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Letters to the Editor

Postovulatory effects of levonorgestrel in emergency contraception

To the Editor:

The debate over the strictly preovulatory vs. preovulatory and postovulatory effects of levonorgestrel in emergency contraception (LNG EC) seems endless [1], in spite of the published evidence of its postovulatory action [2–4]. These data show definite postovulatory effects of LNG EC with a probability distribution of pregnancies issued from daily intercourses within the fertile period of the menstrual cycle (fertility window). Here, we obtain that probability distribution from (1) Wilcox et al. [5], with women who wanted to get pregnant and probably were previously using contraceptives; (2) Simpson [6], with women participating in natural family planning programs. Accurate estimates or sophisticated methods are unnecessary in this case. Wilcox et al. [5] present probabilities of pregnancy for an intercourse occurring in a day of the fertility window; these probabilities were transformed in a probability distribution by assuming that intercourses occur, on each day, with equal probability. If we allow for a cumulated probability of coitus between 14 and 6 days before ovulation of 0.02 and between 3 and 13 days after ovulation of 0.01, and give a coefficient 0.7 to the data of Simpson (without contraceptives) and a coefficient 0.3 to that of Wilcox et al., the probability distribution for the entire cycle can be generated. Table 1 presents that probability distribution. Figures are similar to most published ones. The maximal effectiveness when LNG EC acts exclusively as an anovulatory drug (with 100% of effect), on pregnancy prevention, can be tested directly from the cumulative probability. If LNG EC is used 0 to 24 h after the intercourse (12 h average), it shall not have any effect at the day of ovulation or after; so, in this condition, its maximal effectiveness should be 56.1%. The maximal effectiveness of LNG EC used 25–48 h after coitus should be 38.2%, and so on. Table 2 shows the maximal expected effectiveness of LNG EC, as an exclusive anovulatory drug, used from 1 to 5 days postcoitus and the observed effectiveness found in the three studies [2–4]. The observed effectiveness for the nine independent comparisons was at least 22% over the expected maximal anovulatory action. These nine additional contraceptive percentages should be due to postovulatory effects. These conclusive results do not depend on the ovulation day. Each day of delay in the administration of the drug is a day less in the fertility windows, regardless of the day at ovulation. The critical comparison is the decay pattern of expected and observed effectiveness in relation to the time between intercourse and drug administration.

Table 1
Probability distribution of pregnancies for coitus on days of the menstrual cycle

Day	OP Wilcox	P Wilcox	P Simpson	P Val	Cumulative P
Menstruation 1°	–	–	–	–	
−14 to −6	0.00	0.0000	Cumulated	0.020	0.020
−5	0.08	0.0575	Until	0.042	0.062
−4	0.17	0.1223	−1	0.089	0.151
−3	0.08	0.0576	–	0.042	0.193
−2	0.36	0.2590	–	0.189	0.382
−1	0.34	0.2446	0.510	0.179	0.561
0 (ovulation)	0.36	0.2590	0.396	0.338	0.899
+1	0.00	0.0000	0.075	0.073	0.972
+2	0.00	0.0000	0.019	0.018	0.990
+3 to +13	0.00	0.0000	0.000	0.010	1.000
Menstruation 2°	–	–	–	–	

OP Wilcox indicates the original probabilities of Wilcox et al. [5]; P Wilcox, the probability distribution of Wilcox et al.; P Simpson, Simpson's probability distribution [6]; P Val, the calculated probability distribution for the entire cycle; cumulative P, cumulative probability distribution of P Val.

Table 2
Maximal expected and observed effectiveness of LNG EC as an exclusive anovulatory drug

Hours postcoitus[a]	Expected	Observed			
		WHO 1[b] (2 doses)	WHO 2[c] (2 doses)	WHO 2[c] (1 dose)	Retal[d]
0–24	56.1%	95.0%	Cumulative		Cumulative
25–48	38.2%	85.0%	0–72 h		0–71 h
49–72	19.3%	58.0%	79%	84%	87.1%
73–96	15.1%	–	73 ≥ 96 h		72–120 h
>96	6.2%	–	60%	63%	72.7%

[a] Hours after coitus when LNG EC was administered.
[b] Ref. [2].
[c] Ref. [3].
[d] Ref. [4].

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Response to Letter to Editor

To the Editor:

I have several objections to the conclusions presented in the letter to the editor entitled "Postovulatory effects of levonorgestrel in emergency contraception (LNG EC)," signed by Dr. Carlos Valenzuela.

The first objection is to the first sentence that cites as evidence of postovulatory action of LNG three efficacy studies (references 2–4 in his letter) that have no built-in mechanism of action studies. It is a sound and rigorous practice in science today that the only valid method for testing a hypothesis or answering a defined question based on scientific evidence requires an appropriate specific experimental design. Neither one of those studies comes close to meet even at a minimal level a specific design to test mechanism of action hypotheses.

The second objection is to a serious misuse of Wilcox et al. data, which becomes obvious upon examination of the second column headed OP Wil in Table 1. The figures quoted there correspond to probabilities of conception, which result from detection of hCG in urine and not to probabilities of clinical pregnancy, which are much lower. As a consequence, the expected pregnancy rate in his calculations has no relevance to the clinically observed pregnancies reported in efficacy studies reported in references 2 to 4 in his letter, which are used in Table 2.

The third objection is to attributing the properties of actual measurements to the reported efficacy of LNG in the cited trials when, in reality, they are mere estimates known to be plagued with erroneous assumptions and miscalculations derived from lack of objective methods to determine in each case on which day of the six fertile days sexual intercourse took place [1–4]. The wide range of reported estimates of efficacy from 60% to 85% attests to the softness of those estimates. Furthermore, there are strong reasons to believe that those figures represent an overestimation of efficacy due to the fact that a large proportion of cases requesting EC in those studies correspond to "condom failures," and up to 36% of those have no sperm in the vagina or cervical canal within 6 h after coitus [5]. Those cases are included in the "at-risk group" in the efficacy studies leading to an overestimation of the efficacy of EC.

Furthermore, alienation from reality in the analysis presented by Dr. Valenzuela results from complete absence of well-documented effects of LNG upon cervical mucus and sperm migration in the equation of factors contributing to the contraceptive efficacy of LNG [6–8].

Finally, I object to contrasting the effectiveness of LNG for interfering with the ovulatory process, which is based on actual hormonal and ultrasonographic data in a small number of subjects, with dubious estimates of EC contraceptive efficacy in large cohorts, as a scientific method to determine how LNG prevents pregnancy and why it fails to do so in 15% to 40% of cases.

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Response to letter to editor: Quantitative assessment of postovulatory effects of levonorgestrel emergency contraception

To the Editor:

Dr. Valenzuela proposes quantitative estimation of postovulatory or postfertilization effects of levonorgestrel