Original research article

Effect of oral administration of a continuous 18 day regimen of meloxicam on ovulation: experience of a randomized controlled trial☆,☆☆

C. Jesam⁎, a,c, A.M. Salvatierra a, J.L. Schwartzb, A. Fuentesc, H.B. Croxatto d

a Instituto Chileno de Medicina Reproductiva (ICMER), José Victorino Lastarria 29, apt. 101, Santiago, Santiago, Chile, 8320165
b CONRAD/Eastern Virginia Medical School, 1911 Fort Myer Drive (Suite 900), Arlington, VA 22209
c Instituto de Investigaciones Materno Infantil (IDIMI), Faculty of Medicine Universidad de Chile, Santa Rosa 1234, Santiago, Santiago, Chile, 8360160
d Faculty of Medicine, Universidad Andrés Bello, Echaurren 283, Santiago, Santiago, Chile 8370071

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Abstract

Background: Cyclooxygenase-2 (COX-2) is expressed in all female reproductive organs. Therefore, inhibitors of COX-2 may affect reproductive function. We evaluated the effect of extended administration of meloxicam on ovulation and the menstrual cycle. Our hypothesis was that meloxicam administered from menstrual cycle day 5-22 could interfere with follicular rupture, without disrupting the menstrual cycle, and could be a potential non-hormonal contraceptive method.

Methods: The study was conducted in 56 healthy sterilized women. Before the onset of treatment and after the end of treatment, participants were observed during a control cycle to ensure that they had progesterone (P₄) serum levels (>12 nmol/l) consistent with ovulation. Participants were treated for 18 days, during three consecutive cycles. They were randomized to 15 or 30 mg/day. The menstrual cycle was monitored with serial ultrasound and hormone assays in blood.

Results: Fifty-six volunteers completed the study. In 55% of cycles treated with 15 mg/day and in 78% of cycles treated with 30 mg/day (p < 0.001) we observed dysfunctional ovulation defined as 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 an elevated serum P₄ level >12 nmol/l. Ovulation was observed in 44.6% and in 21.7% of women in the lower dose group and the higher dose group, respectively. There were no differences between the two doses in other parameters measured. There were no serious adverse events and adverse events were not different between doses or between control and treated cycles.

Conclusions: Although administration of meloxicam on menstrual cycle days 5-22 resulted in a dose-dependent inhibition of ovulation, more than 20% of subjects had normal ovulation with the highest dose.

Implications: Previous studies have shown that oral meloxicam can delay follicle rupture. This study investigated daily oral meloxicam as a non-hormonal contraceptive. Since ovulation occurs in over 20% of cycles even with a high dose of 30 mg daily, it is not likely that the approach would be a highly effective contraceptive strategy.

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Keywords: NSAIDs; Female contraception; Ovarian cycle; Delayed ovulation; LUF

1. Introduction

Hormonal contraceptives are an effective and prevalent method for pregnancy prevention. However, some women have contraindications to hormone use, and some are concerned about possible risks and would prefer using non-hormonal methods. We evaluated the effect of meloxicam, a non-steroid anti-inflammatory drug (NSAID), on the ovulatory process when administered during 18 consecutive days (cycle days 5-22) starting in the early follicular phase, which covered all possible days of ovulation [1]. This drug inhibits cyclooxygenase, an essential enzyme in the production of prostaglandins, which play a crucial role in ovulation [2].

Previous studies [3–6] have shown that drugs inhibiting cyclooxygenase delay ovulation and null mutation of the COX-2 gene results in defective ovulation and infertility in
mice [7,8]. A recent study indicated that a selective inhibitor of COX-2, celecoxib did not have this effect [9].

In a previous study by our group, meloxicam was given for 5 consecutive days beginning when the dominant follicle had reached a diameter of 18 mm [4]. In 20/22 (91%) of women treated, ovulation was delayed for more than 48 hours. We hypothesized that if meloxicam was given continuously and initiated in the early follicular phase, the treatment could delay or prevent follicular rupture in a greater percentage of cases. Meloxicam has the advantage of being inexpensive and well tolerated [4], although the use of a higher dose has not been evaluated in safety trials.

2. Materials and methods

2.1. Study design

This was a randomized, double blind dose finding study at the Instituto Chileno de Medicina Reproductiva (ICMER), Santiago, Chile. The study was approved by the local Scientific and Ethics Review Committee and by the Eastern Virginia Medical School Institutional Review Board.

Healthy volunteers, with proven fertility, aged 18 to 40 years with regular menstrual cycles (24-35 days) were eligible for inclusion if they had been surgically sterilized in the past, were non-lactating, and had no contraindications for the use of COX-2 inhibitors. Volunteers gave informed consent and agreed to participate during 5 menstrual cycles. Volunteers were enrolled and randomized 1:1 to either 15 or 22. Thirteen additional placebo tablets were supplied to be initiated on menstrual cycle day 1, followed by 18 meloxicam tablets to be taken from menstrual cycle day 5-22. Thirteen additional placebo tablets were supplied to be taken from the 23rd day of the cycle until the first day of menses when participants were instructed to start a new blister pack.

The tablets were to be taken at home after breakfast. The hour of the intake was recorded on a diary card. Participants and investigators were blind to dose until all data collection and analysis were completed.

Blister packs were numbered to match an ad hoc randomization list by Andrómaco Laboratories S.A., Santiago, Chile. The study coordinator provided the assigned treatment according to the randomization list.

Trial registration number is NCT01346137.

2.2. Follow-up

In the first control cycle two blood samples were drawn to measure P₄ levels in serum on days 19±1, 22±1 or 26±1 depending on the cycle length. At least one P₄ value >12 nmol/L was required in order to be eligible for enrollment.

During treatment cycles trans-vaginal ultrasound (TVU) was performed three times a week starting on day 8±1 of each cycle to assess the mean diameter of the leading follicle. When the follicle reached 15 mm, TVU was performed daily for 5 consecutive days to determine the occurrence of follicular rupture, defined as an abrupt >50% reduction in size. We chose this schedule of observation because once the follicle reaches a diameter of 15 mm, rupture occurs within the next 5 days in 76% of cycles [10].

After completion of 5 days of daily TVU or an observed follicular rupture, whatever occurred first, TVU was performed twice a week to follow corpus luteum or luteinized follicle development. Each participant started the next treatment cycle on the first day of bleeding, for a total of three cycles.

We used a Medison SA 6000C or ALOKA prosound SSD-3500SX ultrasound scanner system, with a 7.5-MHz vaginal transducer (Sony Corp, Tokyo, Japan).

During treatment cycles, blood samples were drawn daily for 5 consecutive days starting when the leading follicle had reached a diameter of ≥15 mm to detect the LH surge. Blood samples were also drawn on days 8, 10, 12, 14, 17 and 19±1 to measure Estradiol (E₂) and on days 22, 24, 26 and 28±1 day to measure P₄.

In the post treatment control cycle, P₄ was measured on the same days as in the pre-treatment cycle and hemoglobin was measured on day 22±1.

2.3. Recording chart

During the entire study, all participants kept a diary to record the time of drug intake, occurrence and severity of adverse events, concomitant medications used, and bleeding data. This diary was reviewed at each visit and the data were recorded in the participant clinical record.

2.4. Serum assays

LH, E₂, P₄ and hemoglobin were assayed locally using standardized laboratory procedures. For hormone measurements, all samples from the same subject were run simultaneously. Serum LH was assessed using enzyme immunoassay (EIA, Immunometrics, UK Ltd.). For low- and high-quality control samples, the inter-assay coefficient of variation was 6.0 and 7.4%, respectively, and the intra-assay coefficient of variation was 3.5 and 5.1%, respectively. E₂ and P₄ were measured using a radioimmunoassay (Siemens Healthcare Diagnostics Inc., Los Angeles, CA, USA). For low- and high-quality control samples, the inter-assay coefficient of variation was 5.7 and 4.6% for E₂ and 6.8 and 5.3% for P₄, respectively; and the intra-assay coefficient...
of variation was 5.1 and 4.0% for E2 and 4.0 and 3.9% for 
P4, respectively.

2.5. Data analysis

Sample size calculation was based on the power to detect differences in rates of delayed follicular rupture (more than 48 hours from LH surge) between dosing groups. Obtaining cycle data from 25 women in each group provided greater than 80% power to detect difference in rates of 35% or more using a two-sided \(\alpha=0.05\) level test. Obtaining three repeat cycles of use data from each enrolled woman provided 80% power for even smaller differences in rates of dysfunctional versus ovulatory cycles per dose.

We estimated that up to 10% of enrolled participants would not complete the study, and planned to enroll 28 women per group to achieve at least 150 treatment cycles and 100 control cycles (i.e., 25 completers in each dose group).

Cycles were classified according to the occurrence of follicular rupture within the 5-day period and hormone concentrations of the cycle. The following end-points and definitions used by our group in previous studies [11], were pre-established for data analysis using ultrasound and hormonal parameters (which both correlate with ovulation):

1. Length of the cycle: number of days from the first day of menses until the day before the next menstrual-like bleeding, both inclusive.
2. Length of the luteal phase: number of days from the first day after the LH peak until the day before the next menstrual-like bleeding.
3. 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, but not more than 25 mm.
4. Ovulation: follicular rupture preceded 24–48 h earlier by an LH peak of at least 21 IU/l and followed by serum P4 concentration > 12 nmol/l.
5. 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 an elevation of serum P4 level > 12 nmol/l.
6. Luteinized unruptured follicle (LUF): persistent echo-image of a follicle associated with P4 level > 12 nmol/L. The appearance of these echoimages maintains the ovoid form of pre ovulatory follicles and are clearly different from luteum corpus image where the echo image turns irregular with a high signal using power doppler.

The proportion of treated cycles with ovulation; ovulatory dysfunction or luteinized un-ruptured follicles were compared between doses. Differences in the number of cycles with ovulation, ovulatory dysfunction or follicular rupture were analyzed by Chi square test by 2 by 3 tables. A t-test was used to analyze differences in the length of the cycles, length of luteal phase, number of bleeding days, and highest values of E2, P4 and LH between doses.

The proportion of women reporting adverse events during treatment were compared across different doses using Fisher’s exact test or Chi-square test as appropriate.

Data are presented as mean±SEM unless otherwise stated. Statistical analyses were performed using SPSS (version 12).

3. Results

A total of 56 healthy sterilized female volunteers were enrolled between January 24th, 2011 and July 17th, 2011 and 55 women completed the study. Each participant was randomized to one of the doses of meloxicam. One participant in the 30 mg dose group completed only two treatment cycles. One cycle in the 15 mg dose was excluded from the analysis because the participant missed 4 active tablets during the third treated cycle. A total of 166 treated cycles were analyzed, split equally between the two doses (Fig. 1).

Anthropometric measures of the participants are shown in Table 1. There were no statistical differences between the two dose groups. All women had ovulatory pretreatment cycles with P4 values that ranged from 16.7 to 94.6 nmol/l.

3.1. Normal ovulation

Ovulation occurred in 44.6% and 21.7% of the cycles treated with the 15 mg and 30 mg dose, respectively (p<0.001) (Table 2).

3.2. Ovulatory dysfunction

Ovulatory dysfunction was observed in 34.9% and 42.2% of the cycles treated with the 15 mg and the 30 mg dose, respectively (Table 2).

3.3. LUF

LUF was observed in 20.2% and in 36.1% of cycles treated with the 15 mg and the 30 mg dose, respectively (Table 2). All women with LUF eventually presented signs of a ruptured follicular according to TVU, before the onset of the next menstrual bleeding.

We found that 55.4% of cycles in the 15 mg group and 78.3% in the 30 mg group (p<0.001) presented either ovulatory dysfunction or LUF cycles. With both doses, dysfunctional and LUF cycles were characterized by larger follicular diameters than those observed in ovulatory cycles (Table 3).

All treated cycles presented an LH peak, although in 6 dysfunctional cycles we found a blunted LH peak (4 with the lower dose and 2 with the higher dose). However, the mean of the highest LH level was normal (>21 IU/L) in cycles treated with both doses and was not different between ovulatory, dysfunctional or LUF cycles (Table 4). The mean of the highest level of estradiol was not different between cycles in the different groups. All dysfunctional or LUF cycles had lower P4 levels during their luteal phase compared to ovulatory cycles (p<0.001), however the values were still within the normal range.
We observed a greater proportion of normal ovulations occurring within 2-3 days of the LH surge in the lower dose compared to the higher dose ($p<0.001$). We included 5 cycles in the 15 mg group and 7 in the 30 mg group who demonstrated follicular rupture at 72 h after LH surge (Table 5).

A greater proportion of dysfunctional ovulations occurred after $\geq 3$ days of the LH surge with the higher dose compared to the lower dose ($p<0.001$) (Table 5).

When we reviewed the proportion of cycles in each category, there were no noticeable differences between consecutives cycles of the same woman, indicating no cumulative effect of the drug.

### 3.3.1. Cycle length and bleeding patterns

Cycle length and duration of luteal phase of treatment cycles did not differ between doses or between different outcomes of the leading follicles (Table 4) or from the control cycles (data not shown). There were no differences in the number of bleeding days between doses or between treatment and control cycles.

### 3.3.2. Adverse events

Adverse events were observed in 33.7% of the cycles in women treated with the lower dose and in 27.7% with the

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**Table 1**

Antropometric data of 56 volunteers enrolled

<table>
<thead>
<tr>
<th></th>
<th>Dose 15 mg n=28</th>
<th></th>
<th>Dose 30 mg n=28</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.5</td>
<td>2.7</td>
<td>29–40</td>
<td>36.6</td>
</tr>
<tr>
<td>Parity</td>
<td>3.1</td>
<td>0.7</td>
<td>2–4</td>
<td>3.3</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>68.5</td>
<td>12.8</td>
<td>51.5–92</td>
<td>66.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6</td>
<td>0.04</td>
<td>1.51–1.69</td>
<td>1.58</td>
</tr>
<tr>
<td>B.M.I.</td>
<td>26.7</td>
<td>4.6</td>
<td>21–33.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Hb-Screen (g/dl)</td>
<td>13.2</td>
<td>0.9</td>
<td>11–14.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

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**Table 2**

Proportion of cycles presenting ovulation, dysfunctional ovulation or a luteinized unruptured follicle (LUF) during cycles treated after the administration of oral meloxicam

<table>
<thead>
<tr>
<th>Dose (n)</th>
<th>Ovulatory</th>
<th>Dysfunctional</th>
<th>LUF</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg (83)</td>
<td>37 (44.6%)</td>
<td>29 (34.9%)</td>
<td>17 (20.2%)</td>
</tr>
<tr>
<td>30 mg (83)</td>
<td>18 (21.7%)*</td>
<td>35 (42.2%)</td>
<td>30 (36.1%)</td>
</tr>
</tbody>
</table>

* $p=0.002$
higher dose. Upper respiratory infections were the most frequent adverse event occurring in 12% (10/83) of cycles with both doses. Their occurrence did not differ between control and treated cycles. Serious adverse events were not observed.

3.3.3. Post treatment cycle

Out of 56 women who completed the post treatment cycle 52 had ovulatory cycles (92.8%). In the 30 mg dose group P4 values ranged from 1.4 to 87.9 nmol/l and the mean±SE for the highest level was 47.9±4.0 nmol/l. In the 15 mg dose group P4 values ranged from 2.6 to 83.9 nmol/l and the mean±SE for the highest level was 48.0±3.0 nmol/l.

4. Discussion

The aim of this study was to determine the effect of extended administration of two different doses of meloxicam on ovulation, expecting that it would be more effective to delay or inhibit ovulation than when administered for shorter duration during mid-cycle. We observed a significantly higher proportion of dysfunctional and LUF cycles when 30 mg/day meloxicam was administered compared with 15 mg/day, 78% and 55%, respectively, similar to what had been reported previously [4].

As expected, normal ovulatory cycles were observed more frequently with the lower compared to the higher dose, but increasing the duration of treatment from 5 days to 18 days did not increase the proportion of dysfunctional cycles from those previously observed [4]. Therefore the data do not support our hypothesis that efficacy could be improved by initiating treatment earlier in the cycle and for longer duration.

There were no differences between doses in E2, P4 or LH serum levels. We observed higher levels of P4 in ovulatory cycles than in dysfunctional cycles, although the values were within the normal range. In comparison with historical data from the same population, hormonal parameters were not altered with the use of meloxicam, given that the values observed in this study were similar to those found in untreated control cycles in a previous study [10].

Follicular diameters observed for both doses during dysfunctional and LUF cycles were significantly longer in ovulatory cycles as was expected, given a delay in follicular rupture. This difference was also observed in our previous study [4]. However, we found no differences in cycle length, the length of the luteal phase or the number of bleeding days between cycles treated with the two different doses and between treated and control cycles.

Our results differ from those of Edelman et al. [9] who found only a modest effect on ovulation in women treated with celecoxib. They observed dysfunctional ovulations in 30% of cycles when treatment was administered pre LH surge vs. 78.3% (dysfunctional and LUF cycles) found in our study when the higher dose of meloxicam was administered.

Edelman et al. did not report any LUF cycles as would be expected with the use of other COX inhibitors [3–6]. It is important to note that both studies were conducted using the

### Table 3
Maximum follicle diameters during the treatment cycles (mm, mean±SEM)

<table>
<thead>
<tr>
<th>Type of cycle</th>
<th>N</th>
<th>15 mg</th>
<th>N</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>37</td>
<td>21.5±0.3*</td>
<td>18</td>
<td>22.6±0.8*</td>
</tr>
<tr>
<td>Dysfunctional</td>
<td>29</td>
<td>28.9±0.9</td>
<td>35</td>
<td>27.8±0.7</td>
</tr>
<tr>
<td>LUF</td>
<td>17</td>
<td>32.6±1.3</td>
<td>30</td>
<td>32.7±1.5</td>
</tr>
</tbody>
</table>

Note: Follicular diameter in ovulatory cycles were significantly different from diameter in dysfunctional and LUF cycles *p<0.001.

### Table 4
Parameters measured during treated cycles with meloxicam

<table>
<thead>
<tr>
<th></th>
<th>15 mg (mean±SEM)</th>
<th>30 mg (mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ovulation Range</td>
<td>Dysfunctional ovulation Range</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max LH (IU/L)</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Max estradiol (pmol/L)</td>
<td>45.9±2.0</td>
<td>45.1±2.9</td>
</tr>
<tr>
<td></td>
<td>616.4±26.4</td>
<td>613±31.1</td>
</tr>
<tr>
<td>Max progesterone(nmol/L)</td>
<td>58.9±2.2*</td>
<td>49.8±3.0</td>
</tr>
<tr>
<td></td>
<td>25.8-86.1</td>
<td>14,2-81</td>
</tr>
<tr>
<td>Luteal phase length (days)</td>
<td>13.0±0.3</td>
<td>14,6±0,4</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>27.2±0.5</td>
<td>29.0±0,6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>Max LH (IU/L)</td>
<td>50.1±2.1</td>
<td>48.2±2.4</td>
</tr>
<tr>
<td>Max estradiol (pmol/L)</td>
<td>644±32.7</td>
<td>650±32.4</td>
</tr>
<tr>
<td>Max progesterone(nmol/L)</td>
<td>62.1±4.5*</td>
<td>54.9±3.5</td>
</tr>
<tr>
<td>Luteal phase length (days)</td>
<td>14.1±0.7</td>
<td>13.9±0,5</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>28.4±1.0</td>
<td>28.0±0,5</td>
</tr>
</tbody>
</table>

* p<0.001.
same definitions for the main outcomes, but used different NSAIDS, different treatment schedules, and were carried out in different populations. That a more selective COX-2 inhibitor, celecoxib, appears to being less potent at altering the ovulatory process than meloxicam, suggests that not only the COX-2 enzyme is involved, but that the constitutive enzyme COX-1 and other proteolytic enzymes may play an important role in the rupture of the follicle wall.

The safety of the continuous administration of meloxicam was closely monitored and no serious adverse events were observed during the study. The number and type of adverse events per cycle was similar for the two doses, and also when treated cycles were compared with the control cycles, however, safety of the higher dose of meloxicam needs to be further evaluated.

Not all hormonal parameters that were measured in the treatment cycles were measured in control cycles, because in previous studies we did not observe changes in control cycles [10]. Another weakness of this study is that all parameters used to classify cycles were indirect. We do not know if oocytes remain trapped or are unable to be fertilized as was shown by Hester [12].

Given that normal ovulatory cycles were observed in 22% of the cycles, even with 30 mg/day, the daily use of this higher dose may provide only moderately effective contraception.

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### References


