ARTICLE

Medical management of endometriosis

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SUMMARY

Endometriosis is increasingly being recognised as a disease which commonly affects women through the reproductive years.

It is the commonest cause of chronic pelvic pain in developed countries, and frequently begins in adolescence.

Endometriosis is a highly variable condition, and diagnosis can be difficult. Confirmation of diagnosis still requires laparoscopy in most situations, but successful therapy of many, especially milder, cases can be based on a presumptive diagnosis. A careful history needs to be taken to try and exclude other common causes of pelvic pain.

Medical management requires treatment of pain with analgesics, and suppression of disease activity mainly with hormonal preparations. This needs to be integrated with the potential need for surgery.

Patients with persistent pain unresponsive to hormonal treatments and analgesics should be referred for specialist care.

Introduction

Endometriosis is a complex condition of great variability and presentation (see Box 1).[1] In many cases, this variability leads to difficulty and delay in making the diagnosis.[1,2] Most studies report a mean duration of 8–10 years between the onset of symptoms and the diagnosis. Longer delays can occur when the symptoms begin in adolescence.[3,4] Aside from the variability in presentation, the major reasons for delays in diagnosis include the prevalence of pelvic pain symptoms in the community and a lack of awareness by many health professionals that the onset of symptoms often occurs in adolescence. However, it is widely recognised around the world that endometriosis is now the commonest cause of chronic pelvic pain in women in most industrialised societies.

Early recognition of endometriosis

Early recognition of the signs and symptoms (especially in those with a family history) will allow medical management to reduce disease progression and its consequences, including infertility and endometriosis-associated health problems. Educating health professionals and the community to consider the diagnosis of endometriosis in young women with dysmenorrhoea and pelvic pain is important.

Assessing women with suspected endometriosis

Diagnosis based purely on clinical features may have a high rate of error so an important aspect of managing women with suspicious symptoms (Box 2) is knowing when to refer them for a specialist opinion (Box 3). If classic combinations of symptoms are present, especially in the presence of a family history, a diagnosis of endometriosis is highly likely.

The initial assessment involves taking a detailed history of the duration and nature of pelvic pain. Ask about its relationship to the menstrual cycle, the presence of bowel and bladder symptoms and the impact of posture and movement on pain.

There may be overlap between the symptoms of irritable bowel syndrome, pelvic inflammatory disease and endometriosis and it can sometimes be difficult to distinguish clinically between these conditions.[5] There are also a number of co-existing pain conditions in women with endometriosis, such as interstitial cystitis, which should be considered in the assessment of a woman with pelvic pain. Women with irritable bowel syndrome will usually experience relief following a

Box 1 Variable factors leading to a heterogeneous clinical picture of endometriosis

The age of symptom onset – from adolescence through to later reproductive years

The delay to diagnosis – often 8–10 years with onset in adolescence

The types of symptoms experienced – usually much more complex than just pain, including infertility, abnormal menstrual bleeding patterns, exaggerated and painful abdominal bloating, other gastrointestinal symptoms, urinary symptoms, extreme lethargy

The anatomical sites of ectopic lesions – there are possibly different 'phenotypes' of endometriosis (peritoneal, ovarian endometriomas, deep invasive lesions)

The response to medical or surgical treatment

The likelihood of early recurrence of disease

The variable 'natural' history of disease progress over years

bowel motion, whereas this relief does not usually occur with endometriosis.

Initial investigations may include urinalysis, screening for sexually transmitted infections and a transvaginal ultrasound scan. Transvaginal ultrasound scanning by a specialist in pelvic sonography has a reasonably high sensitivity and specificity for diagnosing ovarian endometriotic cysts and deep infiltrating bowel endometriosis,[6,7] but is of little use in identifying the commoner types of peritoneal disease. Diagnostic laparoscopy by an experienced gynaecological endoscopist remains the best way of confirming or excluding most types of endometriosis as there is no consistently reliable non-invasive test.[8]

When no diagnosis is evident

When uterine, adnexal or cervical motion tenderness is present in sexually active young women and no other cause is identified, guidelines recommend treatment for presumptive pelvic inflammatory disease.[9] However, other possible diagnoses may need to be pursued. Endometriosis is under-diagnosed in this group of young women and having a low threshold for referral is important.

When examination and investigations reveal no definitive diagnosis, women should be offered simple analgesia to control their pain, beginning with non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol in effective doses. Patients with persistent pain unresponsive to these analgesics should be referred for specialist care, including a gynaecologist for diagnostic laparoscopy.

Management of women with confirmed endometriosis – factors to consider

The management of endometriosis may be influenced by the woman's presenting complaint, for example pain or infertility.

Endometriosis is a chronic condition that may require lifelong management. Medical treatment is usually based on suppressing ovulation and inducing a steady hormonal environment. Commonly used drugs and their mechanisms of action are listed in Table 1. Both oral progestogens and combined oral contraceptives may be effective in relieving pain. They are generally well tolerated and are initially preferable to danazol, gonadotrophin releasing hormone agonists and aromatase inhibitors.[10] In our clinical experience, in most women progestogen-only methods that induce decidualisation of the endometrial lesions are

Box 2 Symptoms suspicious of endometriosis

- Dysmenorrhoea (moderate to severe in 60–80%)
- Chronic pelvic pain (troublesome in 40–50%)
- Deep dyspareunia (troublesome in 40–50%)
- Infertility (30–50%)
- Premenstrual spotting lasting 1–2 days (common)
- Dyschezia, tenesmus, painful abdominal bloating (10–40%)
- Dysuria, haematuria (5%)
- Heavy menstrual bleeding (10–20%)

Box 3 When to refer women for specialist opinion

- Unexplained persistent pelvic pain
- Symptoms unresponsive to initial supervised hormonal or analgesic treatment
- Primary infertility of greater than one year (or less in older women)
- Finding a pelvic mass or nodule, especially if tender, on bimanual vaginal examination

Table 1 **Treatment options for endometriosis (in addition to necessary analgesia)**

Medical treatment	Mechanism of action	Adverse effects
Combined oral contraceptives	Inhibit ovulation, decidualise endometriotic tissue	Mood changes, nausea, headaches, hypertension, deep venous thrombosis (rare)
Oral progestogens	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Levonorgestrel intrauterine system	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, breast tenderness
Etonogestrel implants	Inhibit ovulation, decidualise lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Gonadotrophin releasing hormone agonists	Down-regulate the pituitary-ovary axis and produce a hypo-oestrogenic state, with lesion atrophy	Hot flushes, change in libido, vaginal dryness, headaches, emotional lability, acne, myalgia, decreased breast size
Aromatase inhibitors	Inhibit oestrogen synthesis with lesion atrophy	Hot flushes, arthralgia, myalgia, osteoporosis
Androgens (danazol)	Complex effects on the hypothalamic-pituitary-ovarian axis and uterus, including mild, impeded androgenic action, resulting in lesion atrophy	Acne, hirsutism, voice changes, emotional lability

more effective than combined oral contraceptives. There is a trend towards use of the delivery systems like the levonorgestrel intrauterine system, which has evidence of efficacy,[11,12] and the subdermal etonogestrel implant, where the benefit has been documented so far mainly in case reports. It is not logical to give an oestrogen-containing preparation (combined oral contraceptive) to a woman with an oestrogen-sensitive disease, but all modern combined oral contraceptives have a strong progestogenic balance and many women do well with this treatment. There is no evidence that one combined oral contraceptive is superior to another.

Fertility

In a woman wishing to conceive, medical treatment will relieve symptoms but there is strong evidence that it does not improve fecundity. The recommended approaches are surgical excision of macroscopically recognisable lesions on the peritoneal surface, deep lesions or ovarian cyst linings by a specialist, or referral for assisted fertilisation techniques.[13]

Management by a gynaecologist

Specialist management of endometriosis involves judicious use of laparoscopy for diagnosis, well-planned laparoscopic surgery and medical management. Excisional surgery is usually the initial treatment of choice, as it confirms the diagnosis, significantly reduces painful symptoms and improves quality of life in 67–80% of patients compared to techniques using diathermy or laser to coagulate or vaporise visible lesions. Such surgery can be difficult but complete excision is the goal. Postoperative medical preventive therapy should always be considered, unless pregnancy is immediately desired. Deep infiltrating pelvic endometriosis involving the bowel requires a multidisciplinary approach with colorectal surgery.

In women with minimal to mild endometriosis-associated infertility, there is evidence that surgery that excises visible deposits, divides adhesions, and normalises pelvic anatomy may enhance fertility.[14] Although there are no randomised controlled trials or meta-analyses available to answer the question of whether surgical excision of deep invasive endometriosis enhances pregnancy rates, observational studies provide some support.[15] Laparoscopic cystectomy for ovarian endometriomas greater than four centimetres in diameter improves fertility, compared to drainage and coagulation of the cysts, but the presence of a small asymptomatic endometrioma may not require surgical intervention before *in vitro* fertilisation.

There is usually amelioration of symptoms during pregnancy and there may sometimes be long-term improvement in pain after pregnancy. However, many women with endometriosis will experience recurrence of symptoms as soon as pregnancy and breastfeeding have been completed.

It is important to recognise that the extent of endometriosis may not correlate with the presenting symptoms, and some women with mild peritoneal endometriosis may have severe debilitating pain while others with severe disease and gross distortion of pelvic anatomy may experience minimal or no symptoms. Further, if endometriosis is found at laparoscopy it may not always be the major cause of pain in an individual, and pain symptoms attributed to endometriosis occur in some women without obvious laparoscopic evidence of endometriosis.

Recurrence after surgery

Endometriosis has a propensity to recur with time after conservative surgery (excision of visible lesions, rather than removal of the ovaries and uterus). At least 10–20% of treated patients developed signs and symptoms of persistent or recurrent endometriosis within one year.[16]

Secondary prevention

There is good evidence that hormonal treatments after surgery reduce symptoms and disease recurrence. The combined pill and oral progestogens have been found to reduce the frequency and severity of recurrent endometriosis-related dysmenorrhoea[17] and endometriomas after surgery.[18] Local pelvic release of levonorgestrel via an intrauterine system is an effective way of delivering progestogen therapy and has been found to be as effective at relieving dysmenorrhoea as gonadotropin releasing hormone agonists[19] or injectable progestogens, without the same degree of systemic symptoms.[20] The role of the subdermal etonogestrel implant in this situation has not yet been clarified.

Treatment

If recurrence occurs, initial treatment should be appropriate analgesics and hormonal treatment. Repeat surgery has the same limitations as primary surgery in terms of disease recurrence. In the most severe and troublesome symptomatic endometriosis, combined off-label use of the two progestogen delivery systems (levonorgestrel intrauterine system and etonogestrel subdermal implant used simultaneously) may have a major beneficial impact on quality of life, but there is only one case report to support this line of management.[21] It also needs to be recognised that a minority of severe

endometriosis sufferers experience persistent pelvic pain, which has a major impact on quality of life. Ongoing management may require involvement of a specialised pain management clinic.

Conclusion

As a greater understanding of the pathophysiology of endometriosis emerges, new targets for treatment will become available. Until then the best approach combines both medical and surgical modalities. The single significant barrier to good management of endometriosis is still timely recognition of the disease, especially in adolescents.

A greater awareness of the variability in the clinical presentation of endometriosis could potentially reduce the social, health and economic impact of this condition on women.

Dr Black is a consultant for Bayer HealthCare on an international advisory board (Bayer is the maker of Mirena). Professor Fraser has undertaken consultancies, lectures and research projects for Bayer Pharmaceuticals, Merck/MSD, Daiichi Sankyo and Vifor Pharma and has received honoraria, lecture fees and expenses. These honoraria and lecture fees are directed to his research program.

Q:

SELF-TEST QUESTIONS

True or false?

3. Medical treatments for endometriosis usually improve fertility.

4. Danazol is one of the first-line treatments of choice for endometriosis.

Answers on page 135

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