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# Nonsteroidal Anti-Inflammatory Drugs and Reversible Female Infertility

## Is There a Link?

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## Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed to women of child-bearing age. Three case series highlight the possibility of a link between NSAIDs and reversible infertility. The pharmacological target of NSAIDs is cyclo-oxygenase (COX), which catalyses the first rate-limiting step in the production of prostaglandins. COX-2, one of two isoenzymes, is active in the ovaries during follicular development. Its inhibition is thought to cause luteinised unruptured follicle (LUF) syndrome, an anovulatory condition characterised by clinical signs of ovulation but in the absence of follicular rupture and ovum release. The evidence linking regular NSAID use to reversible LUF syndrome comes from animal studies and three clinical studies. COX-2–deficient mice have severely compromised ovulation in the presence of apparently normal follicular development. Experimental administration of prostaglandins induced ovulation in rabbits and this was blocked by the administration of indomethacin. The three clinical studies demonstrated the induction of delayed follicular rupture or LUF in previously ovulating women by the administration of NSAIDs. A link can therefore be identified between NSAID use and reversible female infertility and NSAID withdrawal should be considered prior to or concurrent with fertility investigations.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents. They are frequently prescribed for the relief of fever, inflammation or musculoskeletal pain and are often self-administered for the relief of headaches, toothaches and a variety of other minor complaints. It is probable that most bathroom medicine cupboards harbour a bottle containing aspirin (acetylsalicylic acid) or another NSAID. They are also almost universally prescribed as first-line treatment in patients with inflammatory arthritis and other rheumatological disorders.[1] Women with endometriotic pain, dysmenorrhoea or menorrhagia may be prescribed NSAIDs.[2] Therefore not infrequently the recipients of these drugs are women of child-bearing age. This article aims to

review the literature supporting an association between regular NSAID use and reversible female infertility.

## 1. Case Reports

Although a link between NSAIDs and ovulation was proposed in the 1980s largely through evidence derived from animal studies,[3-5] the association was not recognised in clinical settings until recently. A Medline search revealed three case series which highlight the association (see table I).[6-8]

Of the ten cases of women with a rheumatological disorder and investigated unexplained infertility, seven conceived within a short interval after cessation of treatment with NSAIDs. The remaining three were shown by ultrasound monitoring and serum progesterone levels to ovulate only once treatment had been discontinued. In six cases, treatment was discontinued because the possibility of subfertility secondary to NSAID use was considered. No reason was given in two cases; dyspepsia was responsible for cessation in another case and a change of treatment in the last case. The NSAIDs in question were diclofenac (seven cases) and indomethacin (one case), naproxen (one case) and piroxicam (one case).

## 2. Mechanism of Action of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs exert their effect by inhibition of prostaglandin (PG) production, a potent mediator of inflammation. The pharmacological target of NSAIDs is cyclo-oxygenase (COX) which catalyses the first committed step in arachidonic-acid metabolism (see figure 1).[1]

Two distinct COX isoenzymes have been described, COX-1 and COX-2.[9] Their major difference lies in their different patterns of expression and regulation in mammalian cells. COX-1 appears to be constitutively expressed in most tissues and is responsible for the physiological production of PGs. COX-2 is induced by cytokines, mitogens and endotoxins in inflammatory cells and is therefore responsible for the elevated production of PGs during inflammation. However, COX-2 is also known to play a physiological role in the reproductive system, renal and cardiovascular systems.[10] COX-2 is implicated in ovulation, fertilisation, implantation and maintenance of pregnancy.[11] The structures of COX-1 and COX-2 have been described and are highly conserved.[9] The significant difference between them is the presence of a much larger NSAID binding site in COX-2 primarily as

**Table I.** Summary of three case series

| | NSAID use | | Length of infertility | Interval from cessation of NSAID to pregnancy/ovulation | Outcome |
|---|---|---|---|---|---|
| | indication | type | | | |
| **Mendonça et al.**[6] | | | | | |
| 1 | RA/lupus | Diclofenac | 4 years | 1 IVF cycle | Pregnant |
| 2 | RA | Diclofenac | 3 years | 5 months | Pregnant |
| 3 | RA | Diclofenac | Not known | 3 months | Pregnant |
| 4 | RA/ lupus | Diclofenac | 3 years | 6 months | Pregnant |
| **Akil et al.**[7] | | | | | |
| 1 | Back pain | Indomethacin | 2 years | 3 weeks | Pregnant |
| 2 | Ank spond | Diclofenac | 27 months | 1 month | Pregnant |
| 3 | RA | Diclofenac | 2 years | Days | Pregnant |
| **Smith et al.**[8] | | | | | |
| 1 | Ank spond | Naproxen | 1 year | Anovulation | Ovulation |
| 2 | RA | Piroxicam | 5 years | for 2 cycles – | Ovulation |
| 3 | RA | Diclofenac | 8 months | 3rd cycle stopped NSAIDs days 8-10 | Ovulation |

**Ank spond** = ankylosing spondylitis; **IVF** = in vitro fertilisation; **NSAID** = nonsteroidal anti-inflammatory drug; **RA** = rheumatoid arthritis.

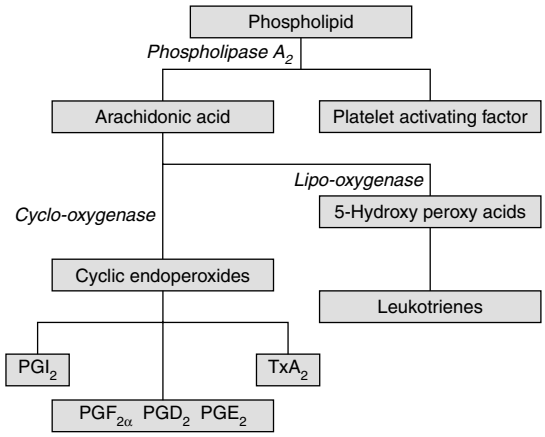


**Fig. 1.** The biosynthetic pathway of prostaglandins (PG) from phospholipid. **$TxA_2$** = thromboxane $A_2$.

the result of the substitution of a valine for an isoleucine in the COX active site. Most NSAIDs inhibit both COX-1 and COX-2 with little specificity. The presence of PGs in a functional role in many body tissues means that adverse effects of non-selective COX inhibitors are frequently reported. These are usually gastric and/or renal in origin. Common gastrointestinal adverse effects are dyspepsia, nausea, vomiting or mucosal damage leading to haemorrhage. In the kidney chronic nephritis and renal papillary necrosis led to the description of 'analgesic nephropathy'.[1] COX-2 selective inhibitors have been developed which exert similar analgesic and anti-inflammatory activity *in vivo* but cause less symptomatic gastroduodenal ulcers and ulcer complications although improvement in tolerability (dyspepsia, nausea, diarrhoea) is less striking.[12,13] Both have a similar pattern of nephrotoxicity.[14] Less clear is the effect of COX inhibitors on fertility.

## 3. Ovulation

Ovulation is a process that depends on the coordinated effects of the pituitary gonadotrophins mediated follicular development, oocyte maturation therein, and follicular rupture in the ovaries. Plasminogen activator from granulosa cells stimulates the conversion of plasminogen to plasmin which converts procollagenase to collagenase and degrades the basement membrane of the follicular wall.[15] An ovulation stigma results through which the mature oocyte is expelled (figure 2).[16] The postovulatory follicle transforms into the corpus luteum, which produces progesterone. This supports the implantation of the blastocyst and the early pregnancy endometrium fostering. However, meiosis and luteinisation can occur without concomitant follicle rupture and ovulation. The existence of such luteinised but unruptured follicles may be viewed on ultrasound or at laparoscopy through the absence of ovulation stigma and/or by the demonstration of low serum estradiol and progesterone levels.[16-19]

## 4. The Luteinised Unruptured Follicle (LUF) Syndrome

The term 'luteinised unruptured follicle' (LUF) was coined by Jewelewicz in 1975 when describing the management of anovulatory conditions.[17] The idea was further developed by two independent

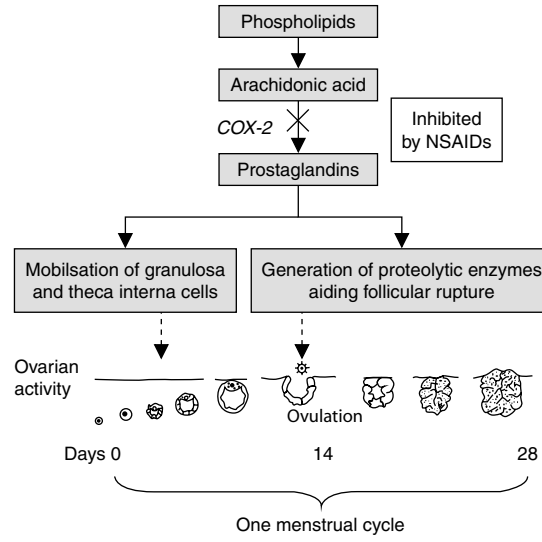


**Fig. 2.** Role of cyclo-oxygenase 2 (COX-2) in ovulation. **NSAIDs** = nonsteroidal anti-inflammatory drugs.

groups in 1978.[16,19,20] Marik and Hulka[16] applied LUF syndrome to a group of infertile women with clinical diagnosis of ovulation based on presumptive signs of the formation of luteinisation: basal body temperature elevations, the presence of secretory endometrium and elevated blood progesterone levels, but who on laparoscopy 3 to 5 days after ovulation failed to show the presence of a stigma or corpus haemorrhagicum (which becomes the corpus luteum), i.e. ovulation had not taken place.

Further studies confirmed the theory of LUF syndrome as an uncommon cause of infertility by ultrasound monitoring[18,21] and follicle growth curve and hormonal patterns.[22] A variety of explanatory concepts were put forward: 'inadequate' follicular phase, psychogenic infertility, hyperprolactinaemia, central disturbance of luteinising hormone (LH) release; locally: pelvic inflammatory disease or subclinical oophoritis, adhesions and endometriosis.[22] The link of LUF with NSAIDs was first suggested in rat studies[5] – following administration of a COX inhibitor, the rat ovaries were significantly heavier with large cystic follicles which on histological examination were identified as luteinised follicles with entrapped ova.

## 5. How NSAIDs Could Cause LUF Syndrome

The physiological process of ovarian follicular rupture or ovulation shares all of the biophysical and biochemical features of a typical inflammatory reaction. Vasoactive, mitogenic and differentiating properties of PGs have been implicated in various female reproductive functions.[23] The pathophysiological effects have been studied for decades by examining the effects of exogenously administered PGs and pharmacological inhibitors of PG synthesis.[3,5] More recently COX-2–deficient mice have added to the evidence.[24]

PGs are considered to participate in follicular rupture (see figure 2). They are thought to induce the mobilisation of granulosa and theca interna cells and also lead to the generation of proteolytic enzymes required for the induction of collagenolytic activity leading to follicular rupture.[15] Experimental administration of PG induces ovulation in rabbits and this can be blocked by the administration of systemic, peritoneal or intrafollicular indomethacin.[25]

It is the inducible pro-inflammatory COX-2 gene and not the constitutively expressed COX-1 'housekeeping' gene,[23] that is thought to be responsible. The participation of COX-2 in ovulation was suggested because of the rapid but transient induction of this isoform in granulosa cells after gonadotrophin stimulation.[26] Severely compromised ovulation with apparently normal follicular development in COX-2–deficient mice, even after superovulatory stimulus, suggests that the absence of COX-2 in the ovary, and not gonadotrophin deficiency or defective responsiveness of the ovary to these hormones, is the primary cause for ovulation failure.[24] This is consistent with gonadotrophin-mediated induction of COX-2 in bovine ovarian follicles preceding ovulation.[26]

PGs are also implicated as important mediators of increased endometrial vascular permeability during decidualisation and implantation. COX-2 is also strongly expressed by the cumulus cells that surround the ovum, thereby implicating a role for PG in fertilisation. This is supported by the fertilisation failure in COX-2–deficient mice.[24]

Centrally, PGs promote LH and luteinising hormone releasing hormone (LHRH) release by direct action on the pituitary gland and hypothalamus. This suggests an alternative mechanism of disturbed fertility by NSAIDs.[5,27]

## 6. Effects of NSAIDs on Follicular Function

If PGs generate proteolytic enzymes for follicular rupture (figure 2), inhibition of COX enzyme by NSAIDS could thereby result in persistent follicles and ovulatory failure. This is supported by three clinical studies[28-30] in which delayed follicular rupture or LUF was induced in previously ovulating women. Killick and Elstein[28] showed in 46 monitored cycles of 20 healthy volunteers that LUF, present in 10.7% of untreated cycles, could

be further induced to 50% in cycles on the NSAID, azapropazone, and 100% if taking indomethacin. In the study by Athanasiou et al.,[29] six healthy women were prescribed indomethacin 50mg three times daily over the peri-ovulatory period. This delayed follicular rupture in five out of the six cases from 2 to 12 days. Most recently Pall et al.[30] showed delayed follicular rupture in four out of six women in the treatment arm of a randomised controlled trial of the COX-2 selective inhibitor, rofecoxib. Interestingly no measurable difference in serum concentration of progesterone, oestradiol, LH or follicle stimulating hormone (FSH) was found in the treatment arm compared with placebo which differs from previous studies. The authors suggested that there may be a dose-dependent effect.

An experimental study also suggested that the incidence of LUF induced by NS-398, another COX-2 selective inhibitor, was dose dependent.[31]

## 7. Clinical Implications

It is often assumed that women with inflammatory joint disease or connective tissue disease are less fertile than the rest of the population and any subfertility is usually explained by disease activity. The above described case reports although not proving a direct cause-and-effect relationship with NSAID use, do highlight that successful outcomes can be achieved in women with these disorders. These cases also provide evidence of the reversible nature of the infertility secondary to NSAID use.[32]

The few clinical studies in the literature provide a poor estimate of the true incidence of NSAID-associated infertility. It is highly likely that this link is often not considered either by the rheumatologist in treating the inflammatory disorder or by the gynaecologist in investigating the failure to conceive.

Patient numbers in the clinical studies summarised, and the numbers used in the animal studies, are too few to identify which of the NSAIDs are implicated. Certainly the COX-2 selective inhibitors would not be expected to lessen the adverse effects on fertility. In the Summary of Product Characteristics for the two COX-2 selective inhibitors, rofecoxib and celecoxib, use of these drugs is not recommended and indeed celecoxib is contraindicated in women attempting to conceive.

Although it is prudent to avoid all drugs where possible during the preconceptual period and pregnancy, treatment is frequently necessary in women with inflammatory or connective tissue diseases. Much anxiety and distress may be avoided by careful consideration of the drug regimen prescribed to women of child-bearing age who may be trying to conceive unbeknownst to her physician. High costs of investigative procedures for infertility and assisted reproductive procedures, both in terms of finance and in terms of the risks of ovarian hyperstimulation with superovulatory drugs, invasive oocyte retrieval techniques and multiple pregnancies mandate that NSAID disuse is at least considered before referral for fertility treatment.

One recent study from Denmark has reported an association between NSAIDs use and miscarriage.[33] This finding has yet to be confirmed in other studies.[34] No association was found between low birth weight, preterm birth or congenital abnormality in the same study. However, the results of another recent study derived from prospective data recording of drug use in early pregnancy suggest an association of NSAIDs and cardiac defects and orofacial clefts.[35] NSAIDs are teratogenic in animals.[36,37] In addition, NSAIDs cross the placenta freely and accumulate in fetal tissue in the first trimester of human pregnancy.[38] NSAIDs should therefore be used with caution in women attempting pregnancy or in the early stages of pregnancy. Later in a pregnancy NSAIDs may cause impaired fetal renal function, oligohydramnios, fetal haemorrhage and premature closure of the ductus arteriosus. Risks to the mother include peripartum haemorrhage. It is therefore advisable to discontinue NSAIDs at least 6 to 8 weeks prior to delivery if they are necessary during a pregnancy.[39]

## 8. Conclusion

Numerous animal studies, supported by the few clinical studies, identify a link between NSAID use and reversible female infertility. Further larger clinical studies are needed to ascertain causality and to determine the prevalence of this problem. The evidence to date would therefore suggest that NSAID withdrawal should be considered prior to or concurrent with the simpler investigations for infertility.

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