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ARTICLE

# Ibuprofen delays ovulation by several hours: prospective controlled study in natural cycles with HCG-triggered ovulation

## BIOGRAPHY

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## KEY MESSAGE

The ovulation inhibiting effect of ibuprofen was investigated in a controlled study. Ibuprofen was proven to delay ovulation. Women trying to conceive should avoid non-selective non-steroidal anti-inflammatory drugs (NSAID) around the time of ovulation. Ibuprofen or other NSAID can be used to delay ovulation in ART and other infertility treatments.

## ABSTRACT

**Research question:** Does ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), delay ovulation?

**Design:** Two-stage, proof-of-concept, controlled study, assessing the percentage of non-ovulated follicles 42 h after HCG injection in patients taking ibuprofen. The intervention group consisted of women undergoing natural cycle IVF treatment taking ibuprofen 3 × 400 mg per day. The control group consisted of women undergoing timed sexual intercourse or intrauterine insemination. The proportion of patients with non-ovulated follicles in the ibuprofen group was first compared against a reference of 50% using a one-sample binomial test, and second against the proportion observed in the control group using an adjusted logistic regression.

**Results:** A total of 26 women were recruited in the ibuprofen intervention group. Twenty-five patients were recruited in the control group. The proportion of patients with delayed ovulation observed (22/26 [84.6%]; 95% CI 65.1% to 95.6%) was significantly higher than the reference of 50% ($P < 0.001$). In the control group, the proportion of patients with delayed ovulation was 20.0% ([5/25], 95% CI 6.8% to 40.7%). Compared with the ibuprofen group, a significantly increased probability of a delayed ovulation was found in the ibuprofen intervention group (adjusted OR 22.72, 95% CI 5.77 to 115; $P < 0.001$). Of the 22 women with delayed ovulation, oocytes were retrieved in 20 women (90.9%) and all oocytes were mature (metaphase II).

**Conclusions:** Women trying to conceive should avoid non-selective NSAIDs around the time of ovulation. Ibuprofen or other NSAID can be used to delay ovulation for several hours in assisted reproductive technology and other infertility treatments if required.

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## KEYWORDS

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## INTRODUCTION

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are frequently used as over-the-counter analgesics by reproductive-aged women (*Werler et al., 2005*). They are highly effective in the treatment of pain conditions, such as dysmenorrhoea, without greatly affecting the gastrointestinal tract when using standard dosages (*Kellstein et al., 1999*).

They also affect ovulation, either by inhibiting cyclooxygenase (COX) (*Vernunft et al., 2022*), or by affecting pro-inflammatory cytokines (*Machelon and Emilie, 1997*) as analysed in animal experiments. Even though the regulation of ovulation is still under debate, prostaglandin oestradiol (*Ricciotti & Fitz Gerald, 2011*), produced by granulosa cells, is assumed to be an important player. Prostaglandin oestradiol stimulates and modulates the production of follicular matrix metalloproteases (MMP), which degrade parts of the cumulus complex surrounding the oocyte and thereby detaching the cumulus complex from the follicular wall. It also induces rupture of the follicle, leading to the release of the follicular fluid and the oocyte into the fallopian tube (*O'Sullivan et al., 1997*). Therefore, it is discussed that NSAIDs should not be taken in women trying to conceive (*Killick & Elstein, 1987*; *Proddy et al., 1990*).

There is also controversy about which NSAIDs inhibit ovulation and which do not. Meloxicam, an NSAID that is much stronger than ibuprofen (*Brune & Patrignani, 2015*), has more side-effects, is not an over-the counter medication and has a much stronger ovulation inhibiting effect. This effect is even that high, that it has been suggested as a new method for emergency contraception (*Jesam et al., 2010*). The intake of other non-selective NSAIDs do not seem to have a notable effect on ovulation as their use did not affect fertility according to studies based on internet based questionnaires (*McInerney et al., 2017*) or daily diaries (*Jukic et al., 2020*).

In assisted reproductive technologies (ART), the ovulation inhibiting side-effect of non-selective NSAIDs is used to delay ovulation. If a beginning LH surge is detected, COX inhibitors are given immediately and follicle aspiration is planned 2 days later. This kind of rescue strategy, which was first described by *Nargund and Wei (1996)*, using indomethacin, is mainly applied in monofollicular or oligofollicular ART treatments in which other LH suppressing agents such as GnRH analogues are not used (*von Wolff, 2022*).

This treatment strategy, however, is based on limited data and mainly on retrospective non-controlled studies for indomethacin (*Nargund et al., 2001*; *Kadoch et al., 2008*), diclofenac (*Kawachiva et al., 2012*) and ibuprofen (*Kohl Schwartz et al., 2020*). Only *Rijken-Zijlstra et al. (2013)* conducted a prospective and randomized study in minimal stimulation IVF treatments using indomethacin. Patients were, however, also treated with daily gonadotrophin releasing hormone (GnRH) antagonist injections, restricting the conclusion of this study, ultimately not allowing a firm conclusion to be reached on the efficacy of NSAID to delay ovulation.

Because of the controversial findings and the limited data on the inhibiting effect of over-the-counter NSAIDs on ovulation, a prospective controlled study was designed to further investigate the matter to draw definite conclusions.

Ibuprofen was chosen as it is an over-the counter medication commonly used in women with dysmenorrhoea and as it is the NSAID without adverse effects on the digestive system if taken at a daily dosage of 400 mg three times a day (*Lanza, 1984*; *Henry et al., 1996*).

## MATERIALS AND METHODS

### Study design and participants

A single centre, prospective, controlled single arm proof-of-concept trial was conducted.

Twenty-six participants underwent natural cycle IVF (NC-IVF) treatment cycles and took ibuprofen 400 g per day three times a day. In parallel, a group of 25 control patients were recruited. The control group consisted of women undergoing timed sexual intercourse or IUI and were not taking ibuprofen. Enrollment began in June 2016 and was completed in August 2022.

Inclusion criteria were as follows: women aged 18–42 years, a regular menstrual cycle of 26–32 days and (intervention group) a wish to undergo NC-IVF or (control group) a wish to undergo timed sexual intercourse or IUI. In both groups, ovulation was triggered with HCG. Exclusion criteria were any kind of gastrointestinal diseases and known ibuprofen intolerance. Participation was limited to one cycle per patient.

For the intervention group, a two-stage protocol was designed. During stage 1, eight NC-IVF cycles in eight patients, each receiving ibuprofen at a dosage of 400 mg three times a day, were examined. In the case that four or more patients showed a positive treatment effect from the ibuprofen intake (follicles not ovulated), the study could then continue to stage 2 with 17 more patients included, totalling 25 patients. In the event that three or fewer patients showed an effect of the ibuprofen intake (follicles not ovulated), the study would be stopped prematurely for futility. The study intervention would be increased to 800 mg of ibuprofen three times a day and the study recommenced at stage 1 with eight more patients. If again, three or fewer patients showed an effect of the ibuprofen intake (follicles not ovulated), the study would be stopped completely.

The intervention would be considered promising if delay of ovulation in the event that at least 16 out of the first 25 recruited patients showed a positive treatment effect from the ibuprofen intake (follicles not ovulated).

### Investigation

Women were informed about the study when being counselled about IVF treatment. Participants were enrolled after all eligibility criteria were verified and informed consent was signed before start of the treatment cycle.

Natural cycle IVF was defined as IVF treatments within the natural menstrual cycle in which women injected 5.000 units of urinary HCG to trigger ovulation. Timed sexual intercourse and IUI cycles were also carried out in natural menstrual cycles and ovulation was also triggered with 5.000 units of urinary HCG. Follicle monitoring was started 1–3 days before the expected LH surge and was repeated every 1–3 days between 08:00 and 12:00 in the morning. Ovulation was triggered if the follicle was wider than 15 mm in diameter and concentration of LH was still lower than 10 IU/l. Women undergoing NC-IVF

received 400 mg ibuprofen every 8 h, starting after the HCG application, totalling five tablets. Follicle aspiration was scheduled 42 h after HCG application instead of the usual time period of 36 h.

If follicles had not yet ovulated, they were aspirated as described elsewhere (*Kohl Schwartz et al., 2020*). In brief, aspiration was carried out with an aspiration pressure of 220 mm Hg, using 19 G single lumen needles (NMS Biomedical SA, Praroman, Switzerland) without anaesthesia or analgesia. The follicles were flushed three to five times with a flushing medium containing heparin (SynVitro® Flush) (Origio, Berlin, Germany). Flushing volume was calculated based on the size of the follicle. Fertilization was achieved by standard intracytoplasmic sperm injection (ICSI) and embryo transfer was carried out two to three days after follicle aspiration.

Intake of ibuprofen was tested by measuring ibuprofen serum concentration 42 h after HCG injection.

In the control group, ovulation was verified by vaginal ultrasound, performed 42 h after HCG injection. Data were added to a REDCap® study registry, a secure web application for managing databases.

### Outcomes

Primary outcome was the proportion of women with delayed ovulation, defined as non-ovulated follicles, 42 h after HCG injection. The secondary outcomes were the rates of aspirated oocytes, mature (metaphase II) oocytes, fertilized oocytes (zygotes) and embryos on day 2.

### Sample size

Sample size was determined using an admissible two-stage design approach as described by *Jung et al. (2004)*. Ovulation was assumed to occur 42 h after ovulation triggering in up to 50% of untreated patients, and ibuprofen treatment was considered to be effective if it can delay ovulation in 80% of patients. With a type I error of 0.05 and a power of 90%, this results in the sample-size/design features for the treatment group as described above.

### Statistical analysis

Baseline patient's characteristics are presented in TABLE 1. Categorical variables are shown as median with interquartile range or as mean with SD, as appropriate. Differences between the ibuprofen and control groups were tested using non-parametric Wilcoxon signed-rank tests for continuous variables and Fisher's exact tests for categorical variables.

In the primary analysis, the proportion of patients with delayed ovulation in the intervention group was compared against the null hypothesis of 50% using a one-sample binominal test at a two-sided alpha-level of 0.05. In the secondary analysis, difference in the proportion of delayed ovulations between the intervention and the control group was assessed using an adjusted logistic regression model. The model included the occurrence of delayed ovulation as dependent variable and the intervention group as independent variable and was adjusted for the effect of age (continuous) (TABLE 2).

IVF outcomes collected in the intervention group are presented in TABLE 3. Binary variables were summarized as number and proportion with 95% confidence intervals, continuous variables as median with interquartile range or mean with SD, as appropriate. The analysis was conducted by an independent statistician using R version 4.2.1.

### Trial registration and approval

The trial was registered at Clinicaltrials.gov (NCT NCT02571543). This study was

**TABLE 1 PATIENTS' BASELINE CHARACTERISTICS**

| Characteristics | Intervention group (with ibuprofen) (*n* = 26) | Control group (without ibuprofen) (*n* = 25) | *P*-value[a] |
|---|---|---|---|
| Age, years, mean (SD) | 34.7 (4.2) | 35.7 (4.2) | 0.35 |
| Body mass index, kg/m$^2$, mean (SD) | 21.6 (3.1) | 21.9 (2.5) | 0.55 |
| Previous IVF treatments, *n* (%) | | | 0.08 |
| None | 18 (69.2) | 23 (92.0) | |
| One or more | 8 (30.8) | 2 (8.0) | |
| Number of births resulting from previous IVF treatments, *n* (%) | | | 1 |
| 0 | 24 (92.3) | 23 (92.0) | |
| 1 | 2 (7.7) | 2 (8.0) | |
| Main reason of infertility, *n* (%) | | | 0.0042 |
| Female | 3 (11.5) | 8 (32.0) | |
| Male | 12 (46.2) | 5 (20.0) | |
| Female and male | 11 (42.3) | 6 (24.0) | |
| Idiopathic | 0 (0) | 6 (24.0) | |
| AMH, pmol /l, median (IQR) | 16.8 (8.0–30.6) | 25.2 (11.7–44.2) | 0.38 |
| LH, IU/l, mean (SD) | 7.2 (1.7) | 7.0 (1.6) | 0.73 |
| Endometrial thickness, mm, mean (SD) | 8.2 (1.6) | 8.2 (2.2) | 0.81 |
| Diameter of follicle, mm, median, (IQR) | 16.5 (15.0–17.0) | 16.0 (15.0–17.0) | 0.93 |

[a] Wilcoxon rank sum test; Fisher's exact test.

AMH, anti-Müllerian hormone; IQR, interquartile range.

**TABLE 2 OUTCOMES RELATING TO THE EFFECT OF IBUPROFEN**

| Outcomes | Intervention group (with ibuprofen) (*n* = 26) | 95% CI | Control group (without ibuprofen) (*n* = 25) | 95% CI |
|---|---|---|---|---|
| Delayed ovulation, 42 h after HCG injection | | | | |
| Yes | 22 (84.6) | 65.1 to 95.6 | 5 (20.0) | 6.8 to 40.7 |
| No | 4 (15.4) | 4.36 to 34.9 | 20 (80.0) | 59.3 to 93.2 |
| Gastrointestinal adverse events after ibuprofen intake | 0 | | 0 | |

Data presented as *n*, *n* (%) and 95% CI.

reviewed and approved by the Cantonal Ethical Committee of Berne, Switzerland (KEK-BE 015/15, 8 March 2016).

## RESULTS

Patient's characteristics are presented in TABLE 1. The mean blood concentration of ibuprofen measured 42 h after HCG in the IVF group was median 106 mg/l (range: 5–268 mg/l). Adverse effects relating to the gastrointestinal system were not observed in any patients.

In the intervention group, delayed ovulation was found in seven out of the first eight recruited patients. The trial then proceeded to stage 2. As delayed ovulation was found in 21 out of the first 25 recruited patients, the trial was considered to be promising. The proportion of patients with non-ovulated follicles (delayed ovulation) observed in the intervention group 42 h after HCG triggering (85% [65–96%]), was found to be significantly higher than 50%, i.e. proportion of women assumed to have not ovulated 42 h after HCG triggering without ibuprofen treatment ($P < 0.001$).

The comparison between the intervention and the control group revealed a significantly higher proportion of patients with delayed ovulation (non-ovulated follicles) (TABLE 2). The probability not to have ovulated due to the treatment with ibuprofen was significantly higher (OR 22.72, 95% CI 5.77 to 115, $P < 0.001$).

The analysis of the secondary outcomes in the ibuprofen intervention group revealed per woman with a follicle aspiration with at least one aspirated oocyte in 90.9% of cases. All oocytes were found to be metaphase II. For each metaphase II oocyte, a fertilization rate (zygote development) of 95.2% a cleavage stage embryo development rate of 85.7% and a transfer rate of 81.0% were achieved (TABLE 3).

Implantation led to four confirmed pregnancies, one being a biochemical and one a tubal pregnancy, which both were lost. Two pregnancies resulted in a live birth, corresponding to a live birth rate per initiated cycle of 7.7%.

**TABLE 3 OUTCOMES OF IVF TREATMENT IN THE IBUPROFEN INTERVENTION GROUP**

| Denominator | Parameter | *n* (%) | 95% CI |
|---|---|---|---|
| Per woman with aspirated follicles (*n* = 22) | Number of aspirated follicles | | |
| | 1 | 21 (95.5) | |
| | 2 | 1 (4.5) | |
| | Number of oocytes | | |
| | 0 | 2 (9.1) | |
| | 1 | 19 (86.4) | |
| | 2 | 1 (4.5) | |
| | Number of metaphase II oocytes | | |
| | 0 | 2 (9.1) | |
| | 1 | 19 (86.4) | |
| | 2 | 1 (4.5) | |
| Per metaphase II oocytes (*n* = 21) | Zygotes | | |
| | Yes | 20 (95.2) | 76.2 to 99.9 |
| | No | 1 (4.8) | 0.12 to 23.8 |
| | Cleavage stage embryos | | |
| | Yes | 18 (85.7) | 63.7 to 97.0 |
| | No | 3 (14.3) | 3.1 to 36.3 |
| | Embryo transfer | | |
| | Yes | 17 (81.0) | 58.1 to 94.6 |
| | No | 4 (19.0) | 5.4 to 41.9 |
| Per woman (*n* = 26) | Biochemical pregnancies | | |
| | Yes | 4 (15.4) | 4.36 to 34.9 |
| | No | 22 (84.6) | 65.1 to 95.6 |
| | Live births[a] | | |
| | Yes | 2 (7.7) | 0.95 to 25.1 |
| | No | 24 (92.3) | 74.9 to 99.1 |

[a] One of the pregnancies resulted in a tubal pregnancy.

## DISCUSSION

In the present study, the probability of a delayed ovulation is significantly increased in women taking the NSAID ibuprofen around ovulation. Evidence is provided that ibuprofen and, therefore, probably also other non-selective NSAIDs should

not be taken around ovulation in women trying to conceive. The study also confirms previous retrospective studies that ibuprofen can be used to delay ovulation in infertility treatments.

The strength of the study is its prospective and controlled design. The study was a two-stage design, which would have allowed the ibuprofen dosage to increase in case the first stage had revealed an insufficient effect of ibuprofen at a dosage of 400 mg three times a day. This dose escalation was not necessary. Another strength is that, because follicle aspiration was postponed by 6 h, the study provided some information on the timewise effect of ibuprofen to delay ovulation. And finally, the study provided limited data on the effect of ibuprofen on the detachment of the cumulus effect from the follicular wall (proportion of aspirated follicles with a collected oocyte), the maturity of oocytes (proportion of metaphase II oocytes), the oocyte fertilization rate and the embryo development rate.

The limitations were the limited number of participants and the postponement of follicle aspiration by only 6 h, which did not allow any conclusion to be drawn about the maximum delay of ovulation. Furthermore, the limited number of patients did not allow reliable data to be generated on the live birth rate in patients being co-treated with ibuprofen. As the study only analysed the effect of ibuprofen, generalization of our findings for other over-the counter NSAIDS is cautioned.

As already described in the introduction, substantial controversy surrounds the ovulation inhibiting effect of NSAIDs. On the one hand, they seem to have no, or only limited, effect on ovulation (*McInerney et al., 2017*; *Tomioka et al., 2018*; *Fattah et al., 2020*; *Jukic et al., 2020*) but, on the other, they are propagated as medications to control ovulation in infertility treatments (*Nargund et al., 2001*; *Kadoch et al., 2008*; *Kawachiva et al., 2012*; *Rijken-Zijlstra et al., 2013*; *Kohl Schwartz et al., 2020*). It is not clear if these controversial findings are dose dependant, if they depend on the cycle phase when the NSAIDs are taken or if they are due to different pharmacological effects of different NSAIDs.

By designing a model using HCG triggering and giving a defined dosage of ibuprofen, we were able to prove that ibuprofen does definitely show an ovulation inhibiting effect if taken around ovulation.

As only analysed ibuprofen was analysed, and as previous studies had revealed different inhibiting effects of other NSAIDs on ovulation, we are reluctant to generalize these findings and to assume that they also apply to other non-selective NSAIDs. As ibuprofen is one of the most frequently used NSAID, however, our findings will affect many women.

We had chosen ibuprofen and had given it in a dosage of 400 mg three times a day, as this medication and dosage does not have any relevant effect on the gastrointestinal system (*Lanza, 1984*; *Henry et al., 1996*; *von Wolff et al., 2022*). In line with this, no adverse gastrointestinal side-effects were found in our study. Furthermore, no influence of ibuprofen on oocyte and embryo competence has been shown (*Kohl Schwartz et al., 2020*), a finding also confirmed in the present study. *Kohl Schwartz et al. (2020)* compared the oocyte and embryo developmental potential in women undergoing NC-IVF who were treated with 400 mg ibuprofen three times a day to delay ovulation with an untreated control group. They did not find a difference in the number of oocytes retrieved, proportion of metaphase II oocytes and fertilization rate. The percentage of aspirations with at least one oocyte was high (90.9%), all oocytes were metaphase II and the fertilization rate per metaphase II oocyte was 95.2%, which is line with the study by *Kohl Schwartz et al. (2020)*. These findings are of clinical relevance as they exclude that ibuprofen inhibits the detachment of the cumulus oophorus complex, which has been described for meloxicam in non-human primates (*Hester et al., 2010*). How can these findings be translated into clinical practice?

First, even though an effect of ibuprofen on fertility could not be found in large studies based on internet-based questionnaires (*McInerney et al., 2017*) or daily diaries (*Jukic et al., 2020*), we could demonstrate such an effect. Therefore, NSAIDs such as ibuprofen should not be taken in a daily dosage of 400 mg three times daily around the time of ovulation in women trying to conceive.

Second, the ovulation delaying effect of ibuprofen can be used in infertility treatments in which some delay of ovulation is required. This might include IVF treatments in which a beginning LH surge is detected and ibuprofen is given to delay ovulation, to aspirate follicles 2 days later (*von Wolff et al., 2022*). Further use might also include IUIs in which some delay is required. Whether ibuprofen is the best suited medication or if stronger medications, such as diclofenac, at a dosage of 25 mg three times a day remains to be analysed.

In conclusion, ibuprofen and possibly also other non-selective over-the counter NSAIDs delay ovulation, which could limit the chance to conceive in spontaneous cycles if these medications are taken around the time of ovulation. The effect of these NSAIDs on pregnancy, however, can be assumed to be limited. Over-the counter NSAIDs can also be used to delay ovulation in infertility treatments, especially in cases in which an LH surge has been detected and a follicle aspiration or IUI require some delay of ovulation.

## DATA AVAILABILITY

Data will be made available on request.

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