Reference


Emergency contraception: an unresolved issue

To the Editor:

Noé et al. [1] have to be congratulated on their study of the efficacy of emergency contraception with levonorgestrel (LNG-EC). They confirm that LNG inhibits ovulation if taken early in the cycle. After ovulation, LNG does not prevent pregnancy, at least to a level that would be detected with their sample size. A larger study would be required to fully exclude the prevention of 10–20% of expected pregnancies from postfertilization effects. The authors found that “follicle rupture occurred in some two thirds of women taking LNG-EC preovulatory; this suggests that other mechanism than suppression of ovulation prevents pregnancy in these women.” They recommend evaluation of mucus changes after LNG administration to elucidate its role in pregnancy prevention. But other mechanisms can be proposed to fully explain the preovulatory effectiveness of LNG [2]. They include direct inhibition of fertilization or alterations in oviductal transport, which could impact the ovum or the embryo to prevent proper timing for implantation. If fertilization occurs (ovulation is possible in spite of taking LNG in the preovulatory phase), alteration of endometrial receptivity or interference with corpus luteum could contribute to effectiveness. Noé et al. [1] have not directly addressed these mechanisms, and the possibility of interfering with implantation is not completely excluded [3]. The authors confirmed ovulation occurrence but not fertilization, so the conclusion “LNG-EC prevents pregnancy only when taken before fertilization of the ovum has occurred” cannot be inferred from the data.

A better understanding of the mechanisms of action of LNG-EC would give a better understanding of its effectiveness. The longer the delay between intercourse and LNG-EC intake, the more likely it is that ovulation and fertilization have taken place (even though LNG-EC is taken prior to ovulation). To address this, it would be helpful to have precise information on the delay between intercourse and LNG administration, and on the exact timing of ovulation. These data were not recorded in the study by Noé et al. [1].

There appears to be a mistake regarding the number of pregnancies in Table 4: there should be 6 in the bottom line instead of 3 (because an effectiveness of 77% would come from 6 observed pregnancies).

Finally, this study shows that the effectiveness of LNG is lower than has been generally presented [4]. Although more accurate calculation of effectiveness and new data about the effect on ovulation have improved our knowledge about the mechanism of action of LNG, it is still an unresolved puzzle.

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Response to the Letter to the Editor

To the Editor:

We thank Carmen Lopez-del Burgo et al. for their interest in our recent paper on levonorgestrel emergency contraception (LNG-EC) [1]. Lopez-del Burgo et al. writes that, “A larger study would be required to fully exclude the prevention of 10–20% of expected pregnancies from postfertilization effects.” We assume that the 10–20% refers to the difference between the 7.1 expected and 6 observed pregnancies in Table 4 of our paper [1]. This difference is not statistically significant (p=1.00) and is similar to that reported by Novikova et al. [2]. Since the submission of our paper last year, we have continued data collection and now have data on altogether 450 women using LNG-EC. We will shortly submit these additional data for publication.

Several women in whom there was evidence that ovulation occurred in the 5 days following LNG intake did not get pregnant. This was expected to occur because the highest probability of pregnancy, under optimal conditions, does not exceed 30% according to Wilcox et al. [3]. Therefore, there is no need to search for an explanation based on mechanism of action. Nonetheless, Lopez-del Burgo et al. propose several mechanisms to “fully explain preovulatory effectiveness of LNG-EC”: direct inhibition of fertilization,
alterations in oviductal transport, alteration of endometrial receptivity or interference with corpus luteum.

For obvious ethical reason, inhibition of fertilization cannot be directly studied in humans in vivo. In vitro studies show negligible effects on fertilization \[4,5\].

As we wrote, the interference with sperm migration to the site of fertilization is the most probable mechanism of LNG for inhibiting fertilization when ovulation is not suppressed \[1\]. Change in the viscosity of cervical mucus has been proven for LNG administered as EC, albeit with a different dose, and in low doses as contraceptive implant \[6,7\].

Alterations in oviductal transport which could prevent proper timing for implantation is an unlikely mechanism for preovulatory LNG-EC efficacy. When LNG-EC is taken after ovulation, pregnancies occur at the expected rate in our and in Novikova studies \[1,2\]. Furthermore, a systematic review published after our paper was submitted, reports that “the rate of ectopic pregnancy when treatment with emergency contraceptive pills fails does not exceed the rate observed in the general population” \[8\].

As we noted in the introduction of our paper, the action of LNG-EC on endometrial histology and function has been widely investigated \[9,10\]. One recent study demonstrates no effect of LNG on human implantation in vitro \[11\].

Lopez-del Burgo et al. write that we “confirmed ovulation occurrence but not fertilization,” so the conclusion “LNG-EC prevents pregnancy only when taken before fertilization of the ovum has occurred cannot be inferred from the data.” As indicated, the direct effect of LNG-EC on fertilization cannot be investigated in vivo in humans. Hence, the ratio observed/expected pregnancies has become the acknowledged means to estimate the efficacy of LNG-EC. In the group of women taking LNG after ovulation in our study and in that of Novikova et al, the rate of pregnancy negates that postfertilization effects play a role in the mechanism of action of LNG-EC \[1,2\].

Our study was not designed to explore effects on the corpus luteum, not withstanding that out of 57 women in whom ovulation was confirmed, 45 had blood samples taken in their luteal phase, and 42 of them (94%) had progesterone values over 12 nmol/L.

Lopez-del Burgo et al. claim that we did not record precise information on the delay between intercourse and LNG administration and on exact timing of ovulation. We did record, analyze and report these data. The delay between unprotected intercourse and LNG-EC intake was reported in the Results section as percentage of women who took LNG-EC with delays of less than 24, between 24–47 and 48–72 h after intercourse. The recorded timing of ovulation in all women who had intercourse during the fertile days was essential information for estimating the number of expected pregnancies in this group.

Finally, there is no mistake regarding the number of pregnancies in Table 4. There are six pregnancies on the bottom line. The effectiveness of LNG-EC is correctly calculated using the equation described in statistical methods.

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