

Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study

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BACKGROUND: Levonorgestrel (LNG) consistently prevents follicular rupture only when it is given before the onset of the ovulatory stimulus. As locally synthesized prostaglandin (PG) plays a crucial role in follicular rupture and cyclooxygenase-2 (cox-2) catalyses the final step of PG synthesis, we reasoned that adding a cox-2 inhibitor to LNG would prevent follicular rupture even after the ovulatory process had been triggered by the gonadotrophin surge. **METHODS:** Forty-one women were divided into two groups. One was treated when the size of the leading follicle was 15–17 mm ($n = 10$) and the other when it was ≥ 18 mm ($n = 31$). Each woman contributed with one cycle treated with LNG 1.5 mg single dose plus placebo and another treated with LNG + meloxicam (Melox) 15 mg, in a randomized order. Serial blood sampling for the assay of LH and follicular monitoring by transvaginal ultrasound were performed before and after treatment. **RESULTS:** Follicular rupture failed to occur within the 5-day period that followed treatment in 50 and 70% of cycles treated with LNG + Placebo and LNG + Melox, respectively, in the 15–17 mm group ($P = 0.15$) and in 16 and 39% of cycles treated with LNG + Placebo and LNG + Melox, respectively, in the ≥ 18 mm group ($P < 0.052$). The overall proportion of cycles with no follicular rupture or ovulatory dysfunction increased significantly by the addition of Melox to LNG (66 versus 88%, $P < 0.012$; $n = 41$ -matched pairs). **CONCLUSIONS:** The trend towards increased incidence of no follicular rupture when Melox was combined with LNG suggests that the addition of a cox-2 inhibitor has the potential to improve the contraceptive efficacy of LNG by a pre-fertilization effect.

Key words: cyclooxygenase-2 inhibitor/emergency contraception/levonorgestrel/meloxicam/ovulation

Introduction

Emergency contraception (EC) has been considered critical for full exercise of sexual and reproductive rights (Croxtatto and Diaz, 2006) owing to its potential for preventing unplanned or unwanted pregnancies (Consensus statement on emergency contraception, 1995). Although levonorgestrel (LNG) is more effective than the Yuzpe method estrogen combined with LNG (Yuzpe *et al.*, 1974), its contraceptive efficacy is well below that of regular hormonal contraception. The estimated proportion of pregnancies prevented by LNG has been reported in several large studies to vary from 60 to ~90% (Ho and Kwan, 1993; WHO Task Force, 1998; Arowojolu *et al.*, 2002; Von Hertzen *et al.*, 2002).

Various studies have reported that LNG can inhibit or postpone the gonadotrophin surge or follicular rupture or interfere with the formation of the corpus luteum or have no effect on the measured parameters depending on how close to the LH peak the treatment is given (Durand *et al.*, 2001; Hapangama

et al., 2001; Marions *et al.*, 2002; Croxtatto *et al.*, 2004). These studies suggest that disturbances of the ovulatory process caused when LNG is given before the pre-ovulatory gonadotrophin discharge are responsible for most, if not all, prevented pregnancies. At the same time, they suggest that failure of method may happen when it is given after the gonadotrophin surge has triggered the ovulatory process.

Complex biochemical and hormonal processes are involved in the dynamics of follicular development and ovulation (Chabbert Buffet *et al.*, 1998; Richards, 2001). The pre-ovulatory surge of gonadotrophins triggers the synthesis of follicular prostaglandins (PGs), and cyclooxygenase-2 (cox-2) is a key rate-limiting enzyme in their synthesis. PGs play a crucial role in follicular rupture and oocyte-cumulus complex extrusion from the follicle. Cox-2 is expressed in granulosa-lutein cells isolated from women undergoing IVF (Narko *et al.*, 1997). In the rat and bovine ovary, cox-2 expressed in granulosa cells is responsible for increased synthesis of prostanoids during

ovulation, which leads to increased blood flow, vascular permeability and protease production and eventually to rupture of the follicular wall (Richards, 1994). Cox-2 induced in the ovary mediates the expression or activation of proteolytic enzymes that are necessary for the release of oocyte (Richards, 1994; Richards *et al.*, 1995). Animal studies have shown that cox-2 inhibitors can prevent follicular rupture (Salhab *et al.*, 2001; Mizuyachi *et al.*, 2002; Salhab *et al.*, 2003) and oocyte release (Duffy and Stouffer, 2002), and cox-2-deficient mice fail to ovulate (Lim *et al.*, 1997).

Non-selective cox inhibition in women having an autoimmune disease increases the incidence of luteinized unruptured follicles (LUFs) (Killick and Elstein, 1987; Smith *et al.*, 1996) and has been found to be associated with infertility (Akil *et al.*, 1996). Treatment of healthy women with the cox-2 inhibitor rofecoxib (25 mg) for 9 days starting with a follicular diameter of 14–16 mm results in delayed follicular rupture (Pall *et al.*, 2001).

On the basis of the above antecedents, we explored the possibility of enhancing the contraceptive efficacy of LNG by adding an agent that will disturb the ovulatory process after it has been triggered. To this end, we tested whether LNG combined with a cox-2 inhibitor is more effective than LNG alone for preventing follicular rupture in women.

Materials and methods

The study was conducted at ICIMER in Santiago, Chile and PROFAMILIA in Santo Domingo, Dominican Republic. Approval was granted by the Ethics Committee of each centre and by the Eastern Virginia Medical School Institutional Review Board.

Volunteers

A total of 41 healthy women were enrolled, 21 at ICIMER and 20 at PROFAMILIA, after signing informed consent. Volunteers were 18–39 years old, with regular menstrual cycles within the range of 24–32 days in the previous 3 months, non-lactating, protected from pregnancy by surgical sterilization or non-hormonal intrauterine devices (IUDs) and had no contraindications to the use of oral contraceptives.

Treatments and randomization

LNG pills were two tablets of LNG 0.75 mg: Postinor-2 (Grünenthal Chilena Ltd., Chile at ICIMER) or Imediat-N (Gador S.A., Buenos Aires, Argentina at PROFAMILIA). The cox-2 inhibitor chosen was meloxicam (Melox) 15 mg, provided as tablets for oral use (Meloxicam (Chile), Chemopharma S.A., Chile, at ICIMER, and Mobicox (Dominican R), Böehringer Ingelheim, Canada, Ltd. at PROFAMILIA). Placebo and drug pills were sealed within non-transparent capsules by Laboratorios Silesia in Santiago, Chile. Capsules were placed in vials numbered to match a randomization list. Volunteers were randomized using a computer-generated random block number table, stratified by follicular size and order of drug administration, in a 3:1 ratio. The study medications assigned to each individual were taken at once at the clinic.

Study design

This was a two-centre, randomized, double-blind, placebo-controlled study. It was designed to determine whether LNG combined with Melox improves the efficacy of LNG alone for disrupting the ovulatory process. We compared the effect of treatment with LNG + Placebo versus LNG + Melox, given in the advanced follicular phase, on the outcome

of the leading follicle, including the occurrence and timing of follicular rupture. LH and progesterone serum levels were measured at selected time points deemed convenient for the interpretation of ultrasonographic data. Bleeding patterns and incidence of adverse events associated with treatment were also compared.

Each woman was assigned to either one of the two groups, differing in the diameter of the largest follicle at the time of treatment. Women in one group were treated when the dominant follicle reached 15–17 mm ($n = 10$) and in the other group when it reached ≥ 18 mm ($n = 31$). Each subject was in the study for two treated cycles, separated by a resting cycle. One cycle was treated with LNG + Melox and the other with LNG + Placebo, in a randomized order.

Treatment was administered at the clinic, and no replacement was given to repeat intake in case of vomiting. No anti-emetic drugs were prescribed.

Follow-up

The intervention variables under study were the drug added to LNG and the timing of treatment administration. The primary response variable was the outcome of the leading follicle within 5 days after treatment administration, including the occurrence and timing of follicular rupture. Secondary response variables were LH and progesterone levels in serum, bleeding pattern and the incidence of adverse events.

The following procedures were done in treated cycles.

Ultrasonography

Transvaginal ultrasonography (TVU) was used to assess the mean diameter (two-axis measurements) of the largest (leading) follicle and the occurrence of follicular rupture. Starting on day 8 of the cycle, TVU was done three times per week, until the follicular diameter pre-assigned for drug administration was reached. Then, daily TVU was performed for the next 5 consecutive days. Thus, a total of six daily TVUs were performed, including the one done immediately before administering the drugs. These six TVUs encompass, from the first to the last, five periods of 24 h or 5 days. This interval will be referred to as the 5-day period. At the end of the daily follow-up period, TVU was continued twice a week until menses, if follicular rupture had not occurred. TVU was performed with a real-time scanner, using a Medison SA 600C ultrasound system, 7.5-MHz vaginal transducer in Santiago and Shimadzu SDU-400 using a 5.0-MHz vaginal transducer at Santo Domingo. Operators at both centres had been previously trained together to match their assessment of follicular measurements.

Blood sampling

A blood sample was taken immediately before starting treatment and daily thereafter for 5 consecutive days. LH was measured in the daily samples and progesterone only in the last sample. To avoid missing the initiation of the LH surge in the ≥ 18 mm group, we took additional daily blood samples for measuring LH levels, starting when a 14–15 mm follicle was observed.

Recording chart

All subjects were given a diary to record adverse events and bleeding during the study, which was checked at each visit.

Serum assays

Hormone assays were done locally at both centres, as previously described. Serum LH was measured using enzyme immunoassay (Immunometrics, UK Ltd.) (Croxtatto *et al.*, 2006), and progesterone was measured using a radioimmunoassay (DPC, Diagnostic Products Corporation, Los Angeles, CA, USA) (Croxtatto *et al.*, 2004). All samples from the same subject were analysed in the same assay.

Data analysis

The effect of treatment on the occurrence and timing of follicular rupture was focused to the 5-day period starting on the day of treatment. Spermatozoa do not remain fertile longer than 5 days after coitus (Wilcox *et al.*, 1995); therefore, if follicle rupture does not occur within this period, the probability of conception would be zero when intercourse has taken place before treatment (Wilcox *et al.*, 1995). The proportion of cycles presenting no follicular rupture, ovulatory dysfunction (discussed below) or ovulation within the 5-day period was compared between LNG + Placebo and LNG + Melox, stratified by timing of treatment administration relative to follicular size as well as to the LH surge.

Each cycle was classified according to the occurrence of follicular rupture within the 5-day period and hormone levels available. The following end-points and definitions were pre-established for data analysis:

(i) Length of the cycle—the number of days from the first day of menses until the day before the next menstrual-like bleed both inclusive.

(ii) Follicular rupture—abrupt disappearance or a reduction in size of at least 50% of the echo-image of a leading follicle that had attained at least 15 mm in diameter.

(iii) Ovulation—follicular rupture preceded 24–48 h earlier by an LH peak of at least 21 IU/l and followed by serum progesterone concentration >12 nmol/l.

(iv) Ovulatory dysfunction—follicular rupture not preceded 24–48 h earlier by an LH peak or preceded by a blunted LH peak (<21 IU/l) or not followed by elevation of serum progesterone level >12 nmol/l.

(v) Persistent follicle—a follicle developing beyond 15 mm and persisting for at least 1 week, without rupture and without increase in progesterone levels.

(vi) LUF—persistent echo-image of a follicle, associated with serum progesterone level >12 nmol/l.

(vii) Follicular atresia—no further growth or reduction in size of the dominant follicle.

When the LH serum level was >15 IU/l on the same day of treatment, it was considered that treatment was given after the ovulatory process had been triggered by the gonadotrophin surge, and the cycle was classified as ‘treatment after the onset of the LH surge’.

The number of cycles presenting ovulation, ovulatory dysfunction or no follicular rupture, within the 5-day period, was compared between treatments by McNemar’s test. This non-parametric test uses the number of discordant pairs among matched pairs, to discriminate differences due to individual response from differences attributable to treatment. Differences in the distribution of follicular outcomes in subsets of cycles with limited number of matching pairs (e.g. subset in which cycles with no LH peak were excluded, Table II) were analysed using chi-square test. Differences in mean progesterone concentration were analysed using Student’s *t*-test.

All statistical analyses were performed using Graph Pad Prism software, version 3.02. Data are presented as mean ± SEM unless otherwise stated. Statistical tests used are indicated in the text and tables, as appropriate.

Results

All subjects enrolled completed the study. Age, weight, height and BMI of the volunteers did not differ between the centres; therefore, data were pooled together. Data from 41 cycles treated with LNG + Placebo and 41 cycles treated with LNG + Melox were analysed.

Lack of follicular rupture within the 5-day period

The proportion of cycles presenting no follicular rupture within the 5-day period is summarized in Table I. Lack of follicular

Table I. Proportion of cycles presenting no follicular rupture, ovulatory dysfunction or ovulation within the 5-day period following administration of a single dose of LNG (1.5 mg) + Placebo or LNG + Meloxicam (15 mg)

Classification	LNG + Placebo		LNG + Meloxicam		Both	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
15–17 mm						
No rupture	5/10	50	7/10	70	12/20	60
Ovulatory dysfunction	4/10	40	3/10	30	7/20	35
Ovulation	1/10	10	0/10	0	1/20	5
≥18 mm						
No rupture	5/31	16	12/31*	39	17/62	27
Ovulatory dysfunction	13/31	42	14/31	45	27/62	44
Ovulation	13/31	42	5/31*	16	18/62	29
All no rupture	10/41	24	19/41	46		
All disrupted ^a	27/41	66	36/41**	88		

LNG, levonorgestrel.

^aNo rupture and ovulatory dysfunction.

P* = 0.052 and *P* = 0.012 versus LNG + Placebo; McNemar’s test.

Table II. Incidence of no follicular rupture, ovulatory dysfunction and ovulation according to timing of treatment relative to the onset of the LH surge^a

Treatment and outcome	LNG + Placebo		LNG + Melox		% Points difference w/Melox
	<i>n</i>	%	<i>n</i>	%	
After the onset of the LH surge					
No rupture	2/14	14	3/11	27	+13
Ovulatory dysfunction	1/14	7	3/11	27	+20
Ovulation	11/14	79	5/11	46	–33
Before the LH surge					
No rupture	2/14	14	6/16	37	+23
Ovulatory dysfunction	9/14	64	10/16	63	–1
Ovulation	3/14	22	0/16	0	–22
All no rupture ^b	4/28	14	9/27	33	+19
Ovulatory dysfunction ^b	10/28	36	13/27	48	+12
All ovulation ^b	14/28	50	5/27	19	–31

LNG, levonorgestrel.

^aA total of 27 cycles not presenting LH surge were excluded from this table.

^bDistribution of outcomes between treatments are statistically different *P* < 0.005 (chi-square test).

rupture was more frequent in cycles treated when the leading follicle was 15–17 mm than with larger follicles and was more frequent in cycles treated with LNG + Melox than with LNG + Placebo. However, in the analysis stratified by follicular size, these differences were not statistically significant. In the ≥18 mm group, the difference between the two treatments (5/31 versus 12/31) was at the borderline of statistical significance (*P* = 0.052; McNemar’s test).

In approximately a quarter of all cycles, treatment was given after the onset of the LH surge. This occurred in 14 cycles treated with LNG + Placebo and in 11 treated with LNG + Melox (Table II). We expected a higher incidence of no follicular rupture in these cycles after treatment with LNG + Melox, and in fact it was twice as high as with LNG + Placebo, but the sample size was too small to reach statistical significance. Most of the other 22 cycles corresponded to ovulation (LNG + Placebo, *n* = 11; LNG + Melox, *n* = 5) (Table II). The most

striking differences found in Table II are the incidence of ovulation after LNG + Placebo when treatment was after or before the onset of the LH surge (79 versus 22%, respectively) and the incidence of ovulation with the two treatments when they were given after the onset of the LH surge (79% with LNG + Placebo and 46% with LNG + Melox). On one hand, these data confirm the low efficacy of LNG to prevent ovulation once the process has been triggered by the gonadotrophin surge, and on the other hand, they show partial ability of Melox to intercept follicular rupture at the dose used. The bottom of Table II shows the distribution of follicular outcomes within the 5-day period when cycles lacking an LH peak were excluded. The data indicate that the frequency of no rupture and the frequency of ovulatory dysfunction are increased while that of ovulation is decreased by the addition of Melox ($P < 0.005$ chi-square test).

The most frequent outcome of follicles that did not rupture within the 5-day period was persistent follicle, being similar between treatments (LNG + Placebo = 6/10, 60%; LNG + Melox = 13/19, 68%). The remaining cycles had LUF, except for a single one with follicular atresia. Mean maximal follicular size among anovulatory cycles did not differ between treatments (LNG + Placebo = 37.6 ± 2.7 mm; LNG + Melox = 36.0 ± 6.0 mm; mean \pm SD). The highest diameter did not exceed 50 mm.

Ovulatory dysfunction within the 5-day period

As summarized in Table I, there was no effect of the addition of Melox on the incidence of cycles with ovulatory dysfunction. In most cases, this condition was characterized by follicular rupture not preceded by an LH peak (LNG + Placebo = 16/17; LNG + Melox = 12/17). Three other cases had blunted LH, and the remaining one had the LH peak coincident with day of follicular rupture. Only in 5 of 34 cycles with ovulatory dysfunction the progesterone level measured in the sixth day blood sample was <12 nmol/l. Follicular diameter attained before rupture was LNG + Placebo = 19.3 ± 1.5 mm and LNG + Melox = 20.2 ± 1.9 mm ($n = 17$ each; mean \pm SD).

When cycles with no follicular rupture or ovulatory dysfunction were added together, the overall percentage of disrupted ovulatory processes among cycles treated with LNG + Melox was significantly increased over LNG + Placebo (Table I; 88 versus 66%; $P < 0.012$; McNemar's test).

Ovulation within the 5-day period

The proportion of cycles in which ovulation took place within the 5-day period was decreased after giving LNG + Melox with a leading follicle of ≥ 18 mm, but the difference (13/31 versus 5/31) was at the borderline of statistical significance ($P = 0.052$; McNemar's test) (Table I). The mean follicular diameter attained before follicular rupture did not differ between treatments (LNG + Placebo = 19.7 ± 2.2 mm, $n = 14$; LNG + Melox = 21.1 ± 3.8 mm, $n = 5$; mean \pm SD).

Mean progesterone levels on day 5 after treatment are summarized in Table III, stratified by follicular outcome. Mean progesterone concentration was lower in unruptured follicles than in the other two categories and it was also lower, in at least two of the outcomes, when treatment was given with smaller as compared with larger follicles. Mean progesterone

Table III. Mean progesterone levels on day 5 after treatment according to follicular outcome

Follicle size at treatment Outcome	Progesterone (nmol/l)	
	LNG + Placebo (n)	LNG + Melox (n)
15–17 mm		
No rupture	6.3 ± 3.2 (5)	6.2 ± 1.7 (7)
Ovary dysfunction	13.6 ± 5.1 (4)	14.6 ± 2.2 (3)
Ovulation	26.7 (1)	(0)
≥ 18 mm		
No rupture	9.0 ± 3.4 (5)	11.8 ± 6.9 (12)
Ov. Dysfunction	27.7 ± 2.6 (13)	28.0 ± 2.6 (14)
Ovulation	27.3 ± 2.6 (13)	34.0 ± 1.6 (5)*

LNG, levonorgestrel.

* $P < 0.025$ versus LNG + Placebo (Student's t -test).

concentration was almost identical with the two treatments, except in ovulatory cycles of the 18 mm group, in which progesterone levels were significantly higher after LNG + Melox treatment than after LNG + Placebo treatment ($P < 0.025$, Student's t -test). Detailed scrutiny of the data showed that this difference was associated with the occurrence of shorter intervals between the LH surge and progesterone measurement in cycles treated with LNG + Placebo than with LNG + Melox. From progesterone levels summarized in Table III, it can be inferred that, as pointed out earlier, most of the ovulatory dysfunctions were classified as such owing to absent, blunted or mistimed LH peak associated with follicular rupture, rather than progesterone level not surpassing the 12-nmol/l threshold. It is interesting to note that, regardless of treatment given in the 15–17 mm group, ovulatory dysfunction was associated with half as much progesterone production as compared with ovulation. This was not the case for the 18 mm group, suggesting that there seems to be a critical stage of follicular maturation after which LNG is unable to inhibit what appears to be an 'LH surge-independent luteinization'.

Follicular outcome after the 5-day period

All follicular ruptures took place within the 5-day period. Unruptured follicles disappeared within the same or the following cycle, and none was symptomatic.

Bleeding pattern

Cycle length did not differ between groups. Eighty-nine per cent of cycles were of normal length (24–32 days), 7% were short and 4% were long. The mean length of the menstrual cycle was 28.5 ± 8.0 and 28.4 ± 8.1 days for LNG + Placebo and LNG + Melox, respectively (mean \pm SD).

Adverse events

None of the volunteers reported vomiting, whereas two subjects in each treatment group reported nausea. Other adverse events reported were stomach ache, vaginal discharge, lower abdominal pain, headache, sleepiness, diarrhoea, dizziness and breast tenderness. There was no difference in the incidence of the adverse events between treatments. Twenty-two subjects had no complaint at all.

Discussion

The results of this pilot study confirm that administration of LNG during the follicular phase interferes with the ovulatory process, either preventing follicular rupture or causing ovulatory dysfunction. Overall, 77% of the cycles (63 of 82) were affected in either way, closely matching previous data (72%) (Croxatto *et al.*, 2004). By and large, the rate of no follicular rupture is inversely related to the size of the leading follicle at the time of treatment, whereas the rate of ovulatory dysfunction does not follow this trend. The addition of Melox to a single dose of LNG, administered during the advanced follicular phase, increased its efficacy for blocking follicular rupture from 14 to 33%, in cycles in which the LH surge was not suppressed by the treatment (Table II). Likewise, when the mean diameter of the leading follicle at the time of treatment was ≥ 18 mm, a condition in which the efficacy of LNG to prevent follicular rupture is much weaker, Melox increased the rate of no follicular rupture. In fact, the percentage of follicular ruptures prevented was more than doubled (16 versus 39%) by LNG + Melox as compared with LNG + Placebo, when they were given with an 18 mm follicle. The importance of this finding resides in the fact that women taking LNG at a late stage in their follicular phase are less protected from pregnancy by this mechanism. Therefore, doubling the efficacy to prevent follicular rupture in those cases could save an additional number of women from getting pregnant.

When LNG is given before the LH surge, the surge is suppressed or blunted or its temporal relationship with follicular rupture becomes abnormal (Croxatto *et al.*, 2004). Oocytes that have been exposed to such abnormal endocrine milieu have been shown to exhibit impaired fertilizability (Cohlen *et al.*, 1993; Verpoest *et al.*, 2000). These effects of LNG on LH surge were not counteracted by the addition of Melox, and if anything, they were reinforced. When data from both follicular size groups were combined (15–17 mm plus ≥ 18 mm), the incidence of no follicular rupture increased from 24 to 46% by the addition of Melox, whereas the incidence of ovulatory dysfunction did not change (41% with or without). Thus, by almost doubling the incidence of no follicular rupture, the addition of Melox could have a significant impact on the number of unwanted pregnancies prevented by LNG when women need to use EC.

We assumed that administration of LNG + Melox after the onset of the LH surge would be the best scenario to test the hypothesis that a cox-2 inhibitor given after the ovulatory process has been triggered would still prevent rupture. Under these conditions, recorded in only a small number of cycles, treatment with LNG + Melox was twice as effective as LNG + Placebo for preventing follicular rupture. On the contrary, when LNG + Placebo was administered after the onset of the LH surge, 11 of 14 cycles (79%) were ovulatory, confirming that LNG alone has low efficacy for preventing follicular rupture once the ovulatory process has been triggered by a normal gonadotrophin surge (Croxatto *et al.*, 2004). Conversely, LNG + Melox disturbed the ovulatory process in 6 of 11 cycles, in which treatment was given once ovulation had already been triggered by the LH surge.

Although the study was not designed to determine the mechanism through which Melox interferes with the ovulatory process, the bulk of the current data and that derived from animal experiments suggest that it is through a direct effect on the follicle.

No serious adverse events occurred. The incidence of adverse events did not change with the addition of Melox, and they were not different from those reported previously by other authors. In most cases, the length of cycles was unaffected which can be considered an advantage in real life.

In summary, the main consequence of adding Melox to LNG was to disturb the ovulatory process in a higher proportion of cases than with LNG alone. Overall, the proportion of cycles with disturbed ovulation increased 30% over LNG + Placebo (66 versus 88%) and in the higher risk group (≥ 18 mm), in which LNG alone is less likely to prevent ovulation; the proportion increased nearly 50% (58 versus 84%). Therefore, we surmise that the use of LNG for EC in conjunction with a cox-2 inhibitor has a potential to improve the contraceptive efficacy of LNG alone.

The results of this pilot study are sufficiently encouraging to investigate whether a more potent cox-2 inhibitor or higher dose or more prolonged treatment can achieve a higher efficacy.

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