

Non-Steroidal Anti Inflammatory Drugs (Nsaids) Induced Reversible Infertility - Review Article

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Keywords:

Index, NSAIDs, Infertility, Anovulation

Abbreviations

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; COX: Cyclooxygenase; LUF: Luteinized Unruptured Follicle; OR: Odds Ratio; FR: Fecundability Ratios; CI: Confidence Interval.

1. Abstract

1.1. Background: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used have been highly recognized in the worldwide due to their analgesic, antipyretic, and anti-inflammatory properties. However, the use of NSAIDs in women at a reproductive age has the potential harmful effect on ovulation process.

1.2. Objective: The aim of this review is to evaluate the safety of NSAIDs on fertility of women at a productive age through a systematic review of the literature.

1.3. Methods: Electronic databases search in PubMed, Medline, and Google Scholar have been conducted. All the eligible studies that have been published in English language from inception to June 13th, 2019 have been conducted by using appropriate keywords and Boolean operators (AND, OR) search strategy. We scanned the references of the selected literature to identify any further relevant studies.

1.4. Results: A total of 1,724 study reports were originally identified through the database searches and review of article reference lists. Of those, 1354 were excluded based on review of titles and abstracts. At this point, 370 study reports were scanned to select those relevant for our purposes, 321 study reports were excluded, leaving a total of 13 case reports, interventional studies, and observational studies for the comprehensive review. Reversible infertility was reported with nine NSAIDs including meloxicam

(3 studies), ibuprofen (3 studies), naproxen (4 studies), diclofenac (5studies), indomethacin (1study), piroxicam (1study), rofecoxib (1 study), etoricoxib (2 studies), and celecoxib (2 studies). The plausible mechanism between reversible infertility and NSAIDs use could be due to delaying or preventing prostaglandin-mediated rupture of ovarian follicles and selective Cyclooxygenase (COX-2) inhibitors were more potent inductor of Luteinized Unruptured Follicle (LUF) syndrome than nonselective COX inhibitors.

1.5. Conclusion: Based on the available evidence, there is a potential harmful effect of NSAIDs on female fertility. We suggest to hold NSAID in females who planning to have a child and consider discontinuation it in women who have difficulties conceiving or who are undergoing infertility evaluation.

2. Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been highly recognized in the worldwide due to their analgesic, antipyretic, and anti-inflammatory properties in the treatment of inflammatory diseases, rheumatoid disorders, mild to moderate pain, fever, dysmenorrhea, and osteoarthritis. NSAIDs are widely used in Saudi Arabia, ibuprofen and diclofenac are the most commonly used NSAIDs [1].

NSAIDs act primarily via inhibition of Cyclooxygenase (COX1 and 2) iso-enzymes, resulting in decreased formation of prostaglandin precursors. The toxic effects of NSAIDs are related to their

main mode of action, the inhibition of prostaglandin synthesis [2]. The use of NSAIDs may have some adverse effects on ovulation process. In-vitro and in-vivo studies have shown that NSAIDs may lead to delayed ovulation or reversible anovulation [3].

The objective of this review is to perform a systematic review of cases of reversible infertility with NSAIDs.

3. Materials and Methods

3.1. Literature Search Strategy

We identified relevant studies in the literature by searching the databases of PubMed, Medline, and Google Scholar. All the eligible studies that have been published in English language from inception to June 13th, 2019 have been conducted by using appropriate keywords and Boolean operators (AND, OR) search strategy (Table 1).

We also read the reference lists of the selected studies to manually identify further relevant studies. Articles were excluded from this review if they were review article, study had insufficient information and descriptions; or if the full text was unavailable.

4. Results

The process of the literature selection is presented in (Figure1). The literature search of the databases identified 1,707 studies that met the search terms. We found an additional 17 relevant articles in the references of those studies. After removal of duplicated studies, we evaluated 370 studies by screening the titles and abstracts to check that they met the search criteria. Consequently, we excluded 320 studies from the records screened on title and abstracts, and 37 Full-text articles excluded because they were reviewed articles or studies with no outcome of interest. Finally, 13 studies included in qualitative synthesis and analysis in this review.

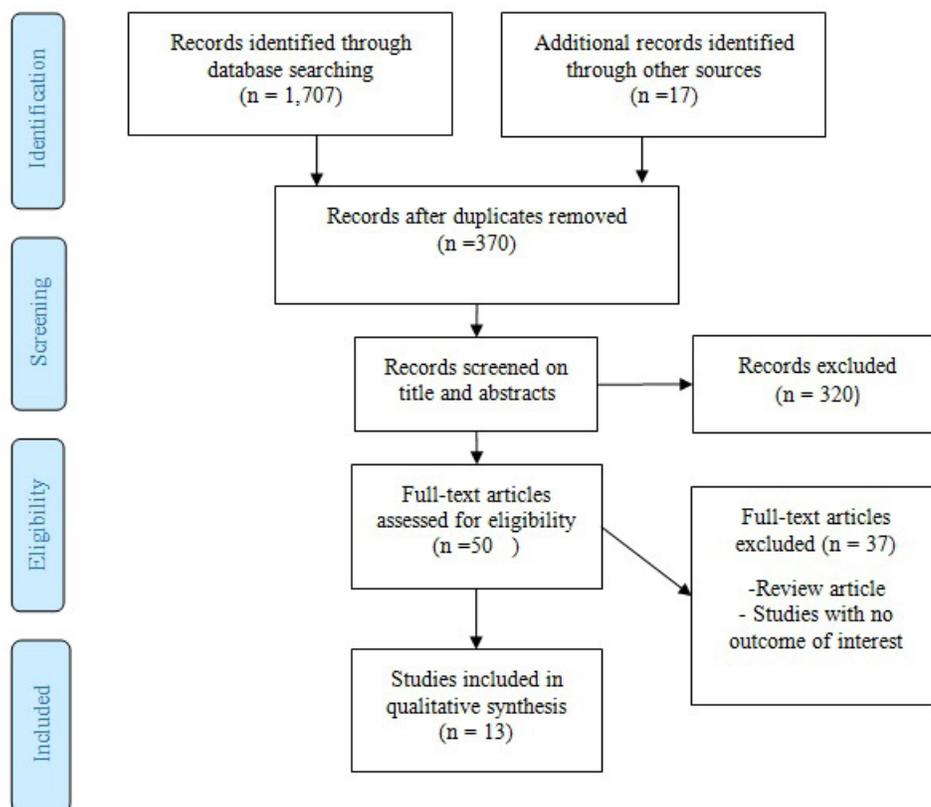


Figure 1: Diagram describing the selection of publications for inclusion in the review reporting reversible infertility

Table 1: Keywords used in the literature search

Search Strategy
Ibuprofen OR advil OR diclofenac OR naproxen OR ketorolac OR indomethacin OR fenoprofen OR ansaid OR ketoprofen OR sulindac OR mefenamic acid OR meloxicam OR mobic OR celebrex OR celecoxib OR piroxicam OR etoricoxib OR Aspirin OR Flurbiprofen OR Nimesulide OR lumiracoxib OR Nabumetone OR Parecoxib OR Tenoxicam OR Lomoxicam OR anti-inflammatory drugs OR cyclooxygenase inhibitors OR non selective cyclooxygenase inhibitors OR COX1,2 inhibitors OR selective cyclooxygenase inhibitors OR COX 2 inhibitors OR nonsteroidal anti-inflammatory drugs OR NSAIDs OR pain killer OR prostaglandin inhibitors OR PG inhibitors OR prostaglandin antagonist AND ovary impairment OR ovarian impairment OR ovarian syndrome OR Fetal ovary OR offspring ovarian OR pregnancy OR congenital ovarian anomaly OR female congenital genital malformation. OR anovulation.

One interventional study showed that follicular rupture failed to occur within the 5-day period in 70% of cycles treated with meloxicam plus levonorgestrel in comparison to the 50% in the placebo plus levonorgestrel group, and the overall proportion of cycles with no follicular rupture or ovulatory dysfunction increased significantly by the addition of meloxicam to levonorgestrel ($P < 0.012$) [4].

In one BioCycle prospective, observational cohort study that evaluated the effect of commonly used over-the-counter pain medication on reproductive hormones and ovulatory function in 259 healthy, premenopausal women not using hormonal contraception. Among users, 45% used ibuprofen, 33% acetaminophen, 10% aspirin and 10% naproxen. The result showed that analgesic use during the follicular phase was associated with decreased Odds Ratio (OR) of sporadic anovulation after adjusting for age, race, body mass index, perceived stress level and alcohol consumption (OR 0.36 [0.17, 0.75]) [5].

There are three case reports of infertility and LUF syndrome in premenopausal women who received diclofenac and indomethacin for the treatment of rheumatoid arthritis [6].

There is a published paper presents the case histories of reversible ovulatory failure in three young women with inflammatory arthritis who received piroxicam, naproxen, and diclofenac. These patients were seeking advice about infertility when they were in NSAID therapy. Biochemical markers of ovulation and transvaginal ultrasound scans were performed to exclude other cause of infertility. Confirmed ovulation was occurred when the NSAIDs was discontinued in the periovulatory period [7].

In a prospective, double-blind, randomized study that was conducted to investigate whether periovulatory administration of a (Cox)-2 inhibitors affect human ovulation. Thirteen healthy women between 30-40 years of age without hormonal treatment and with regular menstrual cycles. Rofecoxib was received by six subjects and seven subjects received placebo in a random double-blind fashion. The result showed that a delayed in follicle rupture in four of six women (66.7%) among rofecoxib received group [8].

There are four cases of premenopausal women who had severe arthritis on diclofenac. All of these patients had a history of unexplained infertility. Successfully conceived was reported immediately after the withdrawal of NSAIDs [9].

In a prospective study were 10 women with rheumatoid arthritis and 4 women with ankylosing spondylitis who received continues NSAIDs including etoricoxib, celecoxib, ketoprofen, diclofenac, and ibuprofen. Etoricoxib was responsible for 75% of LUF syndromes in patients exposed continuously, whereas diclofenac generated 15% of LUF syndromes, and ibuprofen dosage of 1,600 mg/day did not induce LUF syndrome [10].

In a cross-sectional study were 260 female patients who were preg-

nant or trying to conceive between 2002 and 2010 and diagnosed with rheumatoid arthritis received a questionnaire on reproductive history, fertility examinations, and fertility treatments. Eighty-two subjects (46%) had at least 1 sub-fertile episode, and for 61 women a diagnosis for subfertility was available. Unexplained subfertility (48%) and anovulation (28%) were the most common gynecologic diagnoses, and both occurred more often in rheumatoid arthritis patients than reported in the general population. Women with unexplained subfertility more often used NSAIDs during the peri-conceptual period [11].

There is an internet-based prospective cohort study of 2573 female pregnancy planners aged 21–45 years were enrolled and followed from June 2013 through September 2015. Participants completed a baseline questionnaire and bimonthly follow-up questionnaires until a reported pregnancy or for 12 months. Use of pain-relieving medication during the past month was assessed at baseline and on each follow-up questionnaire. Medications were categorized according to type (acetaminophen, aspirin, ibuprofen, naproxen and opioids) and self-reported pregnancy was assessed at each follow-up. Fecundability Ratios (FR) for use of naproxen at baseline was 0.78 (95% Confidence Interval (CI): 0.64–0.97). A dose–response relation was observed between naproxen use and fecundability; FRs for use of <1500 and ≥ 1500 mg of naproxen were 0.85 (95% CI: 0.68–1.07) and 0.58 (95% CI: 0.36–0.94), respectively [12].

In a placebo-controlled, double-blind, crossover study that evaluated the meloxicam effect on delaying ovulation by enrolling 30 healthy fertile volunteers with no history of gynecologic or reproductive disorder, none of the women was using hormonal contraception or any other medication for at least 2 months before the study, and all had a history of regular menstrual cycles. The result showed that meloxicam is reversibly delaying of ovulation, increasing in follicular diameter, and a decreasing in plasma progesterone level [13].

There is an interventional study that included 49 women at fertile age. They were visited the Rheumatology consultation clinic in Baghdad Hospital, suffering from minor aches & were diagnosed and received one of the three test drugs included in this study (diclofenac 100mg once daily (n=16), naproxen 500mg twice daily (n=12) and etoricoxib 90mg once daily (n=11) and 10 women were in a control group. The results showed a significant inhibition of ovulation in patients treated with diclofenac, naproxen and etoricoxib. And the highest inhibitor of ovulation was reported with diclofenac compared to the naproxen and etoricoxib [14].

In a randomized double-blind crossover design study were 20 women distributed equally. Subjects received study drug oral celecoxib 400 mg or placebo; either once daily starting on cycle day 8 and continuing until follicle rupture or the onset of next menses if follicle rupture did not occur (pre-LH surge dosing) or once daily

beginning with the LH surge and continued for 6 days (post-LH surge dosing). Treatment with celecoxib before or after the LH surge increases the rate of ovulatory dysfunction [15].

In a single center, double blind, crossover study designed to assess the effects of meloxicam 15 or 30 mg/day in 22 eligible women aged 18–40 years old, with regular menstrual cycles. Meloxicam was administered orally for five consecutive days during the late follicular phase. Dysfunctional ovulation was observed in 11/22 (50%) cycles treated with 15 mg/day and 20/22 (90.9%) cycles with 30 mg/day ($P=0.0068$) [16].

5. Discussion

From the above finding and from the mechanism of action of NSAIDs, it is thought that use of COX1,2 inhibitors may serve as an alarm of the harmful effects of these drugs on female fertility. The evidence to date would suggest that NSAID withdrawal in females planning to have a child, and consider withdrawal of NSAIDs in women who have difficulties conceiving or who are undergoing infertility evaluation. In women with rheumatic disease responding well to NSAIDs therapy should consult their physicians before stopping treatment. Medical and public awareness (especially that of childbearing women) must be increased about the potential hazards of analgesic use for long term. Further larger clinical studies are needed to ascertain causality and to determine the prevalence of this problem.

6. Conclusion

Available human data supports the association between NSAIDs use and impairment of ovulation by delaying or preventing prostaglandin-mediated rupture of ovarian follicles, thus leading to a reversible infertility in women at reproductive age.

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