

Mechanism of action of the morning-after pill

Teenage pregnancy is a significant public health issue.¹ Worldwide, some 15 million pregnancies occur every year among young women aged 15 to 19,² approximately 1.25 million in the 28 OECD (Organization for Economic Co-operation and Development) nations,³ and between 750.000 and 850.000 in the United States.⁴

As is well known, an estimated fifth of pregnancies World Wide ended in abortion. In Europe this proportion was nearer a third.⁵

Among the various measures proposed is emergency contraception, understanding as such those back up methods for contraceptive emergencies which women can back up methods for contraceptive emergencies which women can use within the first few days after unprotected sexual intercourse or in the event of potential contraceptive failure, to prevent an unwanted pregnancy.⁶ However, the morning-after pill, the active substance of which is levonorgestrel (LNG), is undoubtedly the most widely used method. In Spain alone 506.000 units were issued in 2002.⁷

The oral preparation is marketed as two tablets containing 750 µg of levonorgestrel each or as one 1500 µg tablet. In either case, it is currently recommended to take 1500 µg as a single dose, as soon as possible after unprotected intercourse.⁸ In order to make an ethical evaluation on the use of the morning-after pill, we believe that the main aspect to take into consideration is its mechanism of action since, depending on whether it is anovulatory or prevents implantation, the ethical judgement on its use will be different.

As regards the LNG method, its exact mode of action has not yet been elucidated.⁹ Furthermore, there is very little literature on the mechanism of action of levonorgestrel at present, particularly prior to 2001. Thus, we considered it useful to refer to a 2002 review,¹⁰ in which all articles published in English between 1966 and 2001 were evaluated. This concluded that “there is

¹ REIME B, SCHUECHING BA, WENZLAFF P. Reproductive Outcomes in Adolescents Who had a Previous Birth or an Induced Abortion Compared to Adolescents' First Pregnancies. *BMC Pregnancy and Childbirth* 2008; 8: 1-24.

² UNDP/UNFPA/WHO/WORLD BANK SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION (HRP). *Progress in human reproduction research. Sexual behaviour of young people*. 41, Geneva: Who; 1997.

³ UNITED NATIONS INTERNATIONAL CHILDREN'S EMERGENCY FUND (UNICEF). *A League of teenage in rich nations*. Repond Card n. 3, July 2001 UNICEF Innocenti Research Centre, Florence (Accessed December 12th 2007: <http://www.unicef.org/publications/pdf/repcard3e.pdf>).

⁴ ALAN GUTTMACHER INSTITUTE. *US. Teenage Pregnancy Statistics: National and State Trends and Trends by Race and Ethnicity*. (Accessed December 12th 2007: <http://www.guttmacher.org/pubs/2006/09/11/USTPstats.pdf>); SANTELLI J, DUBERSTEIN L AND FINER L ET AL. *Explaining Recent Declines in Adolescent Pregnancy in the United States: The Contribution of Abstinence and Improved Contraceptive Use*. *Am J Public Health*. 2007; 97: 150-156.

⁵ SEGH G, HENSHAW S, SINGH S ET AL. *Induced Abortion: Estimated Rates and Trends Worldwide*. *The Lancet* 2007; 370; 1338-1345.

⁶ WORLD HEALTH ORGANIZATION. *Levonorgestrel for Emergency Contraception*. (Accessed October 2007: http://www.who.int/reproductive-health/family_planning/ec.html).

⁷ *International Marketing Studies (IMS)*; 2005.

⁸ INTERNATIONAL MEDICAL ADVISORY PANEL (IMAP). *IMAP Statement on Emergency Contraception*. *Med Bull*. 2004; 38; 1-4; CHENG L, GULMEZOLU AM, OEL CJ ET AL. *Interventions for Emergency Contraception*. *Cochrane Database Syst Rev*. 2004; 3.

⁹ BASTIANELLI C, FARRIS M, BENAGIANO G. *Emergency Contraception: A Review*. *Eur J Contracept Reprod Health Care*. 2008; 13; 9-16.

¹⁰ KAHLNBORN C, STANFORD JB, LARIMORE WL. *Postfertilization Effect of Hormonal Emergency Contraception*. *Annals of Pharmacotherapy* 2002; 36; 465-470.

moderately strong evidence that levonorgestrel has a post-fertilisation effect”, i.e. it was accepted that in a certain number of cases, difficult to specify, but objective, the morning-after pill acts by a mechanism which prevents implantation and which is consequently abortive.

From 2001 onwards, although more information is available, it continues to be scant. In our opinion, only 5 studies related with the mechanism of action of the morning-after pill are of adequate technical quality.¹¹ On evaluating the first four (Fig. 1), it was found that the morning-after pill inhibits ovulation or prevents implantation, depending basically on the day of the menstrual cycle. However, in general, it was proven that when taken on days -1 to +2 of the menstrual cycle, considering ovulation as day 0, its action is predominantly post-fertilisation.

One of the authors who defends the anovulatory effect of the morning-after pill is Croxatto. However, when his most significant study¹² was evaluated in detail (Fig. 2), it was found that the anovulatory effect attributable to levonorgestrel varied between 32 and 46%, if to its specific action, we subtract the percentage of cases in the control group in which there was also anovulation. In other words, it appears that the post-fertilisation effect, even in this study by Croxatto, varies between 54 and 69%. Therefore, I do not believe that it can be excluded that the morning-after pill has an anti-implantation effect in probably more than 50% of cases.

However, in order to be able to evaluate this data more critically, we found the paper by Mikolajczyk¹³ particularly interesting. This study evaluated the efficacy of the pill due to the post-fertilisation effect, in function of the total efficacy achieved and the time between sexual intercourse and taking the drug.

To better evaluate this data, it is worth noting that the possibility of pregnancy after a single act of sexual intercourse, without considering the day of the menstrual cycle on which it took place, is approximately 8%.¹⁴ Taking the morning-after pill causes this percentage to fall to 2%, Ho,¹⁵ so it can be considered that the mean efficacy in preventing a pregnancy using the morning-after pill varies between 60-93%.

Returning to Mikolajczyk's paper,¹⁶ if we assume that this efficacy index is correct, and that the pill is taken within 24h after sexual intercourse, the post-fertilization effect would vary between 39 and 49%. However, if the pill is taken up to 72h after sexual intercourse,

¹¹ HAPANGAMA D, GLASIER A, BLAIRD D. *The Effects of Peri-ovulatory Administration of Levonorgestrel on the Menstrual Cycle*. Contraception 2001; 63; 123-129; DURAND M, CRAVIOTO MC, RAYMOND, DURÁN O ET AL. *On the Mechanisms of Action of Short-Term Levonorgestrel Administration in Emergency Contraception*. Contraception 2001; 64; 227-234; MARIONS L, HULTENBY K, LINDELL I ET AL. *Emergency Contraception with Mifepristone and Levonorgestrel: Mechanism of Action*. Obstetrics and Gynecology 2002; 100; 65-71; MARIONS L, CEKAN S, BYGDEMAN M ET AL. *Effects of Emergency Contraception with Levonorgestrel or Mifepristone on Ovarian Function*. Contraception 2004; 69; 373-377; CROXATTO HB, BRACHE V, PAVEZ M ET AL. *Pituitary-Ovarian Function Following the Standard Levonorgestrel Emergency Contraceptive Dose or a Single 0.75- mg Dose Given on the Days Preceding Ovulation*. Contraception 2004; 70; 442-450.

¹² CROXATTO, BRACHE, PAVEZ M ET AL. *Pituitary-Ovarian...*

¹³ MIKOLAJCZYK R, STANFORD J. *Levonorgestrel Emergency Contraception: a Joint Analysis of Effectiveness and Mechanism of Action*. Fertility and Sterility 2007; 88; 565-571.

¹⁴ TASK FORCE ON POSTOVULATORY METHODS OF FERTILITY REGULATION. *Randomised controlled trial of Levonorgestrel Versus the Yuzpe Regimen of Combined Oral Contraceptives for Emergency Contraception*. The Lancet 1998; 352; 428-433.

¹⁵ HO PC. *Emergency contraception: methods and efficacy*. Curr Opin Obstet Gynecol. 2000; 12; 175-179.

¹⁶ MIKOLAJCZYK, STANFORD. *Levonorgestrel...*

the post-fertilization effect increases to 62-74%. Thus, we believe it can be stated, without a risk of error, that the post-fertilization effect of the morning-after pill, when taken up to 72h after sexual intercourse, may vary between 40% and 72%.

In addition to that previously considered and in favour of the levonorgestrel post-fertilization's effect, Gemzell-Danielsson¹⁷ suggested that the *in vivo* effect of LNG may be mediated through an increase in endometrial and serum concentrations of the potent gamete adhesion inhibitor glycodeclin-A, which would be in line with the functional alterations of the endometrium reported in previous studies.¹⁸

As a result of the aforementioned studies, and in accordance with Tirelli,¹⁹ who found that levonorgestrel taken in the late preovulatory phase, prior to the gonadotrophin surge, suppressed ovulation, while in contrast, ovulation was not blocked when LNG was given after the onset of the LH peak and had no effect on ovulation. So we suggest (Fig. 3) that if the morning-after pill is taken between days - 5 and -3 of the menstrual cycle, its effect could be anovulatory; if it is taken between days -3 and -1 it can arbitrarily have both effects, anovulatory and post-fertilization, and if it is taken between days -1 and +2, it would primarily prevent implantation.

Nevertheless, the assessment of the right time in which the LNG is administered and the forecast of its effect are difficult into practice.

This data allows us to conclude that, beyond ideological considerations, and from an essentially medical point of view, the morning-after pill, in a percentage of cases, which very likely exceeds 50%, acts by an antiimplantatory effect, and consequently abortive mechanism.

¹⁷ GEMZELL-DANIELSSON K, MENG CX, ANDERSON KL ET AL. *Effect of levonorgestrel and mifepristone on endometrial receptivity markers in a three-dimensional human endometrial cell culture model.* Fertility and Sterility 2008.

¹⁸ DURAND, CRAVIOTO, RAYMOND, DURÁN O ET AL. *On the Mechanisms...*; CROXATTO, BRACHE, PAVEZ M ET AL *Pituitary-Ovarian...*; MARIONS, HULTENBY, LINDELL ET AL. *Emergency...*

¹⁹ TIRELLI A, CAGNACCI A, VOLPE A. *Levonorgestrel Administration in Emergency Contraception Bleeding Pattern and Pituitary-Ovarian Function.* Contraception 2008; 77; 328-332.

LEVONORGESTREL MECHANISM OF ACTION (2001 – 2004)

Author/Journal	N° of women	Ingestion (day of cycle)*	Inhibition or alteration of ovulation n/%	No alteration of ovulation n/%	
Hapangama et al. Contraception 63; 123, 2001	12	-1	4/33	8/67	
Durand et al. Contraception 64; 227, 2001	45	15	-4	15/100	0/0
		15	0	0/0	15/100
		15	+2	0/0	15/100
Marions et al. Obstet Gynecol 100; 65, 2002	16	-4 a +1	10/63	6/37	
Marions et al. Contraception 69; 373, 2004	7	-2	7/100	0/0	

* Day 0 of the sexual cycle is considered to be the day of ovulation

ASSESSMENT OF WHETHER THE CONTRACEPTIVE ACTION OF LEVONORGESTREL IS DUE TO A ANTICONCEPTIVE* OR POST-FERTILISATION MECHANISM

SIZE OF FOLLICLE		12-14mm		15-17mm		>18mm		12-19mm	
DAYS WITH RESPECT TO OVULATION		9-10		11-13		14*		9-14	
		Number of cycles	%						
P I L	INHIBITION OF OVULATION	15/18	83	8/22	36	2/17	12	25/57	44
	DELAY OF OVULATION	2/18	11	12/22	55	6/17	35	20/57	35
	ANTICONCEPTIVE ACTION	17/18	94	20/22	91	8/17	47	45/57	79
P L A C E B O	INHIBITION OF OVULATION	10/18	56	8/22	36	2/16	13	20/56	36
	DELAY OF OVULATION	1/18	6	2/22	9	0/16	0	3/56	5
	ANTICONCEPTIVE ACTION	11/18	62	10/22	45	2/16	13	23/56	41
ANTICONCEPTIVE ACTION "POST-FERTILIZATION" ACTION %		32/68		46/54		31/69		38/62	

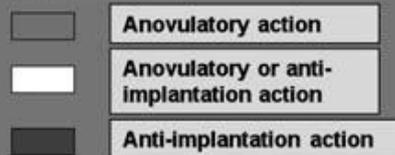
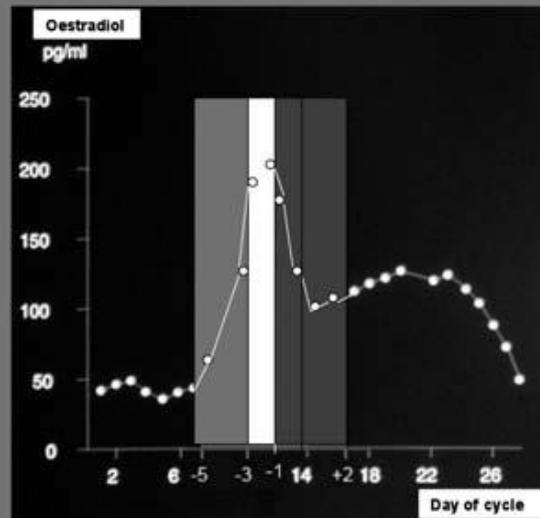
* By contraceptive mechanism we understand the inhibition of ovulation or a delay in ovulation of more than 5 days. All other actions would be due to a post-fertilisation mechanism.

** The percentage of anticonceptive action was obtained by subtracting the percentage anticonceptive action of the placebo from the percentage contraceptive action of levonorgestrel.

Croxatto et al.

Contraception 70; 442- 450, 2004

LEVONORGESTREL MECHANISM OF ACTION



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