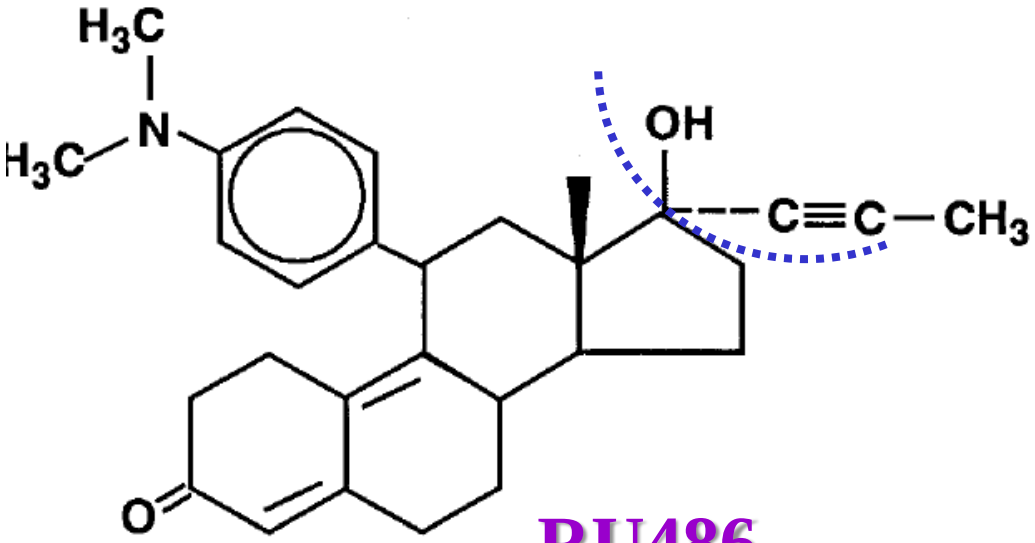
Lancet 2010; 375: 555–62

Published Online January 29, 2010 DOI:10.1016/S0140-6736(10)60101-8

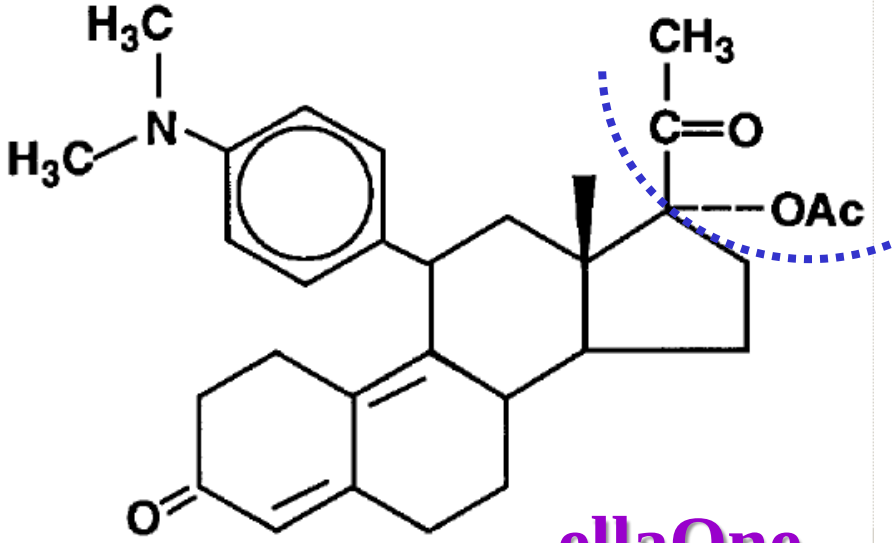
EQUIVALENT to UPA 50 mg unmicronised used in previous studies



Progesterone



RU486

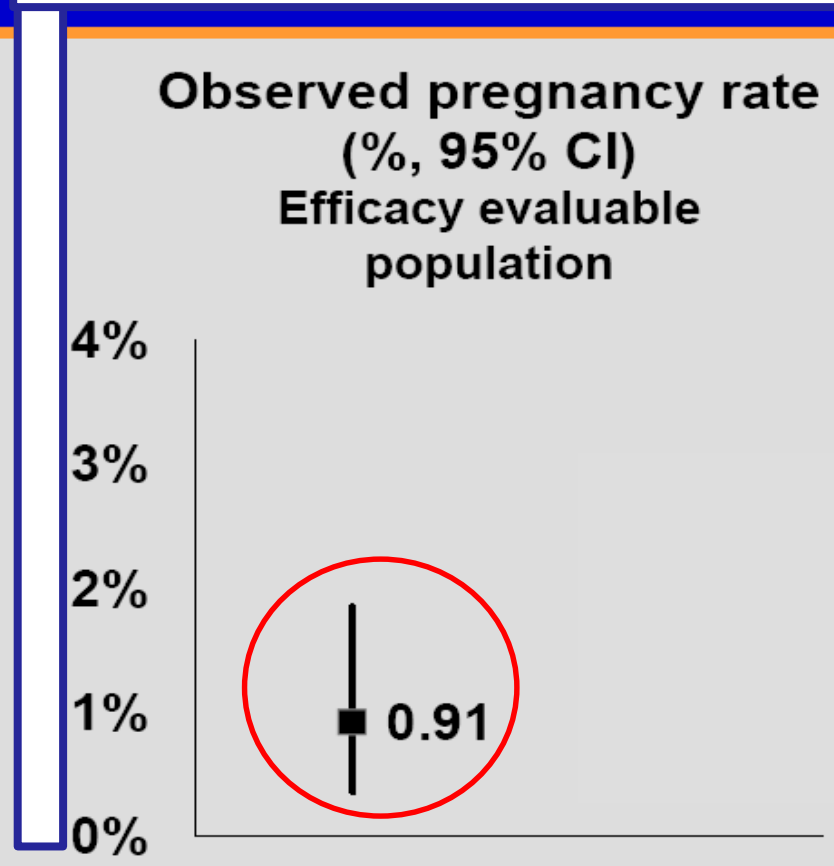


ellaOne

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



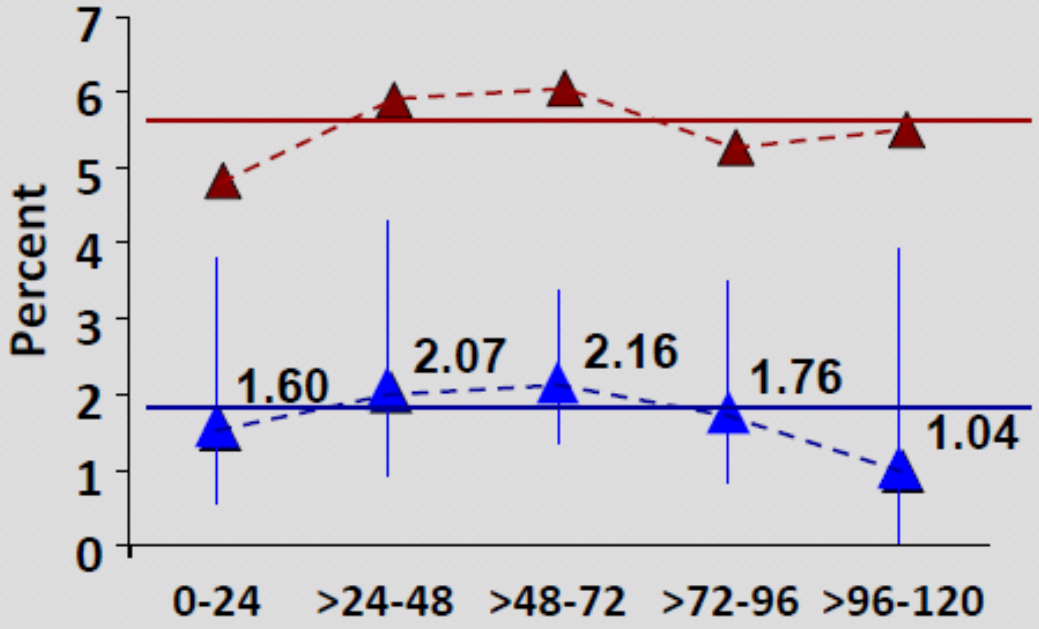
0.9 vs. 5.8

expected

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

Trend in Pregnancy Rates Over Time
mITT Pooled Phase 3 Population
Studies 509, 513—Dose 30 mg

Expected and observed pregnancy rates per 24-hr interval



Expected pregnancy rate 5.62%

Observed pregnancy 1.88%

Time from unprotected intercourse to intake, hrs

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ellaOne

ulipristal acetate

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Product information

30/01/2017 ellaOne -EMEA/H/C/001027 -IA/0044

Name	Language	First published	Last updated
ellaOne: EPAR - Product Information	EN = English GO	13/11/2009	29/06/2017

AUTHORISED
This medicine is approved for use in the European Union

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- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 17-20 November 2014 (21/11/2014)

ANNEX I - Summary of Product Characteristics - 5.1 Pharmacodynamic properties

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator which acts via high-affinity binding to the human progesterone receptor. When used for emergency contraception the mechanism of action is inhibition or delay of ovulation (page 8)



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Product information

30/01/2017 ellaOne -EMEA/H/C/001027 -IA/0044

Name	Language	First published	Last updated
ellaOne: EPAR - Product Information	EN = English GO	13/11/2009	29/06/2017

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ANNEX III - B. PACKAGE LEAFLET - 1. What ellaOne is and what it is used for

How ellaOne works --- ellaOne contains the substance ulipristal acetate which acts by modifying the activity of the natural hormone progesterone which is necessary for ovulation to occur. As a result, ellaOne works by postponing ovulation (page 24)

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human reproduction ORIGINAL ARTICLE *Fertility control*

HRA Study 511

TITLE

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

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

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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

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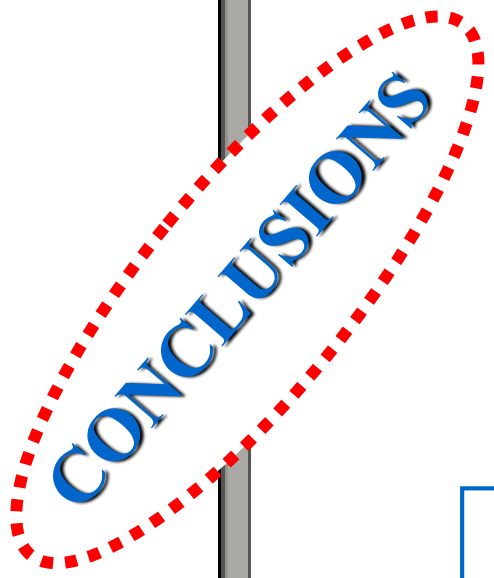
when administered in the advanced pre-ovulatory phase (Croxatto *et al.*, 2001; Gemzell-Danielsson and Marions, 2004; Novikova *et al.*, 2007). In two studies, conducted by the same investigators, using the same design and same conditions of treatment (administration when lead follicle has reached 18 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.

Table I LH status and mean LH levels (U/l) in women at time of treatment with UPA or placebo in a study of the capacity of UPA to block follicular rupture.

	UPA		Placebo	
	n (1st/2nd cycle)	LH (Mean ± SD)	*n* (1st/2nd cycle)	LH (Mean ± SD)
Treatment before LH surge onset	8 (5/3)	4.1 ± 1.8	12 (6/6)	4.8 ± 1.7
Treatment after LH surge onset but before LH peak	14 (7/7)	10.0 ± 2.6	6 (2/4)	11.8 ± 2.3
Treatment after LH peak	12 (5/7)	54.8 ± 21.3	16 (9/7)	47.8 ± 23.5

1

Table II Inhibition of follicular rupture observed 5 days after treatment administration.

Treatment	UPA *n* (%)	
Placebo *n* (%)	No	Yes
No	14 (41.2%)	20 (58.8%)
Yes	0 (0.0%)	0 (0.0%)
McNemar's test		
Statistic (DF)	20.0000 (1)	
P-value	<0.0001	

2

Table III Inhibition of follicular rupture at 5 days after treatment administration, stratified by LH status at time of treatment.

	UPA *n* (%) [95% CI]	Placebo *n* (%) [95% CI]
Treatment before LH surge onset	8/8 (100%)	0/12 (0%)
Treatment after LH surge onset but before LH peak	11/14 (78.6%) [49.2–95.3]	0/6 (0%)
Treatment after LH peak	1/12 (8.3%) [0.2–38.5]	0/16 (0%)

of these cycles, the treatment had been administered on the day of LH peak. Follicular rupture was delayed by 5–10 days or did not occur in the remaining 67.6% (23/34) of cycles.

When treatment was given before the LH peak, the mean time that elapsed from treatment intake to follicle rupture was still significantly longer in UPA cycles (6.85 ± 1.42 days) than in placebo cycles (3.53 ± 0.80 days) ($P = 0.0001$), however, when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54 ± 0.52 versus 1.31 ± 0.48).

Brache

3

Follicular growth and outcome

Table IV shows the final outcome of the follicle at the end of the menstrual cycle. Of the 20 UPA cycles in which follicular rupt[illegible] had not occurred by Day 5, 15 women had a delayed rupture [illegible]) and the mean follicular diameter prior to rupture [illegible] 4.3 ± 2.8 mm) than the one observed in the [illegible] 20.5 ± 2.5 mm) or in the UPA cycles (19.8 ± 2.5 [illegible] ed within 5 days of treatment. Two women had a[illegible] n luteinization occurring prior to delayed ru[illegible] 0 post-UPA (progesterone = 12.8 and 60.7 nmo[illegible] ple pre-rupture), and in three women a luteinized unr[illegible] e was documented. These follicles measured a maximum [illegible], 30.0 and 22.0 mm, but all had decreased to <25 mm diameter by the onset of menses.

RESULTS

Hormones

An immediate drop in LH levels was observed on the day following UPA

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Figure 2

Table IV
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and 1.7 ± 0

Treatment after LH peak	12 (5/7)

Table II **Inhibition of follicular rupture observed 5 days after treatment administration.**

Treatment	UPA *n* (%)	
	No	Yes
Placebo *n* (%)	14 (41.2%)	20 (58.8%)
No	0 (0.0%)	0 (0.0%)
Yes		
McNemar's test		
Statistic (DF)	20.0000 (1)	
P-value	<0.0001	

1

OVERALL RESULTS

2

Table III Inhibition of follicular rupture at 5 days after treatment administration, stratified by LH status at time of treatment.

	UPA *n* (%) [95% CI]		Placebo *n* (%) [95% CI]
Treatment before LH surge onset	8/8 (100%)		0/12 (0%)
Treatment after LH surge onset but before LH peak	11/14 (78.6%)	[49.2–95.3]	0/6 (0%)
Treatment after LH peak	1/12 (8.3%)	[0.2–38.5]	0/16 (0%)

CI, confidence interval

UPA anti-ovulatory effect drops from the 1st to the 3rd-4th fertile day

	n (1st/2nd cycle)	LH (Mean ± SD)	*n* (1st/2nd cycle)	LH (Mean ± SD)
	8 (5/3)	4.1 ± 1.8	12 (6/6)	4.8 ± 1.7
ore LH peak	14 (7/7)	10.0 ± 2.6	6 (2/4)	11.8 ± 2.3
	12 (5/7)	54.8 ± 21.3	16 (9/7)	47.8 ± 23.5

Administered 3-4 days before ovulation UPA delays it 3 days.
We are at the very begininning of the fertile period.

3

occur in the remaining 67.6% (23/34) of cycles.

When treatment was given before the LH peak, the mean time that elapsed from treatment intake to follicle rupture was still significantly longer in UPA cycles (6.85 ± 1.42 days) than in placebo cycles (3.53 ± 0.80 days) ($P = 0.0001$), however, when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54 ± 0.52 versus 1.31 ± 0.48).

Brache

RESULTS

One-two days before ovulation Ulipristal is ineffective.
These are the most fertile days in the cycle and women ovulate.

strual cycle. Of the 20 UPA cycles in which follicular rupture had not occurred by Day 5, 15 women had a delayed rupture (Day 6–10) and

The Fertile Window

David Archer, MD

Probability of conception on specific days near the day of ovulation

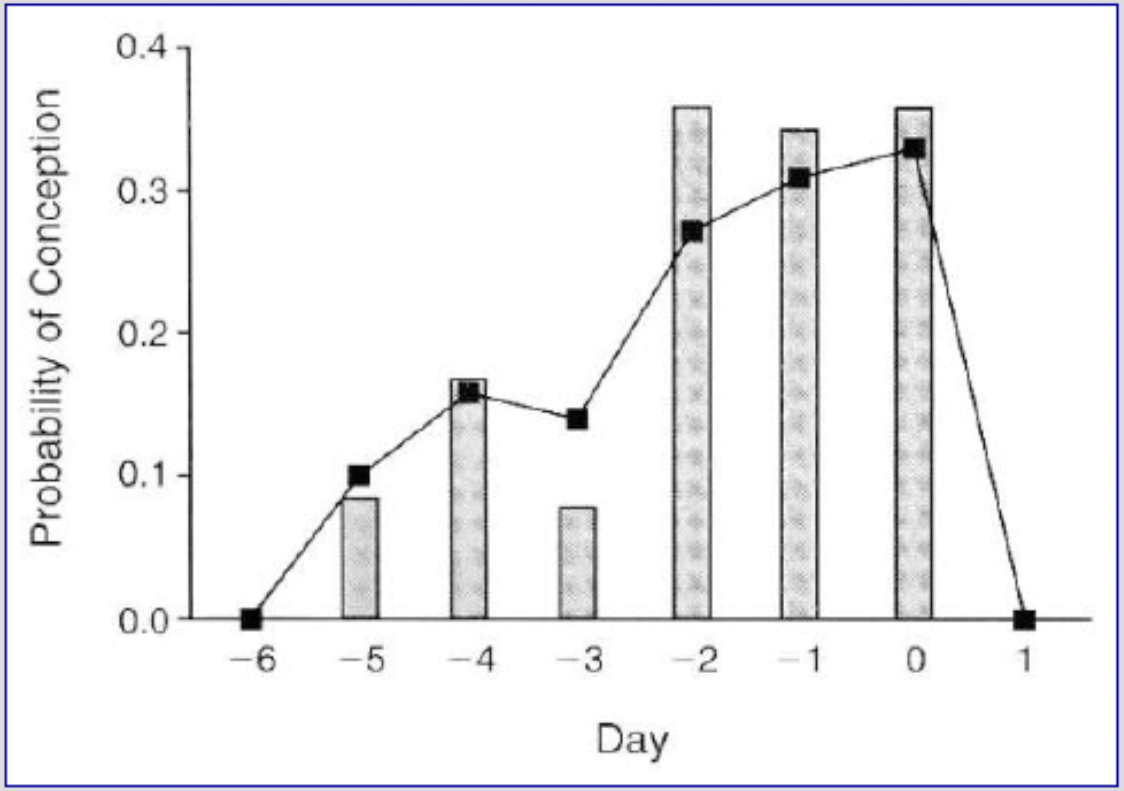


Figure 2 from *Wilcox et al. 1995*

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.

Table III Inhibition of follicular rupture at 5 days after treatment administration, stratified by LH status at time of treatment.

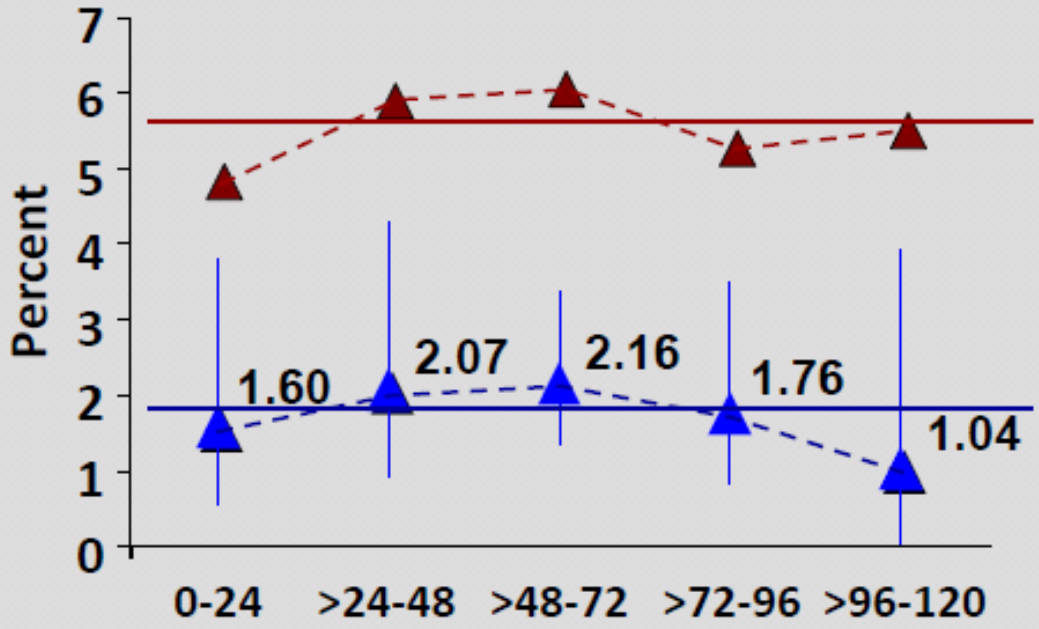
	UPA *n* (%) [95% CI]		Placebo *n* (%) [95% CI]
Treatment before LH surge onset	8/8 (100%)		0/12 (0%)
Treatment after LH surge onset but before LH peak	11/14 (78.6%)	[49.2–95.3]	0/6 (0%)
Treatment after LH peak	1/12 (8.3%)	[0.2–38.5]	0/16 (0%)

CI, confidence interval.

UPA anti-ovulatory effect drops from the 1st to the 3rd-4th fertile day

Trend in Pregnancy Rates Over Time
mITT Pooled Phase 3 Population
Studies 509, 513—Dose 30 mg

Expected and observed pregnancy rates per 24-hr interval



Expected pregnancy rate 5.62%

Observed pregnancy 1.88%

on the contrary, the efficacy is maintained…..

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Ulipristal acetate administration at mid-cycle changes gene expression profiling of endometrial biopsies taken during the receptive period of the human menstrual cycle

Saúl Lira-Albarrán [a, 1], Marta Durand [a, 1], Marco F. Larrea-Schiavon [c], Leticia González [a], David Barrera [a], Claudia Vega [a], Armando Gamboa-Domínguez [b], Claudia Rangel [c], Fernando Larrea [a, *]

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UPA. A menstrual cycle was defined as the time elapsed from the first day of a spontaneous menstrual bleeding until the day preceding the next menses. Follicular phase was considered from the first day of bleeding until the day of appearance of LH in urine and the luteal phase from the day of FR until the day before menses began. Menstrual cycle length was defined as normal when it was in the range of 24–35 days and a luteal phase of at least 12 days of length. All participants were admitted to the outpatient clinic of the Institute during the first 10 days of their menstrual cycle. In the treated cycle, each woman received only one dose of 30 mg of UPA (EllaOne, donated by Laboratorios Elea México, S.A. de C.V.) during the preovulatory phase when the size of the leading follicle was ≥20 mm diameter. This time of the cycle was chosen to assure that treatment was done just previous the follicle ruptures when the probability of pregnancy is high. During both study cycles, each woman was instructed to avoid intercourse otherwise a barrier method was recommended, as well as asked to monitor for urinary

3. Results

3.1. Baseline and hormonal characteristics

The ovarian cycle and hormonal characteristics of volunteers are shown in Table S3. In all cases FR took place with no significant differences between control and UPA treated cycles. With exception of LH at mid-cycle, serum levels of P_4 across the luteal phase were similar between control and treated cycles and within the expected values for a normal ovulatory menstrual cycle.

3.2. Effects of UPA on global gene expression in endometrial samples

in all of the women ovulation took place

	n (1st/2nd cycle)	LH (Mean ± SD)	n (1st/2nd cycle)	LH (Mean ± SD)
	8 (5/3)	4.1 ± 1.8	12 (6/6)	4.8 ± 1.7
re LH peak	14 (7/7)	10.0 ± 2.6	6 (2/4)	11.8 ± 2.3
	12 (5/7)	54.8 ± 21.3	16 (9/7)	47.8 ± 23.5

upture observed 5 days

%)

%)

(1)

rupture at 5 days after

of these cycles, the treatment had been administered on the day of LH peak. Follicular rupture was delayed by 5–10 days or did not occur in the remaining 67.6% (23/34) of cycles.

When treatment was given before the LH peak, the mean time that elapsed from treatment intake to follicle rupture was still significantly longer in UPA cycles (6.85 ± 1.42 days) than in placebo cycles (3.53 ± 0.80 days) ($P = 0.0001$), however, when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54 ± 0.52 versus 1.31 ± 0.48).

Brache

RESULTS

one-two days before ovulation, at LH peak, Ulipristal is ineffective, like a placebo

strual cycle. Of the 20 UPA cycles in which follicular rupture had not occurred by Day 5, 15 women had a delayed rupture (Day 6–10) and the mean follicular diameter prior to rupture was larger (24.3 ±

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Contraception 87 (2013) 300–308

Contraception

Review article

Emergency contraception — mechanisms of action

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Received 8 July 2012; accepted 20 August 2012

Abstract

Concerns regarding the mechanisms of action of emergency contraception (EC) create major barriers to widespread use and could also lead to incorrect use of EC and overestimation of its effectiveness. While the copper intrauterine device (Cu-IUD) is the most effective method available for EC, the hormonal methods are frequently considered to be more convenient and acceptable. Today, the most commonly used method for hormonal EC is levonorgestrel (LNG). More recently, the progesterone receptor modulator ulipristal acetate (UPA) has been shown to be more effective than LNG to prevent an unwanted pregnancy. The main mechanism of action of both LNG and UPA for EC is delaying or inhibiting ovulation. However, UPA appears to have a direct inhibitory effect on follicular rupture which allows it to be effective even when administered shortly before ovulation, a time period when use of LNG is no longer effective.

Gemzell-Danielsson and Lalitkumar

Karolinska Institute

In a series of clinical trials, the effect of UPA at different follicular diameters and temporal relation to the LH peak and ovulation was studied [62,63]. When given prior to the LH rise, UPA inhibited 100% of follicular ruptures. When UPA was administered when the size of the leading follicle was ≥18 mm, follicular rupture failed to occur within 5 to 6 days following treatment in 44% to 59%. Even on the day of the LH peak, UPA could delay ovulation for 24 to 48 h after administration [62]. Taken together, these studies demonstrate that UPA may have a direct inhibitory effect on follicular rupture. This allows

[62] is Brache: UPA behaves exactly as the placebo at LH peak..

ovulation when LH has already started to rise, a time when LNG is no longer effective.

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Emergency contraception

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Lalitkumar and Gemzell-Danielsson

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The effect of mifepristone used for EC is dependent on the dose given and the time of treatment during the menstrual cycle. Mifepristone administered during the follicular phase delays or inhibits ovulation.[23,24] While a single high dose of mifepristone (200 mg) taken on LH + 2 has been shown to prevent endometrial receptivity and embryo implantation[25] low doses such as used for EC have no or minor effect on endometrial receptivity markers[26] and are not effective to prevent pregnancy.[27]

UPA

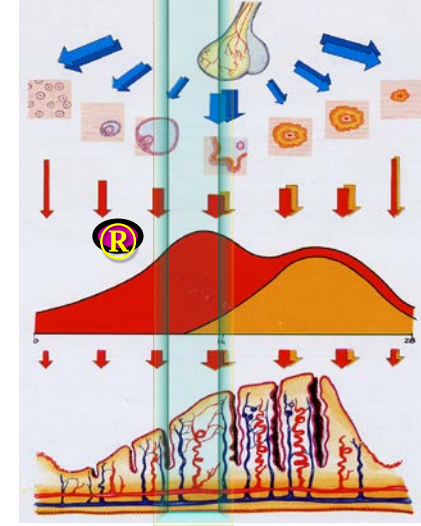
Given prior to the LH rise UPA inhibited 100% of follicular ruptures.[29] When UPA was administered when the size of the leading follicle was ≥18 mm, follicular rupture failed to occur within 5–6 days following treatment in 44–59%. Even on the day of the LH peak, UPA could delay ovulation for 24–48 h after administration.[29] These results indicate that UPA may have a direct inhibitory effect on follicular rupture which allows UPA to be effective even when administered before ovulation when LH has already started to rise, a time when LNG is no longer effective. The effect of UPA on the endometrium has also been demonstrated to be dose-dependent. Treatment with 10–100 mg UPA resulted in inhibition of histological maturation with the highest dose, while the effect of lower doses equivalent to the 30 mg used for EC were similar to that of placebo.[30]

[29] is Brache: UPA behaves exactly as the placebo at LH peak

165 x 240 mm

Human Reproduction vol.15 no.5 pp.1092–1099, 2000

A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women



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[6]To whom correspondence should be addressed

Previous studies in women have shown that the antiprogestin mifepristone delays or inhibits folliculogenesis. The purpose of this study was to explore whether a new analogue, CDB-2914, has similar effects on folliculogenesis, ovulation, or on subsequent luteal phase endometrial mat-

suggesting that these agents compete for the endometrial progesterone receptor to antagonize progesterone action. Surprisingly, mifepristone also has significant effects when circulating progesterone concentrations are low, causing a delay or inhibition of folliculogenesis, steroidogenesis, and ovulation (Liu *et al.*, 1987; Shoupe *et al.*, 1987; Batista *et al.*, 1992b, 1994). These effects in the follicular phase may represent inhibition of oestradiol action by the mifepristone–progesterone receptor complex, independent of progesterone *per se*, as has been demonstrated *in vitro* (McDonnell *et al.*, 1994). Alternatively, mifepristone binding to the progesterone receptor in the absence of progesterone might alter availability of transcription factors available to the oestrogen receptor–ligand complex (Gronemeyer *et al.*, 1992). Although the mechanism of action is not understood, the clinical results (suppression of steroidogenesis and endometrial maturation) have been the rationale for exploring mifepristone efficacy for emergency contraception (Glasier *et al.*, 1992; Bygdeman *et al.*, 1997; WHO, 1999), and for the treatment of endometriosis and fibroids (Kettel *et al.*, 1994; Murphy and Castellano, 1994).

Table III. CDB-2914: effect on menstrual cycle length

Dose	Pre-treatment cycle length[a,b] (days ± SE)	Treatment cycle length[a,c] (days ± SE)	Post-treatment cycle length[b] (days ± SE)	Lengths of abnormal post-treatment cycles (days)
Placebo (n = 12)	30 ± 1.2 (25–37)	29 ± 1.3 (23–37)	28 ± 1.5 (23–42)	23; 42
10 mg (n = 11)	28 ± 1.0 (25–35)	29 ± 1.0 (23–35)	29 ± 1.5 (23–41)	23; 41
50 mg (n = 11)	28 ± 9.5 (25–30)	33 ± 1.5 (26–41)	28 ± 1.6 (17–34)	17
100 mg (n = 10)	28 ± 1.0 (24–35)	33 ± 1.4 (26–40)	28 ± 1.1 (23–34)	23

[a]All pre-treatment and treatment cycles were ovulatory.
[b]No difference in pre-treatment or post-treatment cycle lengths among groups.
[c]$P < 0.01$ for trend for longer treatment cycle by Jonckheere-Terpstra test.

Discussion

At mid-follicular doses of 10–100 mg, CDB-2914 caused a delay in ovulation that was greatest at the highest doses, but inhibited luteal phase endometrial maturation similarly at all doses. Thus, the threshold for altering endometrial morphology was lower than that for altering folliculogenesis, a finding that has not been reported previously after single dose follicular phase administration of an antiprogestin. The mechanism for this effect, noted long after the agent is given, might reflect a direct effect of the antiprogestin to prevent the change from proliferative to secretory endometrium, or may result from altered oestrogen exposure. As progesterone is not thought to be critical to the endometrium prior to ovulation, it is possible that one mechanism by which CDB-2914 might exert such an effect might be or oestrogen receptor β, both of which were recently described as abundant in granulosa cells of developing follicles (Revelli *et al.*, 1996; Enmark *et al.*, 1997). As frequent FSH and LH concentrations were not measured in this study, we cannot distinguish between these possibilities. Other antiprogestins are known to influence LH pulsatility, however, and this may explain the demise of the gonadotrophin-dependent dominant follicle (Permezel *et al.*, 1989). A change in LH pulsatility, amplitude and mean serum LH were not observed on the third day of a mid-follicular dose of mifepristone in a study by Liu (Liu *et al.*, 1987).

The increase in time between the LH surge and follicular collapse, and the unusual observation of two LH surges also must be integrated into a model of CDB-2914 action. In the latter

[a]All pre-treatment and treatment cycles were ovulatory.

[b]...fference in pre-tre... ...cle lengt...
...0.01 for trend for l... ...nckheere...

cycle-day seven, before the fertile period

the controls ovulate six days later

Discussion

At mid-follicular doses of 10–100 mg, CDB-2914 caused a delay in ovulation that was greatest at the highest doses, but inhibited luteal phase endometrial maturation similarly at all doses. Thus, the threshold for altering endometrial morphology was lower than that for altering folliculogenesis, a finding that has not been reported previously after single dose follicular phase administration of an antiprogestin. The mechanism for this effect, noted long after the agent is given, might reflect a direct effect of the antiprogestin to prevent the change from proliferative to secretory endometrium, or may result from altered oestrogen exposure. As progesterone is not thought to be critical to the endometrium prior to ovulation, it is possible that one mechanism by which CDB-2914 might exert such an effect might be through inhibition of oestrogen action. *In vitro*, the antiproges...

Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914

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[a] Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; [b] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, George Washington University Medical Center, Washington, D.C., and [c] Laboratory of Surgical Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Objective: To test potential contraceptive mechanisms of the selective P receptor modulator CDB-2914 in the early luteal phase.
Design: Prospective randomized clinical trial.
Setting: Clinical research center.
Patient(s): Fifty-six women with regular cycles.
Intervention(s): Women received a single dose of CDB-2914 (10, 50, or 100 mg) or placebo given after ovulation and within 2 days of the LH surge. Four to 6 days later, a transvaginal ultrasound scan measured endometrial thickness, and an endometrial biopsy specimen was obtained.
Main Outcome Measure(s): The endometrium was evaluated by thickness and by immunohistochemical analysis for P-dependent markers; safety laboratory tests were performed, and E_2 and P levels were obtained.
Result(s): CDB-2914 caused a significant dose-dependent decrease in endometrial thickness, an increase in glandular P receptors, and a decrease in peripheral node addressins. Estradiol and P levels and menstrual cycle timing were not altered. No adverse effects were observed.
Conclusion(s): The alteration in endometrial thickness and P-dependent markers of implantation in the absence of changes in hormone levels and cycle length suggests that CDB-2914 may have contraceptive properties. (Fertil Steril® 2010;93:2035–41. ©2010 by American Society for Reproductive Medicine.)

Key Words: CDB-2914, endometrium, luteal phase, single dose, selective progesterone receptor modulators

TABLE 1

Effect of CDB-2914 administration compared with placebo on outcome measures.

	Placebo (mean ± SD)	CDB-2914 (10 mg, 50 mg, 100 mg) (mean ± SD)	*P* value
Cycle length			
Baseline cycle length (d)	28.3 ± 2.2	27.8 ± 2.8	.52
Treatment cycle length (d)	28.2 ± 2.0	27.1 ± 3.2	.23
Luteal phase length during treatment (d)	12.5 ± 2.5	13.3 ± 2.4	.32
Posttreatment cycle length (d)	29.6 ± 3.5	28.2 ± 3.9	.23
Midluteal phase (treatment cycle)			
P (ng/mL)	12.5 ± 5.6	16.1 ± 8.5	.13
E_2 (pg/mL)	136.1 ± 67.6	165.3 ± 64.8	.15
Ultrasound endometrial thickness (treatment cycle)			
Baseline (mm)	10.2 ± 3.2	10.3 ± 2.3	.93
At biopsy (mm)	11.5 ± 4.1	9.7 ± 1.8	.03
Change in thickness (mm)	1.3 ± 2.3	−0.6 ± 2.2	.007

Stratton. Endometrial effects of luteal CDB-2914. Fertil Steril 2010.

a treatment cycle of 37 days; all other treatment cycles were normal length. All posttreatment cycle lengths were normal, except for two at 100 mg (20 and 21 days) and one receiving placebo (38 days). For these subjects, the subsequent cycle was of a normal length.

All 52 women who used the kit detected the LH surge in the posttreatment cycle. Of the other four, one was pregnant (10 mg) and the other three had received placebo. Of the latter three, basal body temperature was biphasic in the one woman who provided information. Eight of 56 women had inadequate information to judge corpus luteum function: four did not have a P measurement (three receiving placebo and one

tecture consistent with endometrial hyperplasia. Results of a follow-up luteal phase biopsy performed 2 months after treatment noted only stromal glandular dyssynchrony.

Baseline treatment cycle endometrial thickness was similar between groups (Table 1). The endometrial thickness on the day of biopsy ranged as follows: placebo: 5.8 to 18.7 mm; 10 mg: 8.4 to 12.6 mm; 50 mg: 6.1 to 11.7 mm; and 100 mg: 5.9 to 12.6 mm. There was a significant reduction in endometrial thickness among those subjects receiving CDB-2914 (10, 50, or 100 mg) compared with those receiving placebo (Table 1).

± 3.2	10.3 ± 2.3	.93
± 4.1	9.7 ± 1.8	.03
± 2.3	−0.6 ± 2.2	.007

ellaOne taken after ovulation
endometrial US 4 - 6 days later

tecture consistent with endometrial hyperplasia. Results of a follow-up luteal phase biopsy performed 2 months after treatment noted only stromal glandular dyssynchrony.

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5 had sufficient
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100 mg: 4)
ay of >2 days;
on the day of
14 (50 or 100
ed endometrial
dds ratio: 2.2;
. Additionally,
e of increasing
ating doses of

(Fisher's exact test; $P=.02$) with those receiving higher CDB-2914 doses demonstrating greater staining as evidenced by immunohistochemical analysis (Jonckheere-Terpstra test; $P=.01$). For example, 8 of 15 specimens (53%) in the placebo group had little to no glandular PR staining (≤ 2), DB-2914 demon ferenc noted between the groups for stromal PR or ER in either the glands or stroma (data not shown). MECA-79 staining was similar in the placebo (median: 3.8) and 10-mg (median: 3.5) groups but was significantly reduced in the 50-mg (median: 2.1) and 100-mg groups (1.5) ($P<.001$) with a notable linear decline in the staining with increasing CDB-2914 dosage (point estimate: −0.019; 95% confidence interval: −0.023, −0.015; $P<.001$) (Fig. 1).

Ulipristal taken after ovulation decreases markers of uterine receptivity

peripheral node addressins

Ovarian Cysts

early luteal phase

CDB-2914 inhibited P-dependent markers of luteal phase differentiation. Both CDB-2914 and early luteal phase doses of 200 mg of mifepristone prevent the expected luteal phase decrease in glandular PR staining (1, 2, 4). CDB-2914 also was associated with decreased expression of peripheral node addressins, which are important L-selectin ligands found on the surface of endothelial cells. Recent studies have shown that L-selectin ligands are up-regulated during the implantation window, making the uterus more receptive to the trophoblast (17, 18).

3,2 x 273,0 mm

❖ UPA: prevents nidation

noted above, all posttreatment laboratory values were normal.

ellaOne taken after ovulation

DISCUSSION

A single postovulatory dose of up to 100 mg of the antiprogestin CDB-2914 significantly increased glandular PRs and decreased endometrial thickness. Treatment did not alter corpus luteal function, as assessed by a single midluteal E_2 and P measurement and the length of the luteal phase or menstrual cycle. CDB-2914 appeared to inhibit endometrial development while sparing menstrual rhythm. The current study was the first dose-ranging study to document significant endometrial effects with low doses of CDB-2914 given in the early luteal phase. Similar endometrial effects have been observed among those receiving mifepristone (200 mg) (1, 3, 4); however, these endometrial effects were present at lower doses (10 mg) (15). Whether there is a difference in potency between

200 mg mifepristone is the dose for pregnancy termination

early luteal phase (post-ovulatory)

with a single dose given in either early luteal or midluteal phase. Whether this is a direct endometrial effect or a result of an ovarian effect is not known. Taken together, these endometrial effects in the absence of ovarian and menstrual cycle effects suggest mechanisms by which CDB-2914 might be effective as an emergency contraceptive (28).

Acknowledgments: The authors thank Dr. Negin Hajizadeh M.D., for her assistance in data management and Dorett Sutherland, R.N., for her assistance with scheduling and patient care.

203,2 x 273,0 mm

- **UPA: prevents nidation**

Human Reproduction Vol.18, No.9 pp.1820–1827, 2003 DOI: 10.1093/humrep/deg342

Luteal phase dose–response relationships of the antiprogestin CDB-2914 in normally cycling women*

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BACKGROUND: Progesterone receptor modulators have potential therapeutic use in progesterone-dependent conditions such as endometriosis, fibroids and induction of labour. The synthetic steroid CDB-2914 binds to the progesterone and glucocorticoid receptors. In animals it has antiprogestational activity at doses 50-fold less than those required for antiglucocorticoid effects. METHODS AND RESULTS: We evaluated the biological activity, blood levels and safety of CDB-2914 at escalating single doses, in 36 normally cycling women at mid-luteal phase. CDB-2914 at doses of 1–100 mg did not change luteal phase length, but after 200 mg, all women had early endometrial bleeding. Four women with early menses had concurrent functional luteolysis (one at 10, 50, 100 and 200 mg). There were no biochemical or clinical signs of toxicity, and no effect on urinary cortisol or circulating thyroxine, prolactin, adrenocorticotrophic hormone or renin levels. Higher serum equivalents of CDB-2914 were observed by radioimmunoassay than by high performance liquid chromatography detection, indicating a considerable contribution of metabolites. CONCLUSIONS: Mid-luteal administration of CDB-2914 antagonizes progesterone action on the endometrium, in a dose-dependent fashion, without apparent antiglucocorticoid effects. Further

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mid-luteal phase (implantation window)

Table II. Effects of CDB-2914 on bleeding pattern and luteal phase length

Dose	Women with early bleeding (no./total)	Length of luteal phase (days)	Cycle length (days)
Placebo	0/5	13.4 ± 0.5	27.2 ± 1.5
1 mg	1/6	13.7 ± 1.0	27.0 ± 1.1
10 mg	2/6	13.5 ± 1.1	29.2 ± 0.9
50 mg	3/6	11.8 ± 1.2	27.3 ± 2.0
100 mg	2/7	13.1 ± 1.2	27.6 ± 0.8
200 mg	6/6	9.7 ± 0.3*	23.8 ± 1.5**

EllaOne

*

*$P < 0.02$ 200 mg compared with placebo, 1 mg, 10 mg, 100 mg groups; $P = 0.13$ versus 50 mg.

**$P < 0.04$ compared with 10 mg and 100 mg groups.

oral dose of 200 mg. Early endometrial sloughing occurred in most women despite luteal phase progesterone levels, indicating a direct action on the endometrium, rather than an indirect action on the ovary to reduce steroid production. However, concurrent functional luteolysis was observed in a few women who had early bleeding.

The endometrial effects of CDB-2914 are similar to those of mifepristone, which induces uterine bleeding within 72 h of mid-luteal administration by acting directly on the endometrium to inhibit progesterone activity (Schaison *et al.*, 1985; Shoupe *et al.*, 1987; Garzo *et al.*, 1988; Nieman and Loriaux, 1988). The data from this study suggest that CDB-2914 and mifepristone are roughly equivalent in this regard. At 200 mg (~3–4 mg/kg), CDB-2914 consistently caused early endometrial bleeding. By contrast, the minimal luteal phase dose of

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Ulipristal acetate administration at mid-cycle changes gene expression profiling of endometrial biopsies taken during the receptive period of the human menstrual cycle

Saúl Lira-Albarrán [a, 1], Marta Durand [a, 1], Marco F. Larrea-Schiavon [c], Leticia González [a], David Barrera [a], Claudia Vega [a], Armando Gamboa-Domínguez [b], Claudia Rangel [c], Fernando Larrea [a, *]

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given at the time of LH peak (Brache et al., 2010). These observations, together with those published on the effects of UPA on endometrial progesterone-dependent markers (Stratton et al., 2000, 2010), indicate that part of its contraceptive effects, particularly in those women remaining ovulatory after treatment, might involve the endometrium. This statement contrasts to that of international scientific societies ensuring that the main contraceptive action of UPA is ovulation impairment without affecting implantation (Rosato et al., 2015). In view of this controversy and on the relative lack of information of the effects of UPA on endometrium, especially under *in vivo* conditions, herein we investigated the effects of a single administration of 30 mg of UPA to women just before FR, when follicular diameter reached ≥20 mm, on the global gene expression profile in endometrial biopsies taken during the window of implantation, seven days after the LH peak (LH+7). Serum pituitary and ovarian hormones were measured and immunohistochemistry (IHQ) studies of key endometrial markers involved in receptivity and implantation were also performed. All results were compared to those of untreated control cycles.

3. Results

3.1. Baseline and hormonal characteristics

The ovarian cycle and hormonal characteristics of volunteers are shown in Table S3. In all cases FR took place with no significant differences between control and UPA treated cycles. With exception of LH at mid-cycle, serum levels of P_4 across the luteal phase were similar between control and treated cycles and within the expected values for a normal ovulatory menstrual cycle.

3.2. Effects of UPA on global gene expression in endometrial samples

3.2.1. Differentially expressed genes

In order to determine the effects of UPA treatment on global gene expression patterns in endometrium, twenty-six GeneChip®

3.2.2.3. Activation state of canonical pathways and bio-functions by ingenuity pathway analysis (IPA). Ingenuity pathway analysis of the list of differentially expressed genes in UPA treated cycles *versus* control cycles showed that canonical pathways, such as acute phase response, STAT3, integrin, IL-6 and VEGF signaling pathways were among the top down-regulated (Table 3). These results agreed with those identified by different approaches, such as FatiGO and GSEA since, the majority of these canonical pathways were associated with biological processes involved in inflammatory responses.

In terms of bio-functions: cell survival, movement and cell invasion and those related with chemotaxis, adhesion, formation of gland were among those with a major negative activation z-score and predicted as decreased (Table 4).

inactivated functions that are essential for embryo-implantation

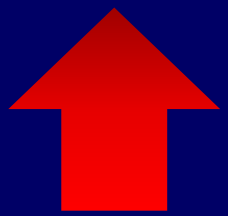
3.2.2.4. Molecule activity prediction of bio-functions associated with endometrial receptivity by IPA. Since the functional analysis by REVIGO and GSEA identified regulation of inflammatory response as the most associated biological process, we performed an *in silico* analysis of MAP by querying the Ingenuity® Knowledge Base using the list of differentially expressed genes. Fig. 4 shows some of the bio-functions associated to regulation of inflammatory response. As depicted, chemotaxis of granulocytes, T lymphocytes, neutrophils, dendritic cells, macrophages, and monocytes was predicted as inhibited. This analysis agreed with the activation state of bio-functions shown in Table 4. Acute phase response signaling, Il-6 signaling and STAT3 canonical pathways were also identified within the regulation of inflammatory response (Fig. 4).

Similarly, since female pregnancy and embryo implantation were biological processes identified significantly associated in endometrium from treated cycles, we querying by IPA the activation state of the bio-function implantation. Fig. S2 shows the results of this analysis. As depicted, and based on the negative gene expression of *LIF*, *STAT3* and *IL6ST*, the bio-functions: embryo and blastocyst implantation were also predicted as inhibited.

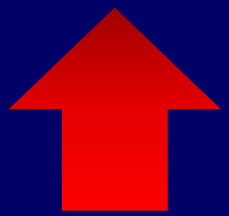
In order to identify genes affected by UPA and involved in implantation, our endometrial differentially expressed gene list of genes from UPA treated *versus* control cycles was compared with two different arrays; one called endometrial receptivity array (ERA), a customized developed array to identify the receptivity status of endometrial samples (Diaz-Gimeno et al., 2011) and with that recently published in women receiving the P_4 receptor antagonist mifepristone (Cuevas et al., 2016). The overlap and differences in gene expression profiles among these microarrays are shown in Fig. 5. In this analysis, comparison showed, in the case of ERA, that 115 genes from a total of 238 genes were in common (Fig. 5A) and 34 for mifepristone from a total of 200 differentially expressed genes (Fig. 5B).

As shown in Table S9, gene expression with UPA, compared with ERA, resulted in opposite directionality in all cases. Of particular importance was the case of *PAEP*, a P_4 responsive gene and the second most up-regulated gene in ERA (FC = 31.43), represented in this study the most down-regulated gene (FC = −91.14) with the highest statistical significance (B = 22). In the case of mifepristone,

antagonists (Batista et al., 1992). Ulipristal like mifepristone is considered a PR modulator; however, its effects on endometrium are poorly understood. In this study, and despite the observed normal increase of serum P_4 levels in the luteal phase, UPA showed an antiprogestin-like activity at the level of the endometrium. This observation was based on the analysis of the gene expression profile of endometrial biopsies taken on day LH+7 from ovulatory UPA treated cycles when contrasted to that obtained in biopsies from control untreated cycles. An important finding in this study to endorse the antiprogestational nature of UPA on endometrium was the fact that *PAEP* expression, a P_4-dependent regulated gene and a key gene in the trophoblast to endometrium attachment process (Uchida et al., 2007), was the most down-regulated in the UPA



discussion



endometrium as a site of action of UPA.

Endometrial decidualization of stromal cells is essential for the establishment of pregnancy. It depends on P_4 and consists in the differentiation of the endometrium into decidua tissue (Gellersen et al., 2007). In this study, lipid modification was identified as a biological process modified by UPA and particularly, the bio-function fatty acid metabolism, was predicted as decreased. This bio-function is critical for embryo implantation as it provides the energy source for decidualization of endometrium (Tsai et al., 2014), suggesting that UPA might negatively affect this critical process. Further support to this observation was derived, in this study, from the low gene expression levels by qPCR of the transcription factor called heart and neural crest derivatives expressed transcript 2 (*HAND2*) that has been shown to play an important role in decidualization (Huyen and Bany, 2011) and for the increased expression of the PR gene. These observations were consistent with the low gene expression levels by microarray or qPCR of prolactin (*PRL*) and interleukin-15 (*IL-15*), two well-known markers of

the low gene expression levels by microarray or qPCR of prolactin (*PRL*) and interleukin-15 (*IL-15*), two well-known markers of decidualization (Daly et al., 1983; Godbole and Modi, 2010).

A number of cytokines and downstream factors are known to be involved in receptivity and embryo implantation. Such is the case of LIF and STAT3 a major effector of LIF signaling. Alterations in this pathway have been associated with repeated implantation failure in humans (Choi et al., 2016). Interestingly, in this study, *LIF*, *STAT3* and *IL6ST* were three genes significantly down-regulated by UPA. In addition, an *in silico* analysis of the bio-functions associated with endometrial receptivity showed that acute phase response

UPA altered pathways essential for embryo-implantation

ELSEVIER

Contraception

Contraception 95 (2017) 586–591

Original research article

Study of the effect of ulipristal acetate on human sperm ability to interact with tubal tissue and cumulus-oocyte-complexes☆,☆☆

Carlos Zumoffen[a,1], Matías D. Gómez-Elías[b,1], Adriana M. Caille[a], Luis Bahamondes[c], Patricia S. Cuasnicú[b], Débora J. Cohen[b], María José Munuce[a,*]

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Received 16 December 2016; revised 15 February 2017; accepted 19 February 2017

Abstract

Objective: Ulispristal acetate (UPA) is a selective progesterone receptor modulator widely used for emergency contraception (EC). The described main mechanism of action is by inhibiting or delaying ovulation; however, the postovulatory effects of the drug are still on debate. Therefore, the aim of this study was to determine whether UPA could interfere with human sperm fertilizing ability.
Study design: Human motile spermatozoa were incubated under capacitating conditions with or without UPA, and then used to inseminate human tubal explants, mouse cumulus-oocyte complexes and zona-free hamster eggs. The ability of UPA to interact with human sperm progesterone (P)-binding sites was investigated by incubating the cells with fluorescent-labeled P and analyzing them by fluorescence microscopy.
Results: UPA did not affect the ability of human sperm to bind to human tubal tissue explants surface or to penetrate the mouse cumulus mass and the zona-free hamster eggs. In addition, concentrations of UPA much higher than those present in the plasma of EC pill users were required to bind to human sperm P-binding sites.
Conclusions: Our study supports a lack of an agonist or antagonist action of UPA on different functional parameters associated with the fertilizing ability of human sperm.
Implications: This study provides new functional evidence supporting that the contraceptive action of UPA is not related to effects on human sperm cells, contributing to a better understanding of the mechanism of action of UPA as EC.
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changes on gene transcription still awaits further investigation.

The findings of the present study suggest that changes observed in gene expression in endometrial samples from women exposed to UPA are associated with a non-receptive endometrial phenotype. Based on these findings, our study provides with molecular and functional evidence the bases to support the endometrium as a target for the UPA contraceptive effects that may be of help to define the mechanisms of action of drugs used either as emergency contraceptives or for other therapeutically purposes. In addition,

Lira-Albarràn conclusion

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Emergency Contraception*

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Abstract

There have been numerous attempts to control fertility after unprotected sexual intercourse (UPSI). From very bizarre methods like the vaginal application of Coca Cola to the more serious attempts using calcium antagonists influencing fertility parameters in sperm to hormonal methods or intrauterine devices. So far, hormonal methods preventing or delaying ovulation have proved to be the most popular starting with the combination of ethinyl estradiol and levonorgestrel (LNG), known as the **Yuzpe regimen**. The first dose had to be taken within 72 hours of UPSI, a second one 12 hours later. Later on, **LNG alone**, at first in a regimen similar to the Yuzpe method (2 × 0.75 mg 12 hours apart) showed to be more successful, eventually resulting in the development of a 1.5 mg LNG pill that combined good efficacy with a high ease of use. Several efficacious and easy to use methods for emergency contraception (EC) are available on the market today with the most widely spread being LNG in a single dose of 1.5 mg

Keywords

emergency contraception, ulipristal acetate, levonorgestrel, mifepristone, "morning after pill", postcoital contraception

History

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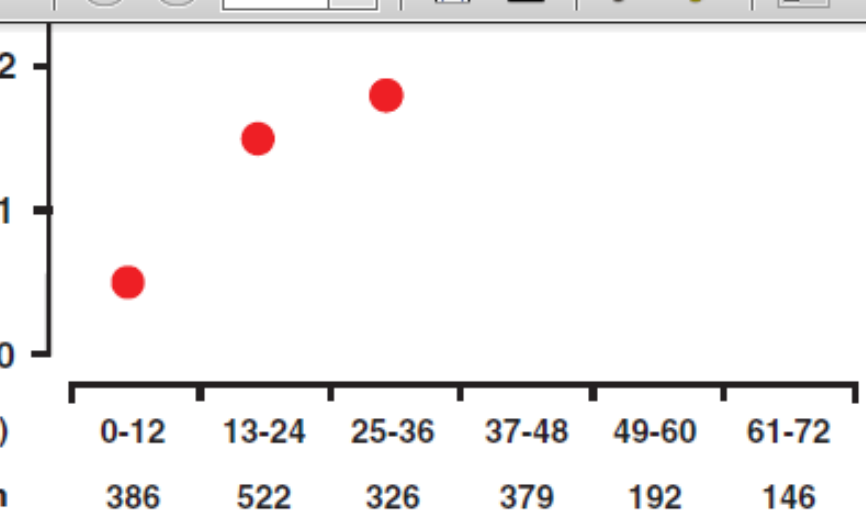

gnancy rate by time after unprotected intercourse in women
pe method and levonorgestrel as emergency contraception

UPA 50 mg unmicronized IMPAIRS endometrium

for EC in China. The effect of mifepristone is well depending on time of treatment during the menstrual dose given. A variety of regimens with a single dose

UPA 30 mg micronized DOES NOT

10 mg mifepristone has little or no effect on the n [22].

A Progesterone Receptor Modulator

metabolised by the cytochrome P450 (CYP3A4).

page 5

Mechanism of action

Inhibition of ovulation

UPA is a synthetic progesterone receptor modulator with oral effect which relies on a high binding affinity at the human progesterone receptor. The main mechanism consists of blocking or delaying ovulation. Clinical trials have shown that UPA depending on its dose (10–100 mg), delays the growth of the leading follicle (Graafian follicle) in the mid of the follicular phase. As a result, this leads to a delay in ovulation which was most significant in the highest doses used (50 and 100 mg micronized). This allows UPA to be effective even when administered immediately before ovulation when LH has already started to rise, a time when use of LNG or Yuzpe is too late for ovulation inhibition. In a study comparing early luteal phase treatment with placebo, 10, 50 or 100 mg unmicronized UPA a significant delay in endometrial maturation was seen in the 50 and 100 mg groups compared to the placebo and the 10 mg group upon biopsy four to six days after ovulation [36]. Treatment with UPA resulted in a significant dose-dependent decrease in endometrial thickness as well as an increase in glandular P receptors. Yet, in the doses relevant for EC use (30 mg) UPA has no significant effect on the endometrium.

Comparison the mode of action of LNG with UPA in clinical studies

Three studies investigated the mechanism of action of levonogestrel and UPA for EC:

taken 12 hours apart. Follow-up was
s after the expected onset of the next
diaries were used from the time of EC use
cord adverse effects and sexual activity.
ve efficacy was evaluable in 775 of UPA
users. Pregnancies occurred in 7 (0.9%,
%, 0.8–2.6%) women, respectively. Based
day of UPSI, 85% and 69% of anticipated
y, were averted.
at le
and
ted t
–120
r old
s afte
treated with a single dose of 30 mg UPA.
determined by high-sensitivity urinary
otropin testing and return of menses.
1241 women were evaluated for efficacy.
ant at follow-up, for a pregnancy rate of
interval 1.4–3.1%). These results satisfy
atistical criteria for success because the
ower than both the estimated expected
edefined clinical irrelevance threshold. In
not decrease over time: pregnancy rates
2.1% (1.0–4.1%), and 1.3% (0.1–4.8%) for

UPA 50 mg unmicronized
And UPA 30 mg micronized
ARE EQUIVALENT

Analysis of the complete study data

Even if the complete data set of [14,37] shows only a trend in favour for UPA versus LNG, the pooled data analysis (called metaanalysis) [14] pooled with [37] shows a significant odds ratio (UPA/LNG) in favour of UPA compared to LNG (Table 4).

Contraceptive efficacy by time after UPSI (Table 4):

LNG: Slight increase up to 2.80% during 49–72 hours in [37], whereas no change over up to 5 days in [14], with low number of
73–96 and 97–120 hours.
pregnancy within 0–24 hours, 2.2%
thin 49–72 hours. No data above 72
g after 72 hours, showed a decline in
9–72 hours), over 2.1% (73–96 hours)
h decreasing number of subjects; no
tatistical relevance.

In [14] trial. there are no real difference within the first 72 hours, but no pregnancy occurred thereafter. After 72 hours the groups are small and there might be a selection bias for recruitment of subjects after 72 hours.

Due to the fact, that the metaanalysis of Glasier is in reality a combined data analysis of two different studies (even if 50 mg UPA equals 30 mg micronized UPA) (different selection criteria of subjects - see table) the final results must be interpreted with caution.

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Analysis of subsets of data (Table 4)

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ISGE STATEMENT ON EMERGENCY CONTRACEPTION

Mechanisms of action of oral emergency contraception

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Abstract

This review gives an overview of the mechanisms of action of oral emergency contraception pills (ECPs), focusing on the levonorgestrel (LNG) and ulipristal acetate (UPA) containing ECPs. *In vivo* and *in vitro* studies have addressed the effect of EC on various possible targets. Based on these studies as well as on clinical trials it is clear that the efficacy of ECPs to prevent an unintended pregnancy depends on their mechanism of action as well as on their use in relation to the fertile window. While the main effect of both available ECPs is to prevent or delay ovulation the window of action for UPA is wider than that of LNG. This provides the biological explanation for the difference observed in clinical trials and the higher efficacy of UPA. Neither LNG nor UPA impairs endometrial receptivity or embryo implantation. Correct knowledge on the mechanism of action of ECPs is important to avoid overestimating their effectiveness and to advise women on correct use.

Keywords

Emergency contraception pills, endometrium, follicular development, implantation, levonorgestrel, ovulation, ulipristal acetate

History

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endometrial receptivity [27]. UPA given in early-luteal phase shows dose-dependent effects with no significant endometrial effects observed follwoing exposure to doses relevant for EC [28].

To be able to study the effect of EC on human implantation, an *in vitro* three-dimensional implantation model has been developed. In this model it has been demonstrated that LNG or UPA at EC concentrations have no effect on the human embryos or endometrial receptivity and cannot impair or prevent implantation [29]. Furthermore, LNG has shown to have no effects on pregnancy or the newborn [26,30,31]. The same is true for the more limited observational data available for UPA exposure during pregnancy (Data on file HRA-Pharma).

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Advanced Access publication on March 3, 2015 doi:10.1093/humrep/dev030

human reproduction

ORIGINAL ARTICLE *Fertility control*

Effects of ulipristal acetate on human embryo attachment and endometrial cell gene expression in an *in vitro* co-culture system

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Submitted on October 3, 2014; resubmitted on November 20, 2014; accepted on January 29, 2015

STUDY QUESTION: Does ulipristal acetate (UPA) used for emergency contraception (EC) interfere with the human embryo implantation process?

SUMMARY ANSWER: UPA, at the dosage used for EC, does not affect human embryo implantation process, *in vitro*.

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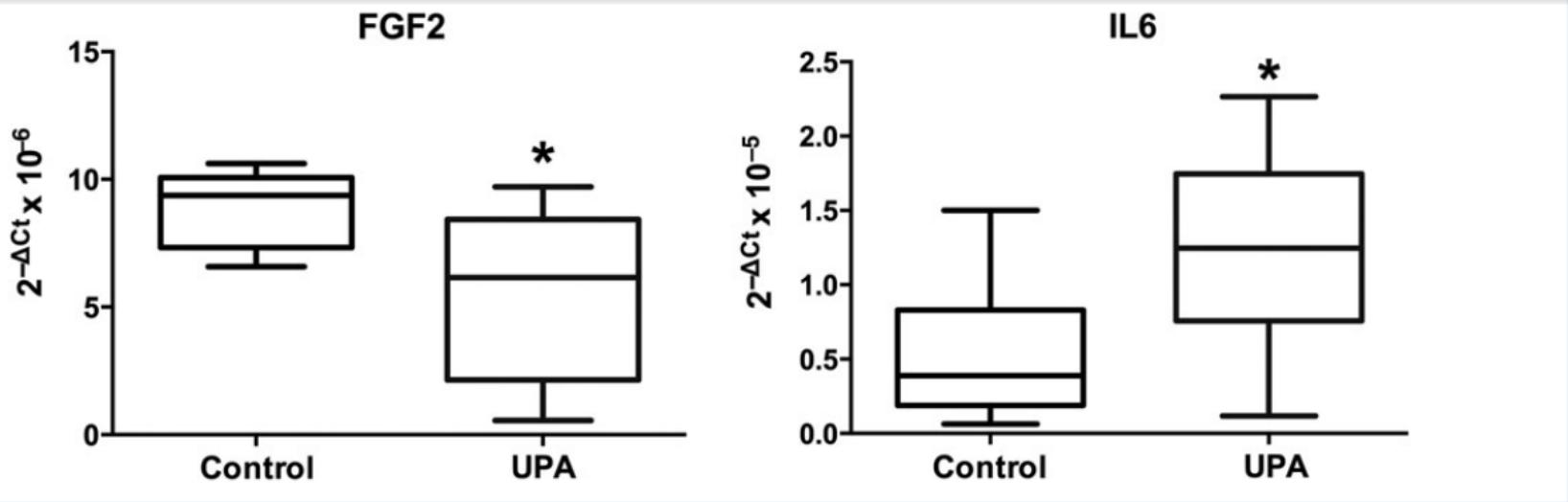

Figure 4 Six out of eleven genes suggested to be involved in endometrial receptivity in the endometrial construct, namely HAND2, OPN, HBEGF, CALCR, FGF2 and IL6 showed significant difference in their expression levels as analysed by real-time PCR on exposure with ulipristal acetate (UPA). The boxes indicate 25–75 percentile and the whiskers spread from the smallest to largest data points.

(Lalitkumar *et al.*, 2007; Meng *et al.*, 2009). Although this culture system is complex, it is now well established and has proven to be robust and reproducible. This model has also been tested and validated for the studies on human embryo attachment using LNG, mifepristone and LIF inhibitor (Lalitkumar *et al.*, 2007, 2013b; Meng *et al.*, 2009).

In this *in vitro* study, we have used a dose of UPA, equivalent to the conventional dose of UPA when used for EC. UPA at a dose of 30 mg orally has a maximum mean serum concentration (C_{max}) of 176 ± 89 ng/ml, which is observed approximately after one hour of administration (Kim and Bridgeman, 2011). However, in our study, the treatment group of cultures were continuously exposed to UPA 200 ng/ml, which is slightly higher than the observed serum concentration as it is known that the endometrial concentration of steroids is higher than the serum levels. Despite using a pharmacological dose, we do not see any significant difference in the attachment of embryos following treatment with UPA compared with controls. Also, there were no observable degenerative changes in the embryos. This further substantiates that UPA at this dose, does not compromise embryo viability nor compromise its ability to attach.

Both, *in vivo* and *in vitro* studies have shown that UPA which is a sPRM binds to progesterone receptor (Attardi *et al.* 2002, 2004). This further impacts the signal transduction mediated by PR and affects endometrial receptivity according to its binding region in the hormone response element. Not all sPRMs act in the same manner on endometrial

200 ng/ml is quite equivalent to 176 ± 89 ng/ml

UPA in tissues is higher

g/ at UniversitÃ degli Studi di Padova on April 25, 2015

STUDY QUESTION: Does ulipristal acetate (UPA) used for emergency contraception (EC) interfere with the human embryo implantation process?

SUMMARY ANSWER: UPA, at the dosage used for EC, does not affect human embryo implantation process, *in vitro*.

WHAT IS KNOWN ALREADY: A single pre-ovulatory dose of UPA (30 mg) acts by delaying or inhibiting ovulation and is recommended as first choice among emergency contraceptive pills due to its efficacy. The compound has also been demonstrated to have a dose-dependent effect on the endometrium, which theoretically could impair endometrial receptivity but its direct action on human embryo implantation has not yet been studied.

STUDY DESIGN, SIZE, DURATION: Effect of UPA on embryo implantation process was studied in an *in vitro* endometrial construct. Human embryos were randomly added to the cultures and cultured for 5 more days with UPA ($n = 10$) or with vehicle alone ($n = 10$) to record the attachment of embryos.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Endometrial biopsies were obtained from healthy, fertile women on cycle day LH+4 and stromal and epithelial cells were isolated. A three-dimensional *in vitro* endometrial co-culture system was constructed by mixing stromal cells with collagen covered with a layer of epithelial cells and cultured in progesterone containing medium until confluence. The treatment group received 200 ng/ml of UPA. Healthy, viable human embryos were placed on both control and treatment cultures. Five days later the cultures were tested for the attachment of embryos and the 3D endometrial constructs were analysed for endometrial receptivity markers by real-time PCR.

MAIN RESULTS AND THE ROLE OF CHANCE: There was no significant difference in the embryo attachment rate between the UPA treated group and the control group as 5 out of 10 human embryos exposed to UPA and 7 out of 10 embryos in the control group attached to the endometrial cell surface ($P = 0.650$). Out of 17 known receptivity genes studied here, only 2 genes, HBEGF ($P = 0.009$) and IL6 ($P = 0.025$) had a significant up-regulation and 4 genes, namely HAND2 ($P = 0.003$), OPN ($P = 0.003$), CALCR ($P = 0.016$) and FGF2 ($P = 0.023$) were down-regulated with the exposure of UPA, compared with control group.

LIMITATIONS, REASONS FOR CAUTION: This proof of concept study was conducted with a few human embryos, as their availability was limited. Although the 3D model used for this study is well established and the artificial endometrial luminal epithelium shown to express progesterone regulated markers of endometrial receptivity it is still an *in vitro* model, lacking all cell types that constitute the receptive endometrium *in vivo*.

WIDER IMPLICATIONS OF THE FINDINGS: This study provides new insights on the mechanism of action of UPA on human embryo implantation, demonstrating that UPA in a dosage used for EC does not affect embryo viability and the implantation process of embryo.

European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/261787/2009

CHMP ASSESSMENT REPORT

FOR

Ellaone

International Nonproprietary Name: ulipristal acetate

Procedure No. EMEA/H/C/001027

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within the agreed timeframe.

2.3. Non-clinical aspects

Pharmacology

Ulipristal acetate (17α-Acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, also known as CDB-2914, VA2914, HRP-2000 and RTI-3021-012) is a compound that is derived from 19-norprogesterone. It is a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects at the progesterone receptor. It binds the human progesterone, but not the estrogen receptor[3]. Ulipristal acetate prevents progesterone from occupying its receptor, thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized.

- Primary pharmacodynamics

The primary pharmacodynamic data originates both from academic and contract laboratories, often in the form of publications in the scientific literature. The binding of ulipristal acetate to hormonal

compete block of gestation was seen at 10 mg/kg and a partial block of gestation at 4 and 8 mg/kg. On days 4, 5 or 6, 32 mg/kg, had no or slight post-coital effect while 64 mg/kg totally blocked gestation in the rabbit.

The ability of ulipristal acetate to terminate pregnancies was investigated in the guinea-pig and monkey. Ulipristal, mifepristone and lilopristone were approximately equipotent at the dose levels of 10 and 30 mg/day in terminating pregnancies in guinea-pigs when the animals were treated on days 43 and 44 of gestation. Pregnant long-tailed macaques (5/group) were administered ulipristal acetate 0.5 or 5 mg/kg/day p.o. or 0.5 mg/kg/day i.m. on days 23-26 of gestation. Pregnant animals were assessed by ultrasound pretreatment (day 23) and then monitored on days 26-28, 30, 32, 35, 55, 80, 100, 130 and 145. At 0.5 mg/kg of ulipristal acetate there was no loss of foetuses, while at 5 mg/kg 2/5 foetuses were lost. When using intramuscular administration of 0.5 mg/kg 4/5 foetuses were lost in ulipristal acetate treated animals. In monkeys in which pregnancy continued and which were allowed to deliver normally, there was no evidence of structural or physiological abnormalities in foetuses.

- Secondary pharmacodynamics

parenteral unmicronized UPA 50 mg (ellaOne) terminates 4/5 pregnancies in “100 kg” macaques (0.5 mg/kg)

direct action on the endometrium. Despite the small number of women, the study clearly showed that a dose of 200 mg is too high, due to the side effects of prolonged bleeding (two women had a dramatic increase in length of bleeding of 15 and 20 days). The 200 mg dose was omitted from **HRA2914-505** and **HRA2914-506**.

- At mid-follicular phase, doses of 10-100 mg ulipristal acetate caused a suppression of growth of the lead follicle and subsequent delay in ovulation that was greatest at the highest doses (50 and 100 mg), but inhibited luteal phase endometrial maturation similarly at all doses. The threshold for altering endometrial morphology thus appears lower than for inhibition of ovulation.
- At early-luteal phase, none of the given doses (10, 50 and 100 mg) affected the length of the follicular, luteal or overall cycle length during the baseline, treatment or post-treatment menstrual cycle. A significant delay in endometrial maturation occurred in the 50 and 100 mg groups compared to the placebo and 10 mg groups ($p=0.02$).

The dose of 50 mg unmicronized ulipristal acetate was chosen in the phase II studies, since this was the minimal dose that alters endometrial maturation and induces inhibition of ovulation.

Since the single-dose studies were performed by the NICHD and data were only available from the publications, limited data are available regarding the adverse effects. Ulipristal acetate at 10-50 mg appears to be well tolerated. Post-treatment cycle characteristics were comparable to baseline. The side effects nausea, headache and abdominal pain were noted during 12-weeks administration (**HRA2914-510**), but no mention is made of these side effects after single-dose administration.

Furthermore, a dose-response relation was observed between the ulipristal acetate dose and the presence of cysts in the single-dose **HRA2914-505** study and the multiple-dose **HRA2914-510** study. It is important to know whether these cysts disappear after single-dose administration. In the majority of the subjects this was the case, but not in all women and some women even required surgery. This is discussed further in the Safety section.

Pharmacodynamic interactions with other medicinal products or substances were not studied.

In conclusion, the mechanism of action, as claimed in 5.1 of the SPC *"The primary mechanism of action is thought to be inhibition or delay of ovulation, but alterations to the endometrium may also contribute to the efficacy of the product"*, is sufficiently documented.

Clinical efficacy

- Dose response studies

Dose selection The 50 mg unmicronized ulipristal acetate dose selected for both phase II studies (**HRA2914-507** and **HRA2914-508**) was based on the aforementioned pharmacodynamic studies.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
Liver effects	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs	
Effect on pregnancy maintenance / off-label use as abortifacient	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs - Peri/post natal toxicity study in rat (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric	Omit any sentence in the SPC and the PL suggesting that the product could be used as an abortifacient. SPC section 4.2: Pregnancy should be excluded before Ellaone is administered. SPC section 4.3: Contraindication : Pregnancy SPC Section 4.6: Ellaone is contra-indicated during an existing or

Summary of the risk management plan for Ellaone

Potential risks

performed if the rat study indicates excretion in milk. Cysts will be followed by routine pharmacovigilance, special attention will be paid to ovarian cysts in PSURs and ruptured ovarian cysts will be mentioned in section 4.8 of the SPC. Concerning amenorrhoea, besides routine pharmacovigilance, special attention will be paid in PSURs and amenorrhea lasting for more than 60 days will be mentioned in section 4.8 of the SPC.

Off-label use as an abortifacient: The applicant has discussed the following options to monitor intended off-label use of Ellaone:

1. Self-reporting of prescribers,
2. Retrospective survey in Ob/gyn departments among women who are hospitalized for incomplete "spontaneous" abortions or miscarriage
3. Use of prescription registries to identify off-label prescriptions.

It is acknowledged that all these approaches suffer from similar, inevitable limitations (prescribers may not report information about off-label prescriptions). However, the applicant has responded with willingness to undertake the best efforts to evaluate the extent of such practice. In particular, the applicant will attempt to collect data from existing prescription registries on frequency and reasons for Ellaone prescriptions in individual cases, which was endorsed by CHMP. However, in order to be

Ellaone prescriptions in individual cases, which was endorsed by CHMP. However, in order to be

meaningful, such measures will have to be implemented only when Ellaone use has reached a certain level of prescription, i.e. not before 1 to 2 years of marketing. The applicant committed to conducting a study using information from prescription registries in countries where it is considered feasible. This will be done after 1-2 years of marketing, depending on the level of Ellaone use. A protocol for such a study should be proposed by the applicant. This issue was resolved by the agreed follow up measures.

Risk Minimization Plan

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

prescriptions have been removed..

The benefit-risk balance is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ellaone in the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure was favourable and therefore recommended the granting of the marketing authorisation.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 December 2014, rev 1
EMA/73099/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ellaOne

International non-proprietary name: ulipristal acetate

Procedure No. EMEA/H/C/001027/II/0021

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

3.4 Even for the minority of women in the EU who do not have access to abortion services delivered by healthcare professionals under medical supervision, ellaOne is an unrealistic option

Women who do not have access to abortion services but want to terminate their pregnancy by themselves find information about their options on the internet (Zamberlin *et al* 2012). Extensive information is readily accessible online about how to perform medication abortion with mifepristone and misoprostol. Although these medicinal products are not readily available in pharmacies, they can be obtained on the Internet.

In contrast, no abortifacient effects have been reported at any dose of UPA or with any duration of therapy in the clinical setting. If women search for methods of abortion they will not be led to any specific information about ellaOne in this regard. In the absence of any clinical data to guide the regimen to be used, a woman could take any number of tablets. The risks of such misuse are deemed low by the MAH.

(EMA/73099/2015 p. 35/76)

Discussion by the CHMP about second criteria

The risk on off-label use should be considered when the product will be available without a prescription. It is important that the product will be used according to the indication, i.e. within 120 hours after unprotected intercourse.

Therefore during the evaluation process of the ellaOne registration dossier the MAH was requested to study any potential off-label use of ellaOne, in particular during pregnancy possibly as an abortifacient. No clinical studies have been performed with ulipristal acetate as an abortifacient, and it is therefore also unknown whether it is possible to use it for abortion. As to the extrapolations from animal data performed by the MAH to inform the question of abortifacient potency, it was not clear to the CHMP on what basis the dose of 13 times 30 mg was calculated. Overall, the dose intervals and group sizes were too limited to base such calculations on, but the main conclusion that can be drawn is that based

- Of 75 prescribers interviewed in both countries, 20% recalled having prescribed ellaOne more than 5 days after unprotected intercourse (UPI). The main reason given for off-label prescription was uncertainty over the time since UPI.
- 2.7% prescribed more than one dose of ellaOne at once, because of risk of vomiting.

When healthcare professionals were asked (HRA2914-544a) for the reasons of off-label prescription, they unanimously responded that they had never prescribed ellaOne with the intent of terminating an existing pregnancy.

The study demonstrates that off-label prescription of ellaOne for abortion does not happen in the real world, dispelling the concern that existed prior to the approval of the original Marketing Authorisation.

1.2 Selective progesterone receptor modulators are used in a variety of reproductive health indications and are not necessarily pe abortion

(EMA/73099/2015 p. 31/76)

UPA belongs to the family of Selective Progesterone Receptor Modulators (SPRM). The structure of SPRMs is believed to generate a specific conformation of the progesterone receptor resulting in a broad spectrum of mixed agonist/antagonist activity (Madauss *et al* 2007, Chabbert-Buffet *et al* 2012).

“did you ever prescribe ellaOne for abortion?”

75, Polish and Swedish, “representative” of all the European MDs

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Effects on pregnancy maintenance/off label use • Risk of incomplete abortion and heavy bleeding • Effects on foetus and newborns • Risk of ectopic pregnancy • Concomitant use of CYP3A4 inducers • Liver effects • Delayed menstrual period >60 days / amenorrhea • Ovarian cysts

Change in the classification from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription".

the CHMP agreed with the removal of the pregnancy contraindication

The PRAC agreed.

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ellaOne

ulipristal acetate

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Product information

30/01/2017 ellaOne -EMEA/H/C/001027 -IA/0044

Name	Language	First published	Last updated
ellaOne: EPAR - Product Information	EN = English GO	13/11/2009	29/06/2017

AUTHORISED
This medicine is approved for use in the European Union

ellaOne RSS feed

News

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 17-20 November 2014 (21/11/2014)
- EMA recommends availability of ellaOne emergency contraceptive

ANNEX I - Summary of Product Characteristics
5.1 Pharmacodynamic properties (page 8)

Name	Language	First published	Last updated
ellaOne: EPAR - Product Information	EN = English GO	13/11/2009	29/06/2017

5. PHARMACOLOGICAL PROPERTIES

(page 8)

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives. ATC code: G03AD02.

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator which acts via high-affinity binding to the human progesterone receptor. When used for emergency contraception the mechanism of action is inhibition or delay of ovulation via suppression of the LH surge. Pharmacodynamic data show that even when taken immediately before ovulation is scheduled to occur (when LH has already started to rise), ulipristal acetate is able to postpone follicular rupture for at least 5 days in 78.6% of cases ($p<0.005$ vs. levonorgestrel and vs. placebo) (see Table).



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Product information

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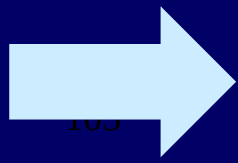
ANNEX III - B. PACKAGE LEAFLET

1. What ellaOne is and what it is used for

How ellaOne works (page 24)



30/01/2017 ellaOne -EMEA/H/C/001027 -IA/0044

Name	Language	First published	Last updated
ellaOne: EPAR - Product Information	EN = English GO	13/11/2009	29/06/2017

(page 24)

How ellaOne works

ellaOne contains the substance *ulipristal acetate* which acts by modifying the activity of the natural hormone progesterone which is necessary for ovulation to occur. As a result, ellaOne works by postponing ovulation. Emergency contraception is not effective in every case. Of 100 women who take ellaOne approximately 2 will become pregnant.

ellaOne is a contraceptive used to prevent a pregnancy from starting. If you are already pregnant, it will not interrupt an existing pregnancy.