Original research article

Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens ☆

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Abstract

Background: The days just prior to ovulation are the most crucial for emergency contraception (EC) efficacy. Ulipristal acetate (UPA) and levonorgestrel's (LNG) capacity to inhibit follicular rupture have never been compared directly at this time of the cycle.

Study Design: Raw data from three pharmacodynamics studies with similar methodology were pooled to allow direct comparison of UPA, LNG and LNG+meloxicam's ability to prevent ovulation when administered orally in the advanced follicular phase, with a leading follicle of ≥18 mm.

Results: Forty eight LNG-treated (1.5 mg) cycles, 31 LNG (1.5 mg) +meloxicam (15 mg), 34 UPA (30 mg) cycles and 50 placebo cycles were compared. Follicle rupture was delayed for at least 5 days in 14.6%, 38.7%, 58.8% and 4% of the LNG-, LNG+meloxicam-, UPA- and placebo-treated cycles, respectively. UPA was more effective than LNG and placebo in inhibiting follicular rupture (p=.0001), while LNG, when administered at this time of the cycle, was not different than placebo. The addition of meloxicam improved the efficacy of LNG in preventing follicular rupture (p=.0292 vs. LNG; p=.0001 vs. placebo; non-significant vs. UPA). UPA was effective in preventing rupture in the 5 days following treatment, even when administered at the time of the luteinizing hormone (LH) surge (UPA 79%, LNG 14% and placebo 10%). None of the treatments were effective when administered on the day of the LH peak. The median time from treatment to rupture was 6 days during the ulipristal cycles and 2 days in the placebo and LNG/LNG+meloxicam cycles (p=.0015).

Conclusion: Although no EC treatment is 100% effective in inhibiting follicular rupture when administered in the late follicular phase, UPA is the most effective treatment, delaying ovulation for at least 5 days in 59% of the cycles. LNG is not different from placebo in inhibiting follicular rupture at this advanced phase of the cycle. No treatment was effective in postponing rupture when administered on the day of LH peak.

1. Introduction

Emergency contraception (EC) provides women a means to reduce the likelihood of becoming pregnant after unprotected intercourse, and since the advent of dedicated products some 15 years ago, utilization of EC has increased significantly worldwide. Oral EC aims at interfering with an ovulation that has not yet occurred. The days just prior to ovulation are the most crucial for EC efficacy, since intercourse these days carries the highest probability of conception [1–3]. Oral EC regimens must be able to prevent ovulation for at least 5 days to be highly effective because spermatozoa can maintain fertilizing capacity in the female genital tract for that long [3,4]. In clinical practice, when a woman presents for EC, we seldom know in which stage of the ovulatory process she is because cycle length and ovulation day may vary, so EC is given as quickly as possible in the hopes of catching the process early.

The progestin levonorgestrel (LNG) at a dose of 1.5 mg has become the most widely accessible and commonly used EC method and is licensed for use within 72 h of unprotected sexual intercourse. In recent trials in western populations, LNG prevented fewer than 70% of expected pregnancies [5,6] while in two earlier World Health Organization-sponsored studies, the estimate was closer to 80–85% [7,8]. However, the precision of the methodology to obtain these estimates has been questioned [9–11]. The primary mechanism of action of oral EC is to interfere with the ovulatory process by preventing or delaying ovulation. From previous studies, it has become clear that the ability of LNG to interfere with the ovulatory process decreases as ovulation nears. Once the ovulatory process has been triggered by the luteinizing hormone (LH) surge, LNG does not appear to prevent the follicle from rupturing, an event that normally takes place shortly after [12–16].

Ulipristal acetate (UPA), a more recent EC option, is a selective progesterone (P) receptor modulator with antagonistic and partial agonistic effects at the P receptor (a P agonist/antagonist). The primary mechanism of action of UPA for EC is inhibition or delay of ovulation. UPA is marketed worldwide as a 30-mg micronized tablet to be taken within 120 h of unprotected sex. In a pooled analysis of two randomized head-to-head efficacy trials, women who received UPA were significantly less likely to become pregnant than women who received LNG [odds ratio (OR): 0.55, 95% confidence interval (CI): 0.32–0.93]. If EC was used within 24 h of unprotected sexual intercourse, when most women tend to present for EC, the risk of pregnancy for women who received UPA was two-thirds lower than for women who received LNG (OR 0·35, 95% CI: 0.11–0.93) [6]. From previous studies, it would appear that UPA interferes with the ovulatory process even in the presence of rising LH, delaying follicular rupture by 5 days in a significant proportion of women [17,18].

For the purpose of studying drug effects on ovulation, the moment of intake in relation to descriptive parameters of the ovulatory process can be standardized. We have previously conducted three randomized, double-blind, placebo-controlled pharmacodynamic studies using similar methodology, each assessing the effect of LNG, UPA or LNG +meloxicam on the ovulatory process during the 5 days following treatment administered in the advanced follicular phase. LNG regimens studied were the standard 1.5-mg dose (either 0.75 mg ×2, with a 12-h interval between doses or a single 1.5-mg dose) and a standard UPA 30-mg micronized dose [15,18,19]. In addition, a novel regimen was studied that associated the standard dose of LNG (1.5 mg) with meloxicam (15 mg), a prostaglandin-endoperoxide 2 inhibitor, previously known as cyclooxygenase-2 (COX-2) inhibitor. The addition of meloxicam was hypothesized to be synergistic in the prevention of ovulation at the level of the ovary, via inhibition of the follicular prostaglandin synthesis that triggers follicular rupture in response to the LH surge [19].

Although clinical efficacy trials suggest that UPA is more effective than LNG for EC, especially when taken rapidly after unprotected intercourse, no pharmacodynamic study has directly compared their capacity to inhibit ovulation. In order to compare the different EC regimens, we pooled the raw data from our three pharmacodynamic studies and assessed the three regimens with respect to the occurrence of ovulation in the days following treatment.

2. Materials and methods

2.1. Study design

The primary objective of this analysis was to estimate and compare the different regimens with respect to the proportion of subjects in whom follicular rupture did not occur in the 5 days following treatment. We also evaluated the effect of treatment on LH and P levels and described the subsequent outcome of follicles.

Analysis was done using data from three studies conducted by the same group of investigators using similar randomized, double-blind, placebo-controlled crossover study designs. The regimens included in this analysis were the following: Study 1: LNG 1.5 mg versus placebo [15]; Study 2: LNG 1.5 mg plus placebo versus LNG 1.5 mg plus Meloxicam 15 mg [19]; and Study 3: UPA 30 mg versus placebo [18]. All studies were conducted in two large reproductive health clinics in Latin America (ICMER in Santiago, Chile, and PROFAMILIA in Santo Domingo, Dominican Republic). Approval was granted for the study protocols and subject information and consent forms by national authorities in Chile and Dominican Republic as well as by the ethics committee of each center.

Each study was designed to evaluate the effect of the study regimens on the outcome of the leading ovarian follicle in the mid to late follicular phase. This analysis is based on the groups of comparable participants who had been assigned to receive study drug in the late follicular phase, at leading follicular diameter ≥18 mm. The number of participants in each treatment arm included in the analysis is shown in Table 1. One subject participated in both Study 1 (placebo vs. LNG) and Study 2 (LNG plus placebo vs. LNG plus meloxicam). For female volunteers to be eligible for the studies, they had to be healthy, 18–40 years old (Study 1, 18–40 years; Study 2, 18–39 years; Study 3, 18–35 years), with regular menstrual cycles in the past 3 months, nonpregnant and nonbreastfeeding, not currently using hormonal contraception and protected from pregnancy by tubal ligation or nonhormonal intrauterine device.

Following a screening visit, eligible women were followed for three to five menstrual cycles with each participant contributing a placebo cycle, one or two drug-treated cycles (depending on the number of treatment groups), each followed by one washout or resting cycle. The order of treatment or placebo cycles was randomized;

Table 1
Number of participants per study per treatment arm

	Follicular diameter at treatment	Placebo	LNG 1.5 mg	LNG 1.5 mg+meloxicam 15 mg	UPA 30 mg
Study 1: Croxatto (2004)[a]	≥18 mm	16	17[a]	–	–
Study 2: Massai (2007)[b,c]	≥18 mm	–	31[b]	31[c]	–
Study 3: Brache (2010)	≥18 mm	34	–	–	34
Total		50	48	31	34

[a] LNG 0.75 mg ×2 with 12 h between the two doses (first dose taken at the clinic).

[b] LNG 0.75 mg ×2 plus placebo taken at once at the clinic.

[c] LNG 0.75 mg ×2 plus meloxicam 15 mg taken at once at the clinic.

the follicular size at treatment was randomized in Study 1 and 2. Screened women who satisfied all inclusion/exclusion criteria entered the study and underwent daily transvaginal ultrasound (TVU) monitoring from Day 8 (Day 5 to 8 in Study 3) of their next menstrual cycle (Cycle 1) until the lead follicle reached the treatment size ≥18 mm, at which time they were randomized and treatment was given on site in front of study staff. From that time on, they were monitored daily by ultrasound and hormone assays until the fifth day following treatment, then twice a week until menses. Follicular rupture was defined as an abrupt disappearance (or >50% reduction in size) of the leading follicle whose mean diameter was 15–25 mm in the TVU performed on the day before.

Daily venous blood samples for measurement of LH began at a follicular diameter of ≥15 mm to avoid missing the initiation of the LH surge and were continued until the fifth day after treatment administration. P was measured in blood samples taken immediately before starting treatment and daily thereafter until the fifth day after treatment administration (a total of six daily samples), followed by measurements twice a week until menses. In one of the centers in one of the studies, P was only measured on Day 5 after treatment [19]. The same procedure was repeated in subsequent treatment cycles. Additional information about randomization procedures, study medications, TVU and hormonal sample processing has been published previously for each study [15,18,19].

2.2. Data analysis

The primary end point for each of the three studies as well as for this analysis was follicular rupture inhibition, defined as persistence of the unruptured dominant follicle during the 5-day period following treatment. Secondary end points for the current analysis include time from the treatment intake day to observed rupture of the leading follicle. End points

were compared between treatment group, and follicular rupture inhibition was compared stratified by LH status (no LH surge, LH surge initiated or after LH peak) at treatment intake. Based on LH values from 100 placebo cycles from studies previously conducted at both centers, the presence of an LH surge onset was defined as an LH increase by at least 40% compared with the day before and greater than 6 IU/L, OR over 8 IU/L for the first time; while LH peak was defined as an LH value ≥15.6 IU/L.

The primary statistical analysis tested the difference on the proportion of subjects with an inhibition of follicular rupture during the 5-day period following treatment between treatment groups with a significance level of 5% (two sided). The statistical test performed was a Cochran–Mantel–Haenszel general association test, followed in case of global significance by an estimation of the risk ratios between treatment groups or by a Fisher's Exact Test.

Time from treatment intake to follicular rupture was analyzed by a time-to-event analysis (Kaplan–Meyer methodology) with an adjustment for multiplicity by the Sidak method. All statistical analyses were performed with the SAS® system version 9.2 (Cary, NC, USA).

Due to the exploratory purpose of the analyses, adjustment for multiplicity was not systematically addressed. However, the inflation of the overall alpha level was limited due to the fact that the analyses were focused on the main clinical questions and that an adjustment method or hierarchical testing was used whenever possible.

3. Results

3.1. Baseline characteristics

A total of 163 cycles were included in the present analysis, 48 LNG, 31 LNG+meloxicam, 34 UPA and 50 placebo cycles (Table 1). The baseline demographic characteristics were similar in the four groups. Subjects were not at risk of pregnancy at the time of treatment; they were all treated at a similar time with regard to day of cycle, mean follicular diameter and baseline estradiol and P levels (Table 2). Mean LH levels at the time of treatment were also comparable (range: 16–26 IU/L) with a large standard deviation, due to the inherent variability of pulsatile LH levels and to the differences in LH status at time of treatment for each subject (Table 2). LH status repartition at the time of treatment administration was relatively similar in all treatment groups. However, almost half of the women in the placebo and LNG groups had already an LH peak at the time of treatment as compared to about one third in the other two groups. Treatment was given before LH had started to rise in 24–32% of cycles, after LH had started to rise but before LH had reached peak level in 20–42% of cycles and after LH had reached its peak levels in 29–48% of cycles.

Placebo cycles were remarkably similar across studies in terms of baseline characteristics and dominant follicle

Table 2
Demographics and hormonal parameters on the day of treatment

Baseline parameters statistics[a]	Placebo n=50	LNG n=48	LNG+meloxicam n=31	UPA n=34
Dose administered	–	1.5 mg	1.5 mg+15 mg	30 mg
Age (years)(range)	31.0±4.1(22–40)	31.4±5.1(18–40)	31.7±5.0(18–37)	31.0±3.5(22–35)
Weight (kg)(range)	62.9±9.3(45–82.5)	63.5±11.5(44.8–87.3)	65.6±12.1(44.8–87.3)	64.4±8.9(45–82.5)
Cycle day of treatment	13.7±3.4	14.4±3.2	14.9±2.4	13.8±2.6
Length of cycle (days)	28.2±3.54	27.3±3.41	27.1±3.55	30.8±3.28
Follicular diameter at Tx (mm)	18.4±0.7	18.5±0.6	18.4±0.5	18.4±0.6
P4 at Tx (nmol/L)median (range)	2.4 (0.7–7.1)	2.2 (0.9–15.3)	2.0 (0.8–4.5)	2.1 (0.7–7.2)
E2 at Tx (pmol/L)median (range)	587.5 (125–944)	622.4 (212–990)	538 (199–965)	517.5 (163–991)
LH at Tx (IU/L)median (range)	12.9 (2.2–111.0)	12.3 (3.3–105.4)	8.3 (2.5–62.6)	10.6 (2.1–103.8)

   [a] Statistics are mean±SD by default. Otherwise, precisions are given case by case. Tx = treatment.

survival time after treatment intake. In addition, the rank test for homogeneity of these two strata indicates no significant difference, suggesting that pooling the data from the studies was valid.

3.2. Follicular rupture during the posttreatment period

3.2.1. Placebo cycles

Overall, the dominant follicle had ruptured in the 5 days after treatment in all but two placebo cycles (4%). Rupture occurred within 2 and 3 days after treatment in 60% and 80% of the placebo cycles, respectively (Figs. 1 and 2). The mean time from treatment to rupture was 2.3±1.2 days. The mean time in days from the initiation of LH surge to dominant follicle rupture was 2.6±1.2 while the mean time in days from LH peak to rupture was 1.6±0.7 days.

3.2.2. LNG cycles

The dominant follicle persisted for at least 5 days in 14.6% (7/48) of LNG cycles, not different than placebo (4%) (Fig. 1). Almost 80% of the dominant follicles had ruptured within 2 days after treatment (Fig. 2). The mean time from treatment to rupture was 1.9±0.8 days.

3.2.3. UPA cycles

The dominant follicle persisted for at least 5 days in 58.8% (20/34) of UPA cycles overall, a significantly higher proportion than with LNG (p=.0001) (Fig. 1). Four days after

treatment, 68% of dominant follicles had still not ruptured (Fig. 2). The median time from treatment to rupture was 6 days during the UPA cycles versus 2 days in the LNG cycles (p=.0015).

3.2.4. LNG+meloxicam cycles

The dominant follicle persisted for at least 5 days in 38.7% (12/31) of LNG+meloxicam cycles, a higher proportion than with LNG alone (p=.0292) and than placebo (p=.0001). This proportion was lower than UPA cycles although not statistically significant (p=.1384) (Figs. 1 and 2). The mean time from treatment to rupture was 2.2±0.7 days.

3.3. Follicular rupture during the posttreatment period according to LH status at treatment, follicular outcome >5 days after treatment and cycle length

When treatment was administered before the LH peak (both before LH surge onset or at the time of LH surge onset), UPA was the most effective treatment in delaying follicular rupture (19/22=86% of the dominant follicles were still present 5 days after treatment), followed by LNG +meloxicam (10/22=45%). In both of these subgroups, UPA was significantly better than LNG at inhibiting follicular rupture during the period of 5 days following treatment,
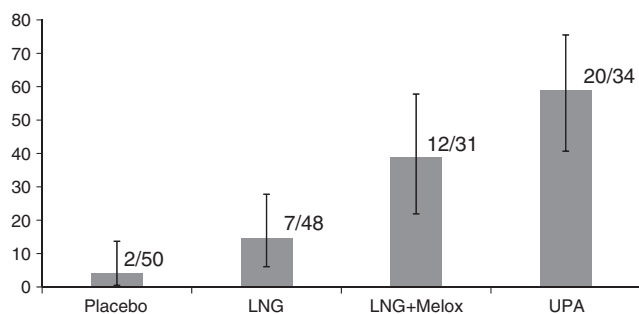

Fig. 1. Proportion (95% CI) of cycles with no follicular rupture at Day 5 following treatment given at lead follicle size ≥18 mm. Fisher's Exact Test, significant differences, UPA versus LNG and UPA versus placebo (p= .0001). LNG+meloxicam versus placebo (p=.0001) and LNG+meloxicam versus LNG (p=.0292).
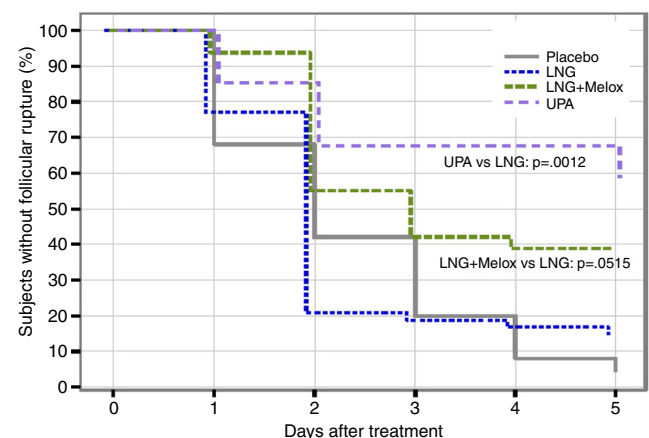

Fig. 2. Survival analysis of time to follicular rupture from treatment intake to the fifth day after treatment by treatment.

Table 3
Proportion of unruptured dominant follicles at 5 days after treatment according to LH status at time of intake

	Placebo *n*=50	LNG *n*=48	LNG+meloxicam *n*=31	Ulipristal acetate *n*=34
Tx before LH surge *n*	0.0% 0/16	25.0% 3/12	55.6% 5/9	100% 8/8 RR* 4 [1.5 – 10.7] (p=.0026)
Tx after LH surge but before LH peak *n*	10.0% 1/10	14.3% 2/14	38.5% 5/13	78.6% 11/14 RR* 5.5 [1.5 – 20.4] (p=.0018)
Tx at LH peak *n*	4.2% 1/24	9.1% 2/22	22.2% 2/9	8.3% 1/12 NS

* Relative Risk of no rupture for ulipristal compared to levonorgestrel. Tx=treatment; NS = non-statistically significant.

while LNG was equally ineffective as placebo in inhibiting follicular rupture when administered before the LH peak. Comparisons between LNG and LNG+meloxicam as well as LNG+meloxicam and UPA were not statistically significant likely due to the small number of cycles when stratified by LH status. It should be noted, that none of the three treatments were effective in inhibiting follicular rupture when administered after the LH peak was present, with rupture occurring shortly after (Table 3).

For the cycles in which the dominant follicle had not ruptured within the 5 days following UPA treatment, the most common outcome (17/34 cycles) was a delayed rupture. Follicle rupture was similarly delayed with a mean time to rupture of 6.9±1.7 and 6.4±0.5 days, when UPA was given before LH surge or after initiated LH surge, respectively. Of note, if rupture was documented when visits occurred twice a week, the earliest possible day of rupture was tabulated.

Luteinized unruptured follicles (LUF) or persistent follicles were the most common outcome in the LNG+meloxicam cycles (11/31), with a proportion significantly higher than in the three other groups (p<.04). LUF and persistent follicles were also the
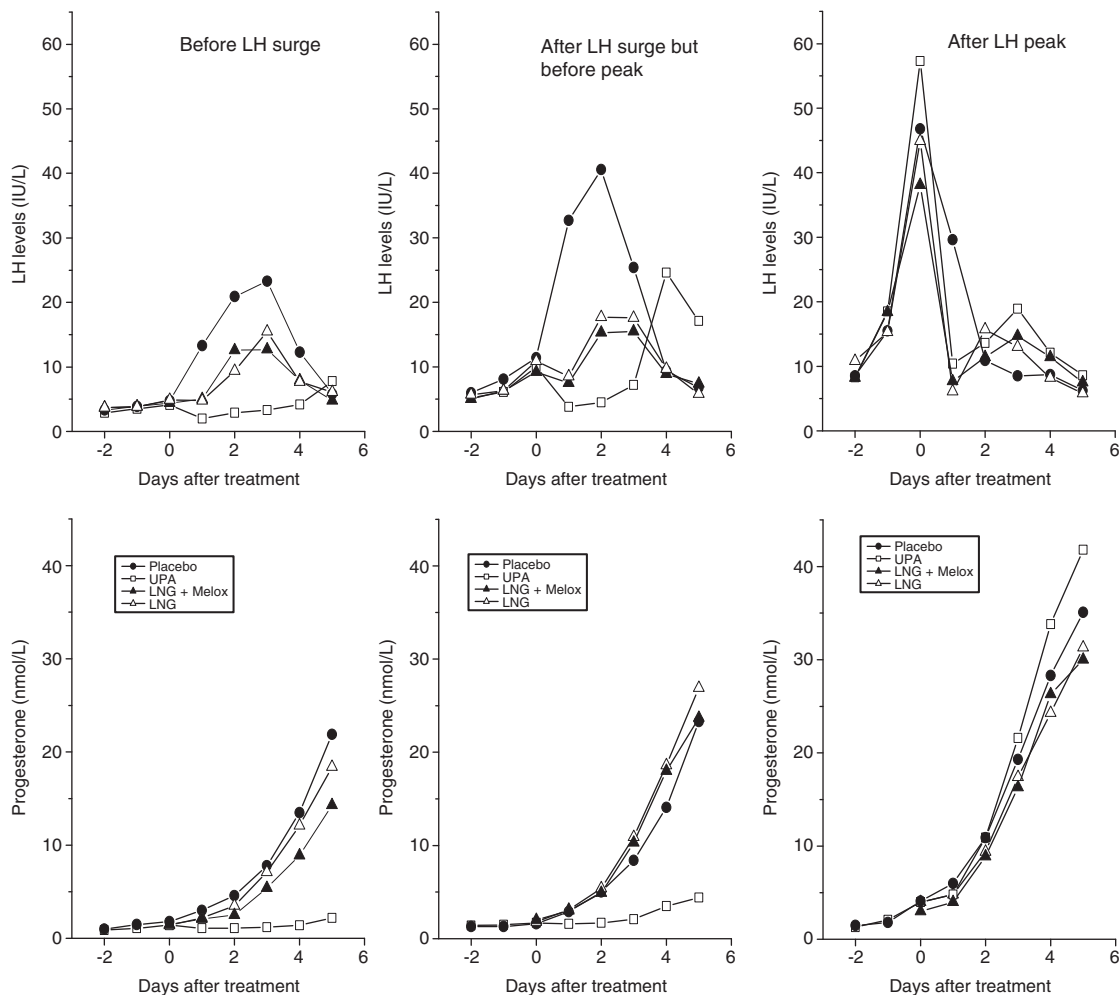

Fig. 3. Mean LH and P levels within the 5 days after treatment stratified by LH status at the time of treatment administration.

outcome of the dominant follicle in 4%, 15% and 9% of the placebo-, LNG- and UPA-treated cycles, respectively.

After rupture (when rupture occurred within 5 days of treatment), the luteal phase length was 13.2±1.9 days in average in the placebo cycles, 12.0±2.1 days in the LNG cycles, 11.6±1.9 days in the LNG+meloxicam group and 13.2±1.8 days in the UPA group. Both LNG alone and LNG+meloxicam-treated cycles had a shorter luteal phase than the UPA and placebo cycles (p<.045). The data indicate that the luteal phase length of UPA cycles with delayed rupture was normal, but since daily visits only took place for 5 consecutive days after treatment, when rupture occurred after this time frame, we do not have the exact day of rupture. Total cycle length (data not shown) was similar in the placebo, LNG and LNG+meloxicam groups (27.3 to 28.2 days), while the UPA cycles were 2 to 3 days longer (mean: 30.8 days).

3.4. Hormones

Treatment induced an immediate drop in mean LH levels to below 7 IU/L on the day following treatment in all treatment groups except placebo. Mean LH levels dropped by nearly 75% (more than 20 IU/L) in the UPA and LNG groups and by 58% (about 10 IU/L) in the LNG+meloxicam group (data not shown).

When treatment was administered before the LH peak, there were differences between treatments (Fig. 3). Following UPA treatment, LH levels remain suppressed for the first 3 days, followed by normal LH peaks (>35 IU/L) that begun on Day 4–5 after treatment. In both LNG groups, LH levels rose to a mean near 15 IU/L on Days 2 and 3 after treatment. However, follicular ruptures that occurred after treatment with LNG or LNG+meloxicam were not preceded by normal LH peaks. In 16/21 (76%) and 10/12 (83%) follicular ruptures following treatment with LNG or LNG+Meloxicam, LH levels preceding rupture never reached a value above 15 IU/L. The LH peaks were either blunted or absent, with maximum levels lower than those observed in the placebo cycles.

All cycles, including placebo, had the same LH profile when treatment was administered after LH peak levels had been reached, with a maximum LH level observed on the day of treatment above 40 IU/L (Fig. 3).

While P levels started to rise as early as the day after treatment in both LNG and placebo cycles, this rise was delayed by 3–4 days in the cycles where UPA treatment was administered, provided that it was taken before LH peak levels had been reached (Fig. 3). Mean P highest level were lower in the LNG and LNG+meloxicam cycles (39.1±16.9 and 34.5±15.6, respectively) than in the UPA (49.2±18.6) and placebo cycles (50.4±16.2) (p<.003).

4. Discussion

The results of the present analysis suggest that UPA is able to delay follicular rupture for at least 5 days in a significantly higher proportion of women than LNG when given in the late follicular phase, at the time when the LH peak is imminent. At this time in the cycle, LNG cannot delay or block ovulation any better than placebo, and follicular rupture occurs shortly and similarly after treatment with LNG or placebo. Since in routine clinical setting we rarely know at what point in the cycle an individual women is, such difference is of crucial importance, especially considering that the probability of conception is highest just before ovulation, and that the vast majority of women seek EC at midcycle when they perceive that their risk of getting pregnant is the highest.

The reason why UPA is more potent than LNG, in the advanced follicular phase, in the presence of an LH surge is unknown. UPA may still have direct effects on P receptor-regulated pathways that modulate rupture of the dominant follicle. It has been hypothesized that a short-lived increase in P is mandatory in the final steps leading to follicular rupture [20], so it is possible that UPA is able to block the ovarian and pituitary effects of this preovulatory P surge and subsequently suppress LH. As a progestin agent, LNG cannot block the preovulatory P signal, and it has furthermore been suggested that LNG administered in the advanced follicular phase, after adequate estradiol priming, may play the role of the progestin trigger to the final ovulatory process inducing LH surge and follicular rupture earlier [21,22]. The data from these studies tend to support this finding, since follicle rupture occurs within 2 days in a higher proportion of LNG-treated women, than in the placebo cycles.

Whether UPA would remain more efficacious than LNG earlier in the follicular phase is unknown; however, a study in which an equivalent dose of 30-mg micronized UPA was administered at midfollicular phase (follicle: 14–16 mm) postponed rupture for a mean of 10.3±1.2 days [17]. On the other hand, LNG is more effective in blocking or delaying follicular rupture when administered earlier in the cycle. When LNG was administered with a follicle between 12 and 17 mm, rupture occurred within the 5 days in only 44% while in 26% the dominant follicles became either a persistent follicle or an LUF, and in 30%, rupture was delayed for over 5 days [15,19]. Similar results have also been shown in other studies [12–14,16].

When meloxicam is added to LNG, their two mechanisms of action probably add to block ovulation, especially when LH has already started to rise. Our results show that adding meloxicam to LNG, more than doubles the proportion of unruptured follicles within 5 days of treatment. The results of the LNG+meloxicam group are encouraging, suggesting that efficacy may be increased as compared to LNG. However, clinical trials to fully evaluate the efficacy and safety of LNG with a PTGS-2 (COX-2) inhibitor must be conducted prior to clinical use. Moreover, evaluation of the potential benefit of adding a PTGS-2 inhibitor to UPA would also be valuable.

UPA mainly delays ovulation, as only three LUFs were observed after UPA treatment. This has clinical implications if UPA is used as an emergency contraceptive at midcycle

since the cycle of treatment may be fertile later in the cycle, at a time when women do not usually think they might be at risk of pregnancy. With LNG, almost all dominant follicles rupture within 5 days after treatment in the advanced follicular phase; therefore, the risk of pregnancy remains at the time of treatment when LNG is administered; however, when administered earlier in the follicular phase, it also may cause delay in rupture.

Notwithstanding potential differences in their biological mechanisms, data from comparative efficacy studies of UPA and LNG show that women who have subsequent unprotected intercourse in the same cycle are at risk of pregnancy with both treatments [23]. Women should be systematically counseled to use a reliable barrier method of contraception after EC until their next menstrual period, regardless of whether the EC agent used is UPA or LNG.

The strength of the clinical study design used across the three pooled trials is that it allows the comparison of treatment effects at a given precise time in the cycle (preovulatory follicular size) in the same subjects (crossover design) and at a precise LH and P status. In this design, the treatment is the only major intervention, allowing the identification of any difference between treatment effects at that specific time in the cycle.

It should be noted that in the three studies pooled in the present analysis, the hormonal definition of the surge initiation and LH peak was based on daily LH measurements and follicular growth monitoring of 100 ovulatory placebo cycles in studies performed in the same two investigation sites. As a result, the categorization of LH status at the time of treatment cannot be as precise as if LH had been measured every 15–20 min in order to identify the variations due to its pulsatility. Therefore, the effect of treatment on LH, while clearly visible in mean levels, is likely underestimated by the methodology. Furthermore, it has to be noted that when displayed by LH status, the number of cycles is very limited. Thus, inferential statistics (CIs or tests) are underpowered: only important clinical differences can be shown statistically different, and it is obvious that with more data, less evident differences could also have been highlighted.

Another limitation is that the present pooled analysis of raw data was conducted post-hoc, not planned at the time when the three original studies were conducted and without a sample size calculation. However, the great similarities of the studies (design, sites, population characteristics and evaluations) and the clinical relevance of the results allow an acceptable degree of confidence in the findings. Although one subject participated in both Study 1 and 2, the protocol and analysis of results for each study were independent. Repeating the analyses excluding the data for this subject from Study 2 did not noticeably change the descriptive results or inferential conclusions presented in this article.

In two recent studies [11,24] in which LNG EC was administered prior to ovulation, women did not become pregnant in spite of the fact that follicular rupture following treatment was observed in some of them, suggesting that some other component of the ovulatory process, such as cumulus expansion, resumption of meiosis or oocyte maturation, must also play a role in the efficacy of LNG EC. Whether the abnormal blunted or absent LH peak preceding follicular rupture in the LNG-treated cycles in which rupture occurs contributes to the alteration of the ovulatory process and has any clinical consequence is unknown but is biologically plausible [25].

Ovulation is a complex process involving many stages at central and ovarian levels and many signaling pathways. Fortunately, this process may be interrupted by different oral EC products that interfere in different ways in the stages of this process. However, the data in the literature clearly show that ovulation can occur, anywhere between Day 10 to 20 of the menstrual cycle, even in women with history of regular cycles [11,26]. The results of this analysis emphasize the importance of taking EC as soon as possible after unprotected intercourse to be able to delay an ovulatory process that might be near. UPA has shown superior efficacy in preventing pregnancies in clinical trials, and its potent ability to delay ovulation, superior to that of LNG even in the advanced follicular phase, may account for this higher efficacy. Nonetheless, data from these pharmacodynamic studies indicate that no oral EC method seems to be able to interrupt the ovulatory process when administered on the day of the LH peak, one of the days of highest probability of conception (1, 3). Follicle rupture within 5 days of treatment occurred in 41% and 85% of the UPA and LNG cycles treated with a follicle $\geq$18 mm in this study. Women deserve clear counseling about available EC methods and their comparative efficacy and the fact that further intercourse after use of EC should be protected with a barrier method since ovulation may be delayed.

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