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Management of endometriosis-related pelvic pain

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Key content

- The variable signs and symptoms of endometriosis contribute to significant diagnostic delay.
- Empirical hormonal treatment of endometriosis-related pain with cycle suppression may be considered without a definitive diagnosis of endometriosis.
- When considering laparoscopy to diagnose and treat endometriosis, a balance must be found between the need to avoid the very long diagnostic delays currently experienced and the likelihood of treatment benefits, set against the cost and risk of laparoscopy.
- Treatment for endometriosis-related pain symptoms includes a range of medical and surgical options with varying levels of evidence.
- Minimally invasive surgery should be performed by a surgeon trained to undertake surgical treatment for mild to moderate disease, thereby avoiding the need for repeat laparoscopy in the absence of severe disease, i.e. a 'see and treat' policy.

 Women with deep infiltrating endometriosis should be referred to an accredited endometriosis centre, such as the British Society for Gynaecological Endoscopy (BSGE) in the UK.

Learning objectives

- To understand the diagnostic difficulties surrounding endometriosis diagnosis and management.
- To identify the supporting evidence for treating endometriosisrelated pain.

Ethical issues

- When should laparoscopy for women with minimal endometriosis symptoms be performed?
- Should radical surgery always be performed in women in whom deep infiltrating endometriosis is found?

Keywords: endometriosis / pain management / surgery / treatments

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Introduction

Endometriosis is a common benign gynaecological condition classically defined as the presence of endometrial glands and stroma in ectopic sites outside the uterus. Both its surgical and clinical manifestations vary, often with poor correlation. Its aetiology and pathogenesis remain elusive and there appears to be a polygenic and multifactorial pattern of inheritance. Endometriosis may progress, remain static or even regress without treatment, and its treatment and management remain controversial.

Endometriosis affects 6–10% of women of reproductive age¹ and has a prevalence rate as high as 35–50% in women experiencing pain or infertility.² Three well-recognised forms of endometriosis have been described.³ Peritoneal endometriosis corresponds to minimal or mild endometriosis and usually no progression is observed. Ovarian endometriosis is characterised by superficial ovarian implants or endometriotic cysts which may be

adherent to the posterior aspects of the broad ligament. Deep infiltrating endometriosis (DIE) involving the bowel, bladder and rectovaginal septum is often associated with pelvic adhesions. It has been proposed that endometriosis is a heterogeneous condition, with peritoneal implants, deep infiltrating and ovarian endometriomas being manifestations of different disease processes.³

The cause of endometriosis-associated pain is unknown, but it has been suggested that peritoneal inflammation involving growth factors and cytokine production by activated macrophages, adhesion formation and irritation or direct invasion of pelvic floor nerves by infiltrating endometriotic implants may be responsible.⁴

Signs and symptoms of endometriosis

If empirical treatment for presumed endometriosis is to be prescribed, then a good understanding of the diagnostic value of specific symptoms is important. Endometriosis is

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frequently associated with dysmenorrhoea, chronic pelvic pain, deep dyspareunia, dyschezia (painful or difficult defecation) and infertility. Ballard et al. found that 83% of women with endometriosis reported one or more of these symptoms to their general practitioners when compared with just 29% of controls.⁵ Dyschezia during menstruation and deep dyspareunia are stronger predictors of DIE (74.5% sensitivity, 68.7% specificity, 2.4 positive likelihood ratio and 0.4 negative likelihood ratio).⁶ Pain symptoms increase as endometriotic lesion depth increases, but no relationship has been found between pain intensity and stage of disease.⁷

Despite the growing awareness of endometriosis symptoms, there are often significant delays between the onset of symptoms to definitive diagnosis, with a mean latency of 6.7 years in Norway, 8 years in the UK and 11.7 years in the USA.8 One reason for this delay is the significant overlap in symptoms with other conditions such as pelvic inflammatory disease, pelvic adhesions, irritable bowel syndrome, inflammatory bowel disease, interstitial cystitis and depression. Indeed, when the records of general practitioners were reviewed, women with endometriosis were 3.5 times more likely to have had a diagnosis of irritable bowel syndrome and 6.4 times more likely to have had a diagnosis of pelvic inflammatory disease when compared with women without endometriosis. A UK study on primary care found that one-third of women consulted their general practitioner six or more times before referral and diagnosis. 10

Examination and investigations

Routine vaginal examination alone is insufficient to make a diagnosis of endometriosis.¹¹ However, the location and extent of endometriosis can sometimes be determined by clinical examination.¹² Particular emphasis should be placed on the visualisation and palpation of DIE or nodules in the posterior fornix of the vagina. These lesions appear as dark blue nodules that are often dense and painful, and increase in size during menstruation.

Recent advances in imaging modalities, including ultrasound and magnetic resonance imaging, have improved the noninvasive preoperative diagnosis of endometriosis. ^{11,12} In specialist centres, transvaginal ultrasound has been shown to be a good test for assessing the severity of pelvic endometriosis and is particularly accurate for detecting severe disease, which could facilitate more effective triaging of women for appropriate surgical care, ¹³ although this has yet to be validated in routine clinical practice.

Strategy

The diagnosis of endometriosis is first suspected based on the history, then investigated by physical examination and imaging. The diagnosis is confirmed by visual inspection and histological examination of tissue excised during laparoscopy.

When endometriosis is suspected, the patient should be counselled about the alternative strategies of empirical hormonal treatment with cycle suppression leading to amenorrhoea, or 'see and treat' laparoscopy. Therefore, the strategy for managing endometriosis-related pain may actually reflect treatment for a clinical diagnosis of presumed/probable endometriosis unsubstantiated by laparoscopy. Once the diagnosis is confirmed by laparoscopy, then the choice of medical or surgical treatment remains.

Medical treatment

Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as a first-line treatment of endometriosis-associated pain even though very limited evidence supports their use. NSAIDs may also be effective analgesics for other conditions such as simple dysmenorrhoea and adenomyosis, and are not specific to the treatment of endometriosis. Studies showing elevated prostaglandin levels in the peritoneal fluid and endometriotic tissue of women with endometriosis support the use of NSAIDs.14 A Cochrane review on the role of NSAIDs in treating endometriosis-related pain analysed one randomised controlled trial (RCT) comparing naproxen sodium (275 mg, four times daily) with placebo but found no significant difference. 15,16 Another study that investigated the use of a cyclooxygenase-2 inhibitor (rofecoxib) against a placebo (n = 28) reported significant improvement of dysmenorrhea, dyspareunia and chronic pelvic pain.¹⁷ Although that study reported no adverse effects, Merck & Co. has since withdrawn rofecoxib because of its cardiovascular toxicity. 18

There are no other RCTs on the use of analgesics (paracetamol, aspirin, ibuprofen, opioids) for treating endometriosis-associated pain. ¹⁹

From a clinical perspective, the use of NSAIDs for managing pain should be discussed, and the discussion should address the adverse effects associated with frequent use of NSAIDs, including inhibition of ovulation and risk of gastric ulceration and cardiovascular disease.^{20,21}

Specialist help from a multidisciplinary pain team may be required for complex cases, where pain-modulating drugs such as pregabalin or gabapentin may be considered, or low-dose amitriptyline.

Hormonal therapies for treating endometriosisrelated pain

Endometriosis is a disease of women in their reproductive years that is associated with cyclical ovarian activity. Therefore, hormonal suppression to achieve amenorrhoea is considered a medical approach for treating the disease and its symptoms. Currently, combined oral contraceptives (COCPs), progestogens, anti-progestogens, gonadotrophin-releasing hormone (GnRH) agonists and aromatase inhibitors are in clinical use. As evidence supporting the use of one hormonal treatment over another is lacking, prescription will therefore depend on selection by the patient and the treatment cost. The European Society of Human Reproduction and Embryology (ESHRE) guideline states that it is reasonable to commence empirical treatment with analgesia and/or hormones before a diagnosis of endometriosis is confirmed, with the important proviso that the woman has been counselled thoroughly about the efficacy, adverse effect profile and availability of the different management options. ¹⁹

Combined oral contraception

A Cochrane systematic review evaluated the efficacy of COCPs for reducing endometriosis-associated pain. Although only one small RCT was included, it concluded that the COCP (0.02 mg ethinyl estradiol with 0.15 mg desogestrel daily, taken cyclically) was as effective as GnRH analogues for the relief of dyspareunia, dysmenorrhoea and non-menstrual pain.²² A more recent double-blind, placebo-controlled randomised, trial studied effectiveness of low-dose COCP compared with placebo for endometriosis-associated pain over four cycles, and concluded that pain scores for the COCP group were significantly reduced compared with placebo. 23 Modern low-dose COCP is now widely used to treat endometriosisrelated pain as it offers many practical advantages, including contraceptive protection and cycle control.

Although current guidelines suggest empirical treatment with analgesia, COCP or progestogens, there remains very limited strong evidence for the efficacy of COCP in treating endometriosis pain. ²² Changing from cyclical to continuous treatment may improve symptoms; however, moderate to severe adverse effects have been reported in 14% of women. ²⁴ There are insufficient data supporting the use of selective estrogen receptor modulators and selective progesterone receptor modulators. ²²

Progestogens and anti-progestogens

Clinical observation of the apparent resolution of symptoms of endometriosis during pregnancy gave rise to treatment with medication containing a progestogen. A recent Cochrane review concluded that medroxyprogesterone acetate (100 mg daily) is significantly more effective in reducing all symptoms when compared with placebo; however, its use was associated with significantly more cases of acne and oedema. There was no evidence of a benefit with depot or oral progestogens over other treatments (COCP or leuprolide acetate) for endometriosis-related symptoms. ²⁶

No studies have assessed the effectiveness of the progestogen-only pill Cerazette[®] for endometriosis, and the recommendation to offer it is a pragmatic approach.²⁶ The assumption is that by inhibiting ovulation, estrogen levels do not peak and the amenorrhoeic state it induces relieves symptoms, thereby yielding the same effect as continuous COCP but with a lower risk and adverse effect profile.

The levonorgestrel-releasing intrauterine system (LNG-IUS) releases levonorgestrel directly into the uterine cavity at a relatively constant rate of 20 microgram per day for 5 years. Levonorgestrel exerts strong local progestational activity and renders the endometrium atrophic and inactive, although ovulation is usually not suppressed. RCTs on LNG-IUS have shown that it significantly improves endometriosis-related pain, but this was not significantly different when compared with the effect of leuprolide acetate, a GnRH agonist. However, LNG-IUS has a significantly better adverse effects profile.

Although danazol reduces endometriosis-associated pain, significant adverse effects are common (e.g. acne, oedema, vaginal spotting, weight gain and muscle cramps), greatly reducing its usefulness.¹⁹

Anti-progestogens exert anti-proliferative effects on the endometrium while maintaining serum estradiol levels in the early to mid-follicular phase, thereby having a better adverse effect profile by avoiding the bone mass loss and hypoestrogenism associated with the use of progestogen only. ²⁶ A 2012 review reported that gestrinone was the only anti-progestogen evaluated in an RCT for endometriosis-related symptoms, and placebo-controlled trials were reviewed. ²⁶ However, there was no evidence of significant benefit when gestrinone was compared with danazol or leuprorelin (a GnRH analogue).

Gonadotrophin-releasing hormone (GnRH) agonists

GnRH agonists deplete the pituitary of endogenous gonadotrophins and inhibit further synthesis, thus inducing a hypoestrogenic state resulting in the interruption of the menstrual cycle, and endometrial atrophy and amenorrhea. A Cochrane review of 41 RCTs concluded that GnRH agonists were more effective than placebo but were inferior to LNG-IUS or danazol for relieving endometriosisassociated pain, given its worse adverse effects profile. 19,31 The hypoestrogenic effects of GnRH agonists include loss of bone mass of up to 13% at 6 months (reversible with discontinuation of therapy), therefore the simultaneous use of hormonal add-back therapy is recommended.³² Hormonal add-back therapy has not been shown to reduce the efficacy of GnRH agonists.³³ This can be explained by the estrogen threshold theory, which suggests that lower levels are needed to protect bone and cognitive function and to avoid/ minimise menopausal symptoms such as hot flushes, sleep

disturbance and mood swings than to activate endometriotic tissue.³⁴

Aromatase inhibitors (AIs)

Aromatase inhibitors (AIs) have been studied for treating endometriosis despite the controversies surrounding the evidence for increased expression of aromatase P450 in endometriotic tissue.³⁵ The most common third-generation AIs letrozole and anastrozole are reversible AIs, competing with androgens for aromatase binding sites. The adverse effects are mostly hypoestrogenic and include vaginal dryness, hot flushes and diminished bone mineral density. Earlier reports of increased cardiovascular risks have not been substantiated.¹⁹

Existing evidence for the use of AIs for endometriosis pain are mostly from moderate-quality, non-randomised studies or case reports that lack evidence of their long-term effects. Due to their severe adverse effects, current (2014) ESHRE guidelines recommend that AIs should only be prescribed after all other options for medical or surgical treatment for endometriosis pain have been exhausted. 19

Laparoscopic treatment

Laparoscopic treatment is ideally performed at initial diagnostic laparoscopy (a 'see and treat' approach) as recommended by the Royal College of Obstetricians and Gynaecologists. The ESHRE supports this approach, but acknowledges that symptoms do not always relate to the severity of clinical disease, and unexpected severe disease may be discovered at initial laparoscopy, which may require further counselling and subsequent surgical treatment. 19,37,38

When considering laparoscopy for diagnosing and treating endometriosis, a balance must be struck between the need to avoid the very long diagnostic delays currently experienced and the likelihood of treatment benefits against the cost and risk of laparoscopy. Also, laparoscopy that reveals minimal or mild endometriosis may be difficult to interpret, as the findings may not represent the cause of pain, and if treated at laparoscopy, might not be successful in treating the pain. Under these circumstances, there must be awareness of the potential for a placebo effect.

The indication for laparoscopy needs to be individualised and should include the woman's choice to have a definitive diagnosis, infertility investigations, signs and symptoms of severe disease, such as ovarian endometriomas, DIE or ongoing pain symptoms. It is important to note that the response to hormonal therapy has not been shown to always predict the presence or absence of endometriosis.³⁹

Surgery for endometriosis-associated pain

A woman with endometriosis should receive appropriate preoperative counselling. Surgery for endometriosis-related pain should be performed by a surgeon trained not only to establish the diagnosis of endometriosis, but also to undertake surgical treatment for mild to moderate disease. This approach would obviate the need for repeat surgical procedures in the absence of severe disease. A minimally invasive approach provides superior views of the pelvic organs and is associated with less pain, shorter hospital stay, quicker recovery and better cosmesis. Laparotomy may rarely be necessary for advanced disease with extensive adhesions or when there is adjoining organ involvement. Surgical procedures include excision, fulguration or laser ablation of peritoneal endometriotic implants; excision, drainage or ablation of endometriomas; resection of rectovaginal nodules; and adhesiolysis. Conservative surgery aims to treat all visible endometriotic lesions and restore normal pelvic anatomy.

A Cochrane review concluded that there were significant benefits of operative laparoscopy of endometriosis at 6 and 12 months after surgery when compared with diagnostic laparoscopy alone or medical treatment. The excision of lesions would be preferred if histological specimens are required, although ablation and excision of peritoneal endometriosis are equally effective for treating chronic pelvic pain in women with mild endometriosis.

An alternative strategy for controlling endometriosisrelated pain is interrupting the nerve pathways. A 2005 Cochrane review concluded that laparoscopic uterosacral nerve ablation conferred no additional benefit over conservative surgery, while presacral neurectomy combined with laparoscopic ablation of endometriotic tissue significantly improved dysmenorrhoea and reduced severe midline pain at 6 months and 12 months. However, performing presacral neurectomy requires a high degree of skill and is associated with increased risk of adverse effects such as bleeding, constipation and urinary urgency, and is seldom performed.

Surgery for endometrioma-associated pain

Laparoscopic excision of ovarian endometriotic cyst walls (≥3 cm) is superior to drainage and coagulation by bipolar diathermy for treating the recurrence of dysmenorrhoea, dysparaeunia and non-menstrual pain as well as reducing the rates of subsequent surgery.⁴² While the superiority of excision over drainage and coagulation/ablation might be expected, concerns about excessive resection of ovarian tissue compromising future fertility remain, with a reported risk of ovarian failure after bilateral ovarian endometrioma cystectomy of 2.4%.⁴³

It should be noted that endometriomas are strongly associated with deep infiltrating endometriosis (DIE).⁴⁴ If suspected, the woman should be referred to an endometriosis specialist centre capable of performing the appropriate surgery.

Surgery for deep infiltrating endometriosis (DIE)-associated pain

Deep infiltrating endometriotic nodules may involve the uterosacral ligaments, pelvic side walls, rectovaginal septum, vagina, bowel, bladder or ureter. Bowel endometriosis usually affects the rectosigmoid colon and can be associated with symptoms such as bowel cramping, diarrhoea or dyschezia. Treating colorectal endometriosis is difficult and challenging.

Medical management of DIE with colorectal extension is based on suppressing the symptoms, is not curative and is often associated with significant adverse effects. ⁴⁶ It is unclear whether medical management prevents disease progression; however, discontinuing medical treatment commonly results in the recurrence of symptoms. ⁴⁷

It is widely agreed that severe endometriosis, especially in symptomatic DIE with colorectal extension, requires surgical treatment. Surgical strategies include superficial shaving, discoid resection or segmental resection of the involved bowel segments to remove the endometriotic nodules. Although there is an ongoing debate about the indication for shaving nodules as opposed to segmental resection, most studies have reported improvement in pain outcome, quality of life and gynaecological and digestive symptoms after surgery for colorectal endometriosis. ⁴⁵ The reported intraoperative complication rate was 2.1%, and the total postoperative complication rate was 13.9% (9.5% minor, 4.6% major). ⁴⁸ The recurrence rates following colorectal endometriosis surgery in studies with more than 2 years of follow-up were 5–25%. ⁴⁵

Surgical treatment for bladder endometriosis is usually excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter; however, segmental excision with end-to-end anastomosis or re-implantation may be necessary if there are intrinsic lesions or significant obstruction.

Hysterectomy for endometriosis

Hysterectomy with bilateral salpingo-oophorectomy is generally reserved for women with debilitating symptoms attributed to endometriosis who have completed childbearing and in whom other medical therapies have failed. There are no RCTs on hysterectomy (with or without oophorectomy) for treating endometriosis-associated pain, but a review concluded that hysterectomy was successful in many women, but not all.⁴⁹ The success of this approach is attributed to debulking of the disease and the resulting surgical menopause causing endometrial tissue atrophy. Ovarian conservation at hysterectomy presents a six-fold greater risk for the development of recurrent pain and an 8.1 times greater risk of reoperation.⁵⁰ Hysterectomy is also used successfully to treat idiopathic dysmenorrhoea and adenomyosis.

Considering the physiology of endometrial tissue, postoperative hormone replacement that includes both estrogen and a progestogen appears sensible. The 2014

ESHRE guidelines suggest estrogen and progestogen therapy or tibolone for treating menopausal symptoms in women with surgically induced menopause because of endometriosis, at least up to the age of natural menopause.¹⁹

Complementary treatments

Surgical and hormonal treatment of endometriosis can have complications or adverse effects. In China, treating endometriosis using Chinese herbal medicine is routine. and there has been considerable research into the role of Chinese herbal medicine in alleviating pain, promoting fertility and preventing relapse. A Cochrane review found two RCTs showing that post-surgical administration of Chinese herbal medicine may have comparable benefits to gestrinone but with fewer adverse effects.⁵¹ Another review found 24 studies involving auricular acupuncture and Chinese herbal medicine for endometriosis; however, only one small trial fulfilled the criteria defining pain scores and cure. In that study, dysmenorrhoea scores were lower in the auricular acupuncture group than in the Chinese herbal medicine group. The total effective rate ('cured', 'significantly effective' or 'effective') for auricular acupuncture and Chinese herbal medicine was 91.9% and 60%, respectively. Evidence supporting the effectiveness of acupuncture for pain in endometriosis is limited.⁵²

A systematic review that assessed transcutaneous electrical nerve stimulation devices found insufficient evidence for determining and assessing the treatments accurately. The reviewers concluded that transcutaneous electrical nerve stimulation represents a suitable alternative for women who prefer not to use medication or who wish to minimise their intake of NSAIDs.⁵³

These findings highlight the necessity of developing future studies that are well-designed, double-blinded, RCTs that assess various complementary therapies in comparison to the conventional therapies.

Nutritional therapy/dietary modification

Nutritional therapy and dietary modification have shown promising effects for dysmenorrhoea, specifically omega-3 fish oil plus vitamin B12 supplementation and a diet high in vegetables and low in animal fats. Parazzini et al. found that intake of fruit and green vegetables decreased the risk of endometriosis, whereas intake of red meat increased it. Fibre intake with increased estrogen excretion also appears to be linked. Patients often adopt a strategy of dietary exclusion, but there is no evidence of any benefit particular to the treatment of endometriosis.

An RCT investigating the use of nutritional supplements on endometriosis demonstrated that 2-month high-dose vitamin E and C therapy was associated with significant improvement in pain.⁵⁶ Two other randomised, double-

blinded, placebo-controlled trials demonstrated significantly decreased median pain scores with vitamin E administration for primary dysmenorrhea. 57,58

It has been suggested that there is an inverse association between body mass index and endometriosis. A 2013 20-year review found evidence of this with a prospective cohort study. ⁵⁹ This association may correlate with lower peripheral body fat distribution and with less estrogen resistance.

Patient support groups and self-management

Physical and psychological trauma can contribute to a negative self-image. A small Italian study in 2014 suggested that some mood or anxiety disorders, high alexithymia, and malfunctioning obsessive-compulsive symptoms are more frequent in women with endometriosis than in the general population. ⁶¹

Thus, some women with endometriosis may benefit from working with a counsellor/psychologist to develop strategies on breaking the pain cycle, dealing with stress and anxiety and resolving personal negative feelings.

Multidisciplinary team

The requirements of a British Society for Gynaecological Endoscopy (BSGE)-accredited centre for treating severe endometriosis include having named colorectal, urological, pain specialist and nurse members. This reflects the problems encountered with recurrent disease and recurrent pain with multisystem involvement. Some departments have gone on to formalise this with multidisciplinary team meetings.⁶²

Chronic pain/pain teams

Women with little or minimal disease and who do not improve with hormonal or analgesic treatments are a challenging group who are labelled as having chronic pelvic pain. Such patients often require long-term pain management with frequent reassessment and adjustment of therapy. The chronic pain model recognises the condition as a combination of physical dysfunction, beliefs and coping strategies, distress, illness behaviour and social interactions.⁶³ Pain management has moved towards the primary care setting, and the quality of pain services and the access to these services across England varies significantly. This variation was highlighted in the Clinical Standards Advisory Group report on services for National Health Service patients with acute and chronic pain in 2000.64 It is important that primary, secondary and tertiary care teams cooperate to provide adequate access to these services.

Conclusions

The clinical presentation of endometriosis is highly variable and often women are referred from their general practitioners, having tried at least one form of hormonal treatment. Although empirical treatment with hormones is feasible, especially in young women with mild symptoms, a referral should be considered when either a trial of hormonal treatment has failed or when signs of deep infiltrating disease are present. Women with endometriosis should be referred to a gynaecologist with a special interest in endometriosis, and women with DIE should be referred to BSGE-accredited centres where gynaecologists work in appropriate clinical teams, audit their outcome and have sufficient workload to maintain their surgical skills. Decisions for laparoscopy should be made with the intention of performing treatment at the primary operation, as repeat laparoscopies are associated with increased risks for the patient and increased related costs. 'Diagnostic laparoscopy' should be an outmoded concept because symptoms suggestive endometriosis should be assessed by a surgeon with the appropriate experience to treat any endometriosis found. Indications for repeat or second laparoscopies should be limited to cases of severe disease, where there is increased risk of surgery that will require further discussion with the patient. Long-term treatment of women with chronic pelvic pain associated with endometriosis involves repeated courses of medical therapy, surgical therapy or both. In such circumstances, a multidisciplinary approach involving a pain clinic and counselling should be considered early in the treatment plan.65

Disclosure of interests

The authors declare no conflicts of interest.

Contribution to authorship

W-LH wrote the paper and KL supervised and revised the draft. All authors read and approved the final version of this paper.

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