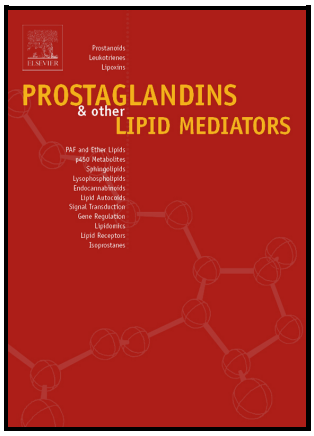
COX Isozymes and Non-Uniform Neoangiogenesis: What is their role in Endometriosis?



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Title: COX Isozymes and Non-Uniform Neoangiogenesis: What is their role in Endometriosis?

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Abstract

This literature review compared the efficacy in of NSAIDs with a placebo in pain relief and disease regression of endometriosis. Despite the poor evidence found, the results showed that NSAIDs were more effective in pain relief with regressive effects on the endometriotic lesions compared to placebo.

We postulate herein that COX-2 is chiefly responsible for pain whilst COX-1 is responsible mainly for the establishment of endometriotic lesions. Hence, there must be a temporal difference in the activation of the two isozymes. We differentiated between two pathways in the conversion of arachidonic acid to prostaglandins by the COX isozymes referred to as 'direct' and indirect', supporting our initial theory.

Finally, we postulate that there are two stages of neoangiogenesis in the formation of endometriotic lesions; 'founding' that first establishes blood supply and 'maintenance' that upkeeps it

This is fertile ground for further research in a niche that needs more literature. Its aspects may be diversely explored. The theories we propose offer information for a more targeted treatment of endometriosis.

Keywords:

Endometriosis; NSAIDs; Inflammation; Pain-relief

Introduction

Endometriosis is the presence of endometrial tissue, including glands and stroma, in the form of lesions outside the uterine cavity (1). The lesions themselves are oestrogen dependent and their effects result in a chronic disease (2). Classification of endometriosis remains controversial but the mainstay of staging the disease was created by the American Fertility Society (AFS). This depends on the size of the lesions around the body and severity of adhesions. It is point-based with the higher score indicating higher severity of the disease (3). Generally, women at risk of endometriosis are between 25 and 29 of age, with few to no pregnancies and an early menarche. There are other factors ranging from genetics to diet, however a lot of the underlying pathophysiology of this condition remains unknown (4).

Diagnosis is difficult, the gold standard being abdominal laparoscopy following a trans-vaginal ultrasound or Magnetic resonance imaging (MRI). Histological studies may help confirm the diagnosis although they are not fully reliable (5). Endometriosis may be asymptomatic (6), however, when it does manifest, the most common symptoms are dysmenorrhea and dyspareunia (2). It can be very incapacitating and debilitating. Severe dysmenorrhea has been linked to a higher incidence of depression, the pain itself can be chronic in nature and usually localized to the pelvis (7). Furthermore, endometriosis is a leading cause of infertility (8).

The chief target for drugs in endometriosis is pain relief. The most effective for pain-relief are hormonal therapies such as the combined contraceptive pill or the progesterone-only medication (9). Such hormonal treatment antagonizes the highly oestrogen-dependent lesions which go as far as to secrete their own oestrogen (10). This hormonal therapy has the drawback of modulating the woman's natural fertility; thus, interfering with the woman's potential wish to conceive as ovulation is antagonized by the exogenous hormones (11). NSAIDs are the most commonly prescribed painkillers (12). Regular use has been linked to infertility, however this is reversible and far less limiting than hormonal therapy. Evidence for the link is poor (13). In addition, there is new evidence pointing to a link between endometriosis and ovarian cancer (14) which may be ameliorated by the anti-inflammatory properties of NSAIDs (15).

Aim: This is a scoping review focusing on the efficacy of NSAIDs for pain relief and disease regression against a placebo, investigating their mode of action and hence the pathogenesis of endometriosis.

Method

The method began by formulation of a PICO question which not only specified our aim but also set basic limiters to the search engines (shown in Table 1). We took care with our search terms, keeping our aim in mind as well as anticipating all possibilities and adding appropriate Boolean operators where necessary (shown in Table 2). The inclusion and exclusion factors were carefully chosen to save time during the search and find us the data we required whilst establishing the limits of our study (Table 3). With the method planned out, we used our search terms within limits to search PubMed, Cochrane and EMBASE via the search engines HyDi by the University of Malta and Google Scholar.

Population	Girls (pre and pubescent) and women suffering from Endometriosis
Intervention	NSAIDs
Comparison	Placebo
Outcome	Pain reduction with or without regression in the pathogenesis of the disease

Table 1. Structure of the PICO Study Model

	Keywords	Other Search Terms
Population	Endometriosis	"Endometriosis-associated pain",
Intervention	NSAIDs, "Non-Steroidal Anti-Inflammatory Drugs"	Ibuprofen, Aspirin, Diclofenac
Comparison	~Placebo, "Sham Treatment"	"No Treatment", Control,
Outcome	"Pain Relief", "Inflammation Relief", Regression, Atrophy	"Pain Reduction", "Less Pain", Inflammation AND Reduction

Table 2. Search Terms Used

Inclusion	Exclusion
Human and Animal Subjects	Post-Menopausal
RCT's upwards on the Hierarchy of Evidence	Basilis Implantation Studies
Experimental Studies (RCT's upwards)	Pelvic Inflammatory Disease

Written in English	Treatment Post-Surgery
Pre-pubescent subjects	Studies >10 years old

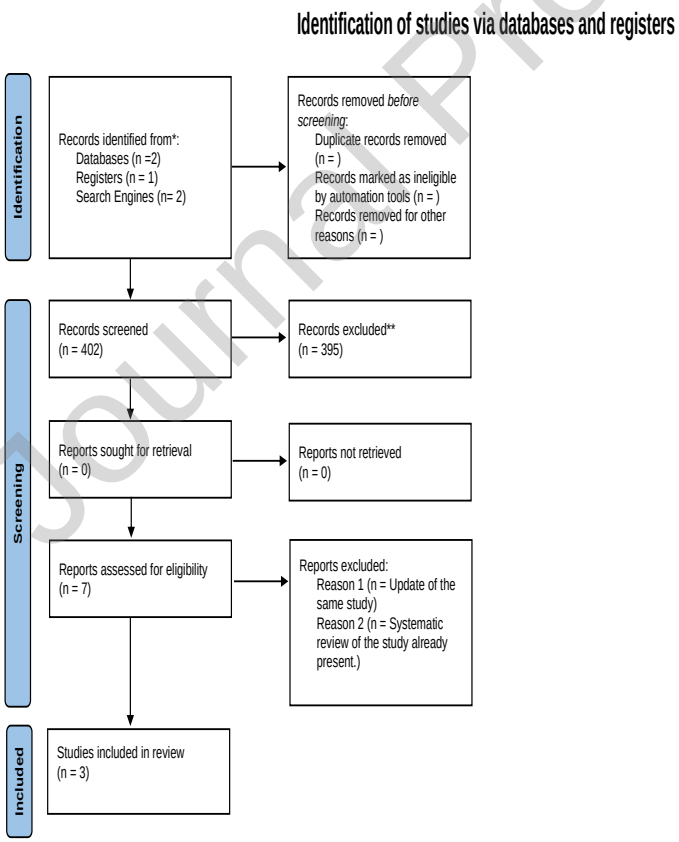
Table 3. Inclusion/Exclusion Criteria

Databases Used: PubMed, Cochrane and EMBASE were searched for this literature review.

Search Engines Used: HyDi by the University of Malta, Google Scholar

Results

Despite a thorough search in each database only three studies were found. Dysmenorrhea was common in confounding results within our exclusion criteria that forced us to exclude many studies due to irrelevance. Furthermore, 3 studies were found which resulted to be updates of the same study some years apart and so the older two had to be excluded as duplicates. This is all summarized in the PRISMA diagram below. Each study was then critically appraised through the use of the CASP checklists (unpublished).



PRISMA Diagram Summarizing the Result Screening Process.

There is indeed a paucity of data related to the pathophysiological role of NSAIDs in endometriosis. In fact, only 3 studies were eligible for inclusion in this review.

Brown *et al*. (2017) (22) analysed a single RCT, with a CI of 95%, and found that the effect of an NSAID (Naproxen Sodium) against a placebo produced unclear evidence of pain relief with an odds ratio of 3.27. It was concluded that NSAIDs do provide pain relief however the quality of evidence is low. Unintended effects of the intervention are unclear for the same reason. The Odds Ratio of 3.27 would suggest there is no link between the unintended effects and NSAIDs but the quality of evidence is poor. The previous 2009 study (19) also highlighted the need of supplementary analgesia showing no statistical difference between intervention and placebo groups. Otherwise, the results were duplicated from the same single RCT of their previous studies and no new data was available.

Cobellis *et al.* (2004) (21) reported that all participants using Rofecoxib claimed it was more effective for pain relief than the placebo with the P value being <0.001 (a P value < 0.005 considered statistically significant). Based on the questionnaire's responses, 6 of the 16 in the intervention group were 'very satisfied' and 5 were 'satisfied' with their treatment compared to the placebo group. The follow-up examination showed that endometriotic lesions did not recur in subjects who were intervention group, while two persons in the placebo group relapsed. No side effects were reported by the intervention group.

Efstathiou *et al.* (2005) (23) reported that the number of implanted endometriotic lesions flourished, measured by lesion growth and burden. The Dunnett t-test showed that there was statistically significant reduction of lesion establishment by celecoxib and indomethacin at 45%, and 46% (p <0.001 and <0.0001 respectively). Each NSAID treatment had reported statistically significant effects with all being P<0.01 except for aspirin with a P=1.0. This was further confirmed on application of the Tukey procedure. Ultimately celecoxib and indomethacin demonstrated the greatest efficacy.

In summary, the collective results tentatively show, based on poor evidence, that NSAIDs have an effect on pain relief, as found by Brown *et al*. (2017) (22). However, the RCT's offer fair evidence that NSAIDs not only provide pain relief but also directly affect the pathogenesis of this disease.

Discussion

NSAIDs act by inhibiting the two COX isoenzymes which convert arachidonic acid to thromboxane, prostaglandins and prostacyclin. This decreases inflammation with prostaglandins being the chief mediators countered by the drugs. They are vasodilators, raise the temperature in the area by interaction with the hypothalamus, and have anti-nociceptive properties (24). NSAIDs are widely used to treat dysmenorrhea due to their availability and affordability as well as minimal side effects and they are the only option for endometriosis patients wishing to conceive (25).

The results show that general NSAIDs are poorly correlated with pain relief. Allen *et al.,* (2009) (19) claim that supplementary analgesia was required in both placebo and intervention groups. That said, the NSAIDs in Efstathiou *et al.,* (2005) (23) actually treated the disease. Moreover, whilst that Randomized Controlled Trial (RCT) did not assess for pain relief, the best pain-relief was reportedly by Rofecoxib which is a specific COX-2 inhibitor in Cobellis *et al.,* (2004)'s (21) RCT. Therefore, we may so far postulate that COX-2 is mainly involved in pain, due to the specific action of Rofecoxib, whilst COX-1 is involved with endometriotic pathogenesis, as the latter was far more receptive to general NSAIDs and actually lead to disease regression. Furthermore, we may differentiate COX-2 as a secondary effector with COX-1 preceding it and being involved in early pathogenesis such as establishment of lesions. In conclusion, there may be a temporal difference in the activation of the respective enzymes in the pathogenesis of endometriosis with COX-1 being followed by COX-2.

The implantation theory serves as the model of choice for the aetiology of endometriosis in the review we are conducting given that only pre-menopausal women, who menstruate, seem to suffer from endometriosis (26). Furthermore, post-menopausal women lack the menstrual cycles which are proven to lead to endometriosis. Evidence of this may be inferred in the wide, successful, use of hormonal therapies for endometriosis.(24) It is important to note, however, that this theory does not explain endometriosis in neonates and pre-pubescent girls. Furthermore, about 70% of women experience retrograde menstruation, yet only a small portion experience endometriosis

(26). With this in mind, we emphasize that we are focusing on only a small component of the pathogenesis of endometriosis, which is known to be highly complex.

The temporal difference of the isozymes sounds plausible with the presence of COX-2 classically thought to be upregulated only by pathology that is only playing a role in inflammatory disease. This consistent presence of COX-2 in disease was the rationale for developing specific COX-2 inhibitors. Furthermore, it offers a simplistic answer to the clinical relevance of the proposed temporal difference. Recent evidence suggests, however, that both these enzymes are near-ubiquitous in human tissue. This means that 'the upregulation of COX-2 by pathology' claim loses much impact and renews the question of why COX-1 acts before COX-2 as has been postulated. Of more importance, however, is the presence of both COX isozymes in uterine tissue (27). This means that if the cause of endometriosis, according to the implantation theory, is haematogenous or lymphatic dissemination of endometrial tissue (25) then wherever the tissue goes, it will 'carry' with it both COX isozymes which will remain functional as long as the tissue survives. This may shed some light on the exact effect of ablative therapy on endometriotic lesions.

The theory that COX-1 acts before COX-2 gains traction by the observation that the pathogenesis of endometriosis precedes the pain. It is only on establishment, invasion and angiogenesis of endometriotic tissue that nerves are stimulated to elicit an inflammatory response and thus pain (28). Indeed, the invasion of endometriotic lesions can be >5mm deep (29) with inflammatory irritation or direct invasion and hence stimulation of pelvic floor nerves by infiltrating endometriotic implants (20). This is proven by the effect of neurectomies for severe endometriosis (28). Furthermore, it is recognized that COX-2 is not only active after the establishment of the condition but is also the enzyme responsible for expansion of the disease. For this invasion, neoangiogenesis is essential (30). It is important to note however, that nerve irritation is not the only source of pain. Indeed, there is evidence that endometriotic lesions are infiltrated by peripheral nerves due to the secretion of neurotrophic peptides, such as NGF, by the lesions. Ultimately, endometriotic lesions increase pain due to the growth of nociceptors (28). Furthermore, there is evidence of the phenomenon of central sensitization contributing to persistent pain (25). This suggests that pain is the product of invasion and establishment of the lesions with the coincident inflammatory response.

The inflammatory response, in turn, is the product of various factors. The sloughing of ectopic endometriotic tissue, overproduction of inflammatory mediators (including prostaglandins) (30), the effect of oestrogen or oestradiol (25) and interestingly of Radical Oxygen Species (ROS) (29), among many others, some of which are yet to be discovered. Following the above reasoning, inflammation is the indirect product of neoangiogenesis which facilitates lesion establishment. Furthermore, there is moderate evidence suggesting a direct link between angiogenesis and inflammation (31). A link has also been established between the genetic causation of angiogenesis and inflammation with inhibition of apoptosis in the lesions (29), the latter being a crucial part of the establishment of the condition.

It is known that neoangiogenesis is affected by various factors, some of which being prostaglandins which leads back to the COX isozymes. Thus, it is logical to hone in on the effects of various prostaglandins and even eicosanoids on neoangiogenesis. Furthermore, it would be fruitful to attempt to tease out any temporal differences in the actions of the COX isozymes and thus support the initial postulate with evidence.

As we are dealing with the COX isozymes, we are necessarily dealing with the production and effects of prostaglandins. The source of all prostaglandins is arachidonic acid, found among the phospholipids in the cell membrane (32). Both COX isozymes catalyse the conversion of arachidonic acid to Prostaglandin G_2 (PGG_2) and then to Prostaglandin H_2 (PGH_2). Each isozyme uses a different biochemical pathway.

There are two routes to obtain the arachidonic acid from the membrane, both hormone-stimulated, which are referred to in this paper as ‘direct’ and ‘indirect’. The ‘direct’ route is of most importance as it utilises phospholipase A2 which releases arachidonic acid immediately, as opposed to the ‘indirect’ route in which utilizes phospholipase C and involves the formation of precursors before arachidonic is synthesized (33). When COX-1 is exposed to calcium ionophore, that is a high concentration of calcium ions, it is inhibited and cannot function in the production of prostaglandins (34). However, it appears that only phospholipase C is inhibited, as phospholipase A2 is actually induced by increases in calcium ions [Ca2+] (35). Therefore, we may tentatively deduce that COX-1 and phospholipase C are directly coupled and utilise the ‘indirect’ pathway in generating prostaglandins. By elimination, we may also postulate then that COX-2 utilises the ‘direct’

pathway and hence phospholipase C. Nevertheless, this does not rule out concurrent use of the phospholipases by COX-2. Interestingly, the inhibition of phospholipase C by Ca2+ may have an inhibition concentration threshold as it has been reported that phospholipase C may be activated by intracellular, endogenous, Ca2+ (36).

Another difference between the isozymes is based on the premise is that aspirin chiefly inhibits COX-1, it has a much lesser effect on COX-2. Aspirin inhibits the binding of arachidonic acid to COX-1 by acetylation of a serine group in the active site. This prevents the reaction due to steric hindrance (37).This gains importance when we consider the results of Efstathiou *et al.* (2005) (23) that the least regression in the murine-implanted endometriotic lesions was found in those treated by aspirin. This suggests that COX-1 has a greater role in establishment of lesions, as the lesions were already established in Efstathiou *et al.* (2005) (23) and perhaps that is why aspirin had little effect. Furthermore, aspirin has little effect on COX-2 (37).

Regarding the production of eicosanoids from the COX isozymes, arachidonic acid is first converted to PGG_2 then to PGH_2 by the COX isozymes. The rest of the prostaglandins and thromboxane are then produced by other enzymes acting on the 'mother prostaglandin' PGH_2; for example, prostacyclin is produced by prostacyclin synthase acting on the PGH_2 substrate (38). It is reasonable to consider that not all PGH_2 produced is used for the production of other eicosanoids, indeed, it has its own respective effects. With PGH_2 and Thromboxane A2, both having their own receptors, the substrate and the product are used interchangeably due to similarity of effects: the aggregation of platelets by platelet activation (39), (36), (38). The enhanced presence of platelets is important due to Platelet-Derived Growth Factor (PDGF) found in platelet A granules. Here we may bolster our theory of COX-1 acting before COX-2 by the experimental proof that mice with COX-1 gene knockout showed markedly decreased platelet aggregation and concurrently less inflammation (40).

The contents of A granules are released on exposure to PGG_2 and PGH_2 (41). Endometriotic tissue has receptors for PDGF which stimulates endothelial, epithelial and stromal cell proliferation *in vitro* (26). More importantly, PDGF upregulates VEGF secretion specifically from endometriotic epithelial cells (26). VEGF is responsible for inducing early neoangiogenesis (42). Further evidence of this is that the use of a VEGF antibody decreases

vascular density (28). The process of neoangiogenesis requires pre-existing capillaries from which new vessels can sprout. This requires the proteolytic degradation of the ECM by MMP's and the migration and proliferation of endothelial cells which has been observed to be carried out by VEGF. It is interesting to note that endometriotic lesions establish a near constant stream of VEGF by their secretion of PGE_2 which also upregulates VEGF expression (26).

There exists evidence however that PDGF and BFGF are also involved (43). Despite the latter statement coming from a cancer analogy, we have shown the presence of PDGF and VEGF in endometriosis. The question remains regarding BFGF; Fibroblast growth factors are near-ubiquitous (44) and so it is reasonable to assume that BFGF is also present in endometriotic lesions. The secretion of basic fibroblast growth factor (bFGF) is shown to be induced by angiogenic mediators associated with white blood cells (WBC) (45). This points to a tentative postulate of initial 'founding' angiogenic mediators that establish the first blood supply to the endometriotic lesion followed by secondary mediators that maintain the blood supply. The former being Platelet-derived growth factor (PDGF) and Vascular endothelial growth factor (VEGF), the latter being bFGF at least. Adding to this theory is the observation that established endometriotic lesions also secrete Monocyte chemoattractant protein-1 (MCP-1/CCL2) as well as Interleukin 8 (IL-8) both of which indirectly contribute to further angiogenesis via their chemotaxis of white blood cells in endometriotic lesions (28).

Since chemotaxis by endometriotic lesions is partially necessary to attract white blood cells and hence our 'secondary' angiogenic mediators, the 'founding' and 'maintaining' theory gains traction. Neoangiogenesis necessarily requires an imbalance in favour of pro-angiogenic factors as opposed to inhibitory factors (26). This supports the need for 'maintenance' angiogenic mediators, which may work concurrently with the 'founding' mediators after establishment of endometriotic lesions. Should angiogenesis be imbalanced towards inhibitors would lead to the atrophy of the endometriotic lesion. This is clearly observed in the effective anti-angiogenic therapies offered for endometriosis (31). The rationale behind such a categorization of 'founding' and 'maintenance' mediators is to differentiate between what drugs to prescribe or synthesize based on the mediators present. Thus, a more targeted therapeutic approach to endometriosis may be possible. Although this approach may be considered simplistic, as certainly many signalling pathways

are involved (31), it is nonetheless fruitful to narrow the list of angiogenic mediators and categorize them.

Regarding the COX isozymes, thus far we have shown that COX-1 is allegedly responsible for all the above while COX-2 is, as of yet inactive, in the pathology of endometriosis. This is not to say that it is necessarily silent; it is unclear whether the ubiquitously-found COX-2 certainly has a role alongside the 'housekeeper' COX-1 (27) What shall be described now is an aberrant stimulation of COX-2.

COX-2 is highly responsive to pro-inflammatory mediators (34) all of which are initially brought about by COX-1 according to our theory. Evidence of this is through COX-1's attraction of WBC's that release IL-8, IL-1 etc. Further evidence is the effectiveness of immunomodulating drugs that target WBC's and their mediators such as pentoxifylline (42). Of importance is its inhibition of tumour necrosis factor α (TNFα) which was found to directly stimulate prostaglandin E_2 (PGE_2) secretion from COX-2 in rats (46), (47). This is but another link between inflammation and angiogenesis (48) specifically of the 'maintenance' type bolstered by the fact that COX-2 is involved. Paradoxically, despite established endometriotic lesions being to secrete PGE_2 (28), it was shown that COX-2 is inhibited by PGE_2 in a dose-dependent manner (46). Based on the strong secretion of PGE_2, two possibilities exist regarding COX-2 still functioning. In the first place, a balance of PGE_2 is secreted where it never exceeds an endogenous 'dose' that would cause inhibition. Secondly, the presence of cyclic adenosine monophosphate (cAMP) which was shown to experimentally negate the effects of inhibition by PGE_2 (46). There is evidence for the latter; the key lies in aromatases specifically found in endometriotic tissue (49) that secrete oestrogen/oestradiol (50). Indeed, this is the rationale for the effective use of specific aromatase inhibitors (30). The sheer complexity of the pathogenesis of endometriosis is shown by the fact that PGE_2 induces aromatases by secretion of cAMP (51). Thus, the inhibitor of COX-2 also has the effect of induction.

It is prudent to mention the limitation to the theory of TNFα's induction and that of PGE_2 inhibition. Firstly, that these experiments were performed on animal models and that the cells tested were intracerebral. The latter, may be remedied by the fact that both COX isozymes were found in the brain by the inference of the discovery of endometriotic lesions

in the human brain (29) and as reported, where there is endometriotic tissue, there are necessarily COX isozymes.

Further evidence that COX-2 functions after COX-1 has established the lesion is through Radical Oxygen Species (ROS). Particularly in patients with abdominal lesions, ROS develop in the peritoneal fluid which is rich in water and electrolytes in endometriosis; this is valid as endometriotic lesions are commonly found in the abdomen (28) Furthermore, there is evidence that haemoglobin is broken down in endometriosis resulting in the release of more ROS. Adding to the amount of ROS is the deficiency of antioxidants (29). The crux is that oxidative species are known inappropriate inducers of COX-2 (46). It is reiterated that the drawing of water and electrolytes into the abdomen as well as the breakdown of haemoglobin is due to previously formed endometriotic lesions which we maintain are by COX-1.

Conclusion

This review has shown that NSAIDs are poorly correlated with pain relief in endometriosis. However, specific COX inhibitors gave superior results and even pointed towards disease regression. This led to the hypothesis that there is a temporal difference between the actions of COX-1 and COX-2, with the former being primary, and useful in establishment of the condition, and the latter being secondary for maintenance and expansion. Initial evidence of this possibility is based on the specific effect of aspirin on COX-1. Further evidence was found by the effect of by COX-1 attracting platelets and contributing to neoangiogenesis which is crucial for establishment. On establishment, white blood cells were reported to invade and their release of mediators specifically induce COX-2. Finally, the induction effects of ROS on COX-2 by species produced by COX-1 were also reported. We further propose differences in the mode of action of the two isozymes as well as the possibility that neoangiogenesis is not uniform and indeed may be divided into ‘founder’ and ‘maintenance’ angiogenesis utilising different growth factors. Further research in this area is needed.

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Highlights

- The effect of NSAIDs were compared to a placebo for pain relief and disease regression for endometriosis in this literature review.
- NSAIDs were found to be overall effective in endometriosis despite lack of robust evidence.
- The results were combined with other literature to elucidate important and more robust points in the pathogenesis of endometriosis.
- We found that the COX isozymes have different temporal behaviour, catalyze arachidonic acid differently and that neoangiogenesis can be divided into two phases.
- Our findings hold promise for further research in a debilitating chronic illness and may pave the way for more targeted therapy.