

Letters to the Editor

To the Editor:

Novikova et al. [1] have attempted to assess the effectiveness of levonorgestrel given after or before ovulation. For the first time, effectiveness is assessed with a more precise method of determining ovulation that provides a more reliable estimate of the time at which unprotected intercourse, and the intake of emergency contraceptive pill (ECP) occurred in relation to ovulation. In addition, this is the first study to assess effectiveness according to the day on which ECP was taken with a more reliable estimate of ovulation. Although this is a pilot study, we believe for the above reasons, that it means important progress in determining effectiveness and the mode of action of ECP.

The findings of the study and their interpretation nevertheless need some clarifications and comments.

1. There is no precise information concerning the day on which the ECP was taken. Table 1 only gives the number of expected and observed pregnancies related to the day of intercourse. A similar table showing the expected and observed pregnancies in relation to the day of intake of the ECP is required. The study only states that when unprotected intercourse occurred on Day -2 or earlier, the “ECP was then taken around or before ovulation.” Without precise information regarding the day on which the ECP was taken among this group of women, we cannot agree with the authors conclusion that the data of the study “are supportive of the concept that LNG has little or no effect in post ovulation events.” Women who joined the study reported a single act of unprotected sexual intercourse within the previous 120 h. Many women who had intercourse on Days -5 to -2 may have taken the ECP on days very near ovulation or even after. Of the 34 women who had intercourse during this period, 18 had it on Days -2 and -3 , accounting for nearly 65% of the expected pregnancies (2.7/4.15) in this group. The delay in taking the ECP in this group can influence significantly the conclusions about postovulation effect.

2. Among the 17 women who had intercourse around Days -1 to 0 (and took the ECP on Day $+2$), three or four pregnancies would have been expected, and three were observed. The authors find that these data support their hypothesis that LNG has no postfertilization effect. It must be pointed out, however, that in the 11 women out of 17 who had their intercourse on Day -1 “and took the ECP on

Day $+2$,” the expected pregnancies were 2.97 and the observed pregnancies 1. Efficacy was 66% in this very small group, supporting the hypothesis of a postfertilization effect. The foregoing shows the limitations of a study with few participants, where the manner of grouping the results can support different hypotheses.

3. To assess postfertilization effect, the authors include only the women who took the pill 2 or more days after ovulation. In this study, ultrasound examination was not performed to determine whether ovulation was blocked; however, earlier studies have shown that when ECP is given 2 days prior to the beginning of the luteal surge, ovulation is blocked in the majority of cases, but when given very near or at the beginning of the luteal surge, it fails to block ovulation most of the times [2–4]. This may be the case of many women in this study. The data about effectiveness in this group are important to assess postovulatory and postfertilization effect, one of the purposes of this study. Effectiveness of the ECP when given around the day of ovulation, when the time from ovulation is insufficient to block it, can only be explained by the drug blocking fertilization or implantation. Fertilization is very difficult to study, and many experts consider that such effect would only be possible if the pill is taken very soon after intercourse [5,6].

4. The failure rate of ECP was 3%, considering the 99 women who joined the study. However, this study allows calculating the real failure rate by considering only the 51 women who were at risk of becoming pregnant. This gives a failure rate of 6%.

5. We agree with the authors that the small number of participants in this study does not allow making any consistent statement on a postfertilization effect of the ECP and that “to obtain more accurate data on both efficacy and mode of action of ECP, more extensive studies of this nature using transvaginal ultrasound in conjunction with endocrine data are required in much larger numbers of women.” The use of ultrasound would, for the first time, permit assessing the effect of ECP on ovulation in the real setting, that is, when ECP is taken after unprotected intercourse. This is important because intercourse could influence ovulation [7]. It would also allow measuring the effectiveness in the group of women whose ovulation was not blocked.

Patricio Ventura-Junca
*Departamento de Pediatría, Centro de Bioética
 Facultad de Medicina, Universidad Católica de Chile
 Alameda 340, Santiago, Chile
 E-mail address: venturaj@med.puc.cl*

Mauricio Besio
*Departamento de Obstetricia y Ginecología
 Centro de Bioética, Facultad de Medicina
 Universidad Católica de Chile
 Alameda 340, Santiago, Chile
 E-mail address: besio@med.puc.cl*

Manuel Santos
*Departamento de Genética y Biología Molecular
 Facultad de Ciencias Biológicas
 Universidad Católica de Chile
 Alameda 340, Santiago, Chile
 E-mail address: msantos@genes.bio.puc.cl*

doi:10.1016/j.contraception.2007.10.014

References

- [1] Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation — a pilot study. *Contraception* 2007;75:112–8.
- [2] Croxatto HB, Brache V, Perez M, et al. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75 mg dose given on days preceding ovulation. *Contraception* 2004;70:442–50.
- [3] Hapangama D, Glasier AF, Baird DT. The effects of pre-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception* 2001;63:123–9.
- [4] Durand M, Cravioto MC, Raymond EG, et al. On the mechanism of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;64:227–34.
- [5] Von Hertzen H, van Look PFA. Research on new methods of emergency contraception. *Fam Plann Perspect* 1996;28:52–7, 88.
- [6] Gemzell-Danielsson K, Marions L. Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception. *Hum Reprod Update* 2004;10:341–8.
- [7] Jochle W. Current research in coitus-induced ovulation: a review. *J Reprod Fertil Suppl* 1975:165–207.

Response to the Letter to the Editor

To the Editor:

We thank Dr. Ventura-Junca et al. for their positive comments about our article [1] and for their questions. We are pleased that they are supportive of our attempts to use endocrine data to try and provide a more reliable estimate of the time at which unprotected sexual intercourse and ingestion of the levonorgestrel emergency contraceptive pill (ECP) occurred in relation to ovulation and subsequent

pregnancy. It will be critical that future studies occur on larger numbers of subjects and have access to good-quality transvaginal ultrasound scanning to supplement the endocrine data.

Dr. Ventura-Junca et al. state that we have not provided precise information concerning the day on which the ECP was taken. We have very precise information about the timing of ECP ingestion in all subjects, but it would have been impractical to present these data for individual women in this article. The day of ECP-taking was an important part of this study. All 18 women who had intercourse on Days 2 and 3 prior to ovulation took their ECP around or before ovulation. We agree that a significantly prolonged delay in taking the ECP in this group could have significantly influenced our conclusions about lack of effect of ECP after ovulation, although it actually did not.

We agree that the numbers of pregnancies are small in this pilot study, for reasons clearly addressed in our article, and that interpretations of the potentially complex interactions between endocrine data, timing of ovulation, timing of intercourse, timing of ECP-taking and chance of pregnancy are difficult. We cannot exclude a small postfertilization effect of ECP, but our data are supportive of the hypothesis (and of other published data) that suggest that the LNG-ECP works primarily by interference with ovulation and has little or no postovulatory effect.

Dr. Ventura-Junca has stated that “to assess post-fertilization effect the authors only included women who took the pill two or more days after ovulation.” This is not correct. As clearly stated in our article, we included women who took ECP at any time in the cycle. It so happened that, in our study of 99 women taking the ECP, the only three pregnancies that we observed occurred in women in whom intercourse happened just before or around ovulation and who took ECP around 2 days postovulation.

They have also questioned our calculation of the failure rate of ECP. We chose to use a calculation in line with the method described by Wilcox et al. [2]. The difficulties of calculating the effectiveness of ECP have been well addressed by James Trussell [3] in a number of articles.

Dr. Ventura-Junca et al. make a statement that sexual intercourse may influence ovulation, and they reference a 1975 review [4] addressing reflex ovulation in various animal species. We are not aware of any clear evidence that supports such an effect in humans.

We agree that our findings do need to be confirmed in much larger studies where the involved clinics have good transvaginal ultrasound facilities immediately available. The combination of endocrine and ovarian ultrasound data to even more precisely determine the timing of ECP ingestion and intercourse in relation to ovulation will be critical to answering the questions raised by Dr. Ventura-Junca et al., and indeed those questions that we posed in our article. We believe that our study has allowed the development of clearer hypotheses that can be tested in much larger studies.