



The pharmacological management of
ENDOMETRIOSIS

Endometriosis is a gynaecological condition in which endometrial tissue is present outside the uterine cavity, causing cyclic symptoms and, often, reduced fertility. A “working diagnosis” can be made based on the patient’s symptoms and evaluation of risk-factors, although laparoscopy is required for a definitive diagnosis. Medical management involves the hormonal suppression of endometriotic lesions and, where possible, the surgical ablation and excision of ectopic endometrial tissue.

Endometriosis: a challenging diagnosis

Endometriosis is defined as the presence of endometrial tissue, glands and stroma outside the uterine cavity. The condition generally has three distinct manifestations: endometrial implantation on the peritoneum causing lesions and endometriomas (generally within the pelvic region, e.g. on the bladder, in the Pouch of Douglas), ovarian cysts (chocolate cysts) and endometriotic nodules in the tissue between the rectum and vagina (see opposite for definitions).¹

The clinical presentation of women with endometriosis varies widely. Some women may be completely asymptomatic (and therefore not aware of the condition) while some women will have chronic pelvic pain, dysmenorrhoea, dyspareunia (pain during sexual intercourse) and painful defecation.² As endometriotic lesions are hormonally-responsive, symptoms will usually be worse at the time of menstruation. During periods of anovulation, such as pregnancy, lactation, menopause and hormone-induced amenorrhoea, symptoms are reduced or eliminated.³ Endometriosis can have a significant effect on female fertility, and many women with undiagnosed endometriosis may first present with difficulty conceiving (See “Endometriosis and fertility”, Page 24).

The exact prevalence of endometriosis is unknown, but it is estimated to affect 5 – 10% of women of reproductive-age, as many as half of all women with reduced fertility,^{1,2} and 70 – 90% of women with chronic pelvic pain.¹ The peak incidence is in women aged between 25 – 30 years.⁴ Endometriosis rarely occurs in younger females and in post-menopausal women.³ Endometriosis is also possible in males taking high-dose oestrogen, although this is extremely rare.⁴

The terminology of endometriosis

Endometriotic lesion – Lesions that occur when endometrial tissue seeds outside the uterus. Bleeding may occur from these lesions at the time of menstruation.

Endometrioma – An oestrogen-dependant lesion that is usually enlarged and filled with old blood. When they occur on the ovaries they are often referred to as chocolate cysts.

Endometriotic adhesion – Internal scar tissue that can bind organs together, causing organ dislocation and pain. The fallopian tubes, uterus, ovaries, bowel and bladder are the most commonly affected organs.

Endometrial stromal nodule – An uncommon, non-infiltrative, confined growth of endometrial stromal cells, which can develop into a rare type of cancer; an endometrial stromal sarcoma, which frequently metastasises.

The cause of endometriosis is unknown

The pathology of endometriosis is not well understood. Retrograde menstruation, where menstrual fluid flows back up the fallopian tubes and into the peritoneum, is believed to be central to the development of endometriosis.^{2, 3} Endometrial cells are thought to move back up the fallopian tubes with the menstrual fluid, and possibly through the lymphatic and vascular network. The cells deposit in various tissues, seeding and developing into endometriotic lesions and endometriomas. When this occurs, internal bleeding and inflammation can lead to fibrosis and adhesion development, which in turn contributes to the symptoms and the physical distortion of pelvic anatomy that is seen in women with more severe endometriosis.

Although retrograde menstruation is estimated to occur in 90% of women, only a portion of these women will go on to develop endometriosis.⁵ Current research is focused on investigating the genetic components of endometriosis.⁶ Hormonal, immunological and environmental components are also implicated in the initial development of the condition.

Risk-factors for endometriosis

Risk factors for endometriosis include:^{1,4}

- A first-degree female relative (mother or sister) with endometriosis
- Shorter-than-normal menstrual cycle (< 27 days)
- Longer-than-normal menstruation (> five days)
- Low body-mass index
- Early menarche
- Nulliparity
- Müllerian anomalies – anomalies that arise during the formation of parts of the female reproductive organs
- Outflow obstructions, e.g. cervical stenosis, a transverse vaginal septum or an imperforate hymen

The distribution of ectopic endometrial tissue is influenced by age. Pelvic endometriomas typically occur in women aged 25 – 30 years.⁴ Ectopic endometrial tissue outside the pelvic area typically occurs in older women, most commonly in those aged 35 – 40 years.⁴

Making a 'diagnosis' of endometriosis

Making a clinical diagnosis of endometriosis can be difficult as symptoms are often non-specific, there are limited clinical signs on examination, laboratory testing is not helpful and imaging is of only limited benefit.^{7,8} Laparoscopy is therefore required to make a definitive diagnosis.⁷ On average, there is a delay of seven to twelve years between the development of symptoms and diagnosis of endometriosis, which impacts significantly on the patient's quality-of-life.⁷ The presumptive diagnosis and medical management of endometriosis in primary care is, therefore, important in reducing avoidable pain and discomfort and managing fertility.

Symptoms are non-specific and common

Approximately one-third of women with endometriosis will be asymptomatic. Most women with symptomatic endometriosis will have cyclical symptoms, such as pelvic pain which is the most frequently occurring symptom. Pain generally begins several days prior to menstruation and ceases within one to two days of menstruation.⁴ Deep pain may also be present during or after sexual intercourse. If endometriotic lesions are present in the bladder or rectum, pain may be present during urination or defecation.³ In severe cases, pain may become constant as the condition worsens and deep endometriotic lesions and adhesions develop.⁵

Rarely, endometriotic lesions can occur outside of the abdominal cavity, such as in the lungs, and can cause pain and other symptoms, such as haemoptysis, coinciding with the menstrual cycle.⁵

Common symptoms of endometriosis include:^{4,9}

- Severe dysmenorrhoea
- Bloating
- Lethargy
- Pelvic pain
- Constipation
- Lower abdominal or back pain
- Dyspareunia
- Painful defecation
- Infertility
- Heavy menstruation or pre-menstrual spotting (may also indicate co-existing adenomyosis, see opposite)
- Cyclic pain upon urination or urinary frequency
- Pain during exercise

Acute exacerbations of pain, swelling or fever may occur due to chemical peritonitis if leakage of blood from an endometriotic lesion or cyst occurs.⁴

Clinical examination may be helpful to rule out other conditions

Most women with endometriosis will have normal examination findings; however, diffuse pelvic or posterior fornix tenderness or palpable pelvic masses are sometimes present. In some women, uterosacral ligament nodules may be palpable on a bimanual vaginal examination.

Examination is therefore primarily for the purposes of differential diagnosis, and should include assessment for sexually transmitted infections (STIs), cervicitis, abnormal vaginal discharge and any other gynaecological abnormalities, such as cervical excitation and adnexal masses.

Imaging and laboratory tests are of limited benefit

Imaging is not usually helpful. If available, transvaginal ultrasound imaging can be considered; however, if cysts and nodules are small or not situated on the ovaries or near the uterus the imaging will not be of any use.¹⁰

There is no laboratory test that can reliably identify endometriosis.¹¹ Investigation of full blood count, ferritin and TSH may be useful in the differential diagnosis.

Other diagnoses are always a possibility

Women with endometriosis often present with diverse, non-specific symptoms, and other possible diagnoses should always be considered.

Acute symptoms caused by STIs, urinary tract infections (UTIs) and pelvic inflammatory disease often mimic endometriosis, however, given the chronic nature of endometriosis, it is likely that these conditions can be ruled out early.

Some long-term conditions have symptoms that overlap with endometriosis and it may be difficult to rule these out. Differential diagnoses that should be considered in women with pelvic pain include adenomyosis, diverticulitis, irritable bowel syndrome, uterine fibroids and interstitial cystitis.

Adenomyosis occurs when endometrial tissue, is present within the muscles of the uterus (as opposed to endometriosis which occurs outside the uterine cavity). It is usually found in women in an older age group than endometriosis (age 35 – 50

years), and often after childbirth. It is almost symptomatically identical to endometriosis and can usually only be distinguished after laparoscopy. Adenomyosis also commonly co-exists with endometriosis.

Generally, presentation and patient history will shift the balance of probabilities for a diagnosis, e.g. uterine fibroids are more common in an older age-group and a patient with irritable bowel syndrome is less likely to present with painful defecation.¹⁰ However, some conditions will be nearly impossible to rule out until laparoscopy is performed or a therapeutic trial of treatment is undertaken.

Always consider the possibility of colon and ovarian cancer which may present concurrently, even in women with laparoscopically diagnosed endometriosis. In addition, in a small number of women, uterine and müllerian abnormalities, both of which are risk-factors for endometriosis, may be present and complicate diagnosis and treatment.

When should a patient be referred for further assessment?

The management of suspected endometriosis depends on the patient's age, desire for conception, the degree of pain, the impact on their capacity to work and their overall quality of life.⁸ Generally, a three-month therapeutic trial with hormonal treatment can be used to help strengthen a working diagnosis. However, this is not appropriate in certain instances.

Referral to secondary care for further assessment should be undertaken if:¹⁰

- Endometriosis is strongly suspected and immediate fertility is desired
- A trial treatment with analgesia and a hormonal medicine is unsuccessful
- The patient has persistent, constant pelvic pain, or significant bowel or bladder pain
- A pelvic mass, especially if tender, is found on examination
- The patient has pain or other symptoms that require a significant amount of time off work or school

Medical management of endometriosis

The aim of medical management is to control symptoms, either prior to, alongside or instead of more curative surgical interventions. Medical management is based on hormonal suppression of endometriotic lesions and is particularly effective when amenorrhoea occurs via down-regulation of the hypothalamic-pituitary-ovarian axis.¹²

Endometriosis is a chronic and often recurrent condition and long-term treatment is usually required. Approximately 50% of women will have a recurrence of symptoms within five years if medical management is stopped. Menopause usually leads to a complete cessation of symptoms, even if hormone replacement treatment is used.⁶

A step-wise treatment strategy

The first-line treatment for females with endometriosis who do not wish to conceive in the near future is a hormonal medicine, and analgesics if required.⁹ Combined oral contraceptives are the most widely used hormonal treatment, followed by progestin hormone treatment.⁸ Other hormonal treatment options include androgenic medicines and gonadotropin-releasing hormone analogues: both of which have comparable efficacy.^{4, 5, 12} However, adverse effects limit gonadotropin-releasing hormones to a second-line choice and androgenic medicines are now rarely used due to their adverse effects.

Pain relief

Non-steroidal anti-inflammatory analgesics (NSAIDs), such as ibuprofen, naproxen or mefenamic acid are recommended for acute pain relief as an adjunct to all medical management options and prior to surgery in women who wish to conceive.^{10,13} All NSAIDs have similar efficacy in the management of endometriosis.¹³ Opioids should generally be avoided due to issues with long-term use.¹²

Combined oral contraceptives

Combined oral contraceptives are widely used as the first-line pharmacological treatment for women with suspected endometriosis, as these medicines are generally well tolerated with less adverse and metabolic effects than other options.⁸

The choice of combined oral contraceptive should be based on any previous use by the patient. If no combined oral hormonal contraceptives have been previously used, a trial of a levonorgestrel + ethinylloestradiol contraceptive, e.g. Ava, is recommended.

Combined oral contraception should be used continuously or semi-continuously, e.g. three or six-month cycles, as monthly uterine bleeds are likely to be painful, although less so than normal menstruation.^{8,10} Patients should be advised that this may result in irregular spotting and occasional breakthrough bleeding.

Adverse effects of combined oral contraceptives are generally mild.¹⁰ They include gastrointestinal disturbance, headache, migraine, metabolic and weight changes, irritability, changes to libido, cramping and spotting in early cycles. Venous thromboembolism is also possible, although rare, in women taking combined oral contraception. Combined oral contraceptives will need to be discontinued if migraines occur.

Progestins and anti-progestins

High-dose progestins (medroxyprogesterone acetate 10 – 100 mg daily or norethisterone 10 – 45 mg daily) are commonly used to treat endometriosis, and are an alternative to combined oral contraceptives.¹⁰ At these doses, progesterone suppresses the hypothalamic-pituitary axis to inhibit ovulation and reduce circulating oestrogen levels.³ Progestins also have an additional, direct effect on the endometrium, causing atrophy to both normal endometrium and endometriotic lesions.³ They are relatively well tolerated and have a more limited metabolic impact than androgenic analogues and gonadotropin-releasing hormones, and are less expensive than these options.

Progestin-only contraceptives are available in a variety of formulations, including oral medicine, implants and depot injections. Adverse effects of progestins include bone mineral density loss, weight-change, acne, oedema, mood changes, depression and headaches.¹⁴ There is little difference in efficacy effect between formulations, however, patients administered depot progestin may experience more adverse effects.¹⁴

Oral medroxyprogesterone acetate (Provera) 10 mg, three times daily, for ninety days is approved for use in endometriosis. Oral medroxyprogesterone acetate should be started on day one of the menstrual cycle.

Depot medroxyprogesterone acetate (Depo-Provera) 50 mg weekly or 100 mg every two weeks, for at least six months is also approved for use in women with endometriosis.¹⁵ N.B. vials come in 150 mg/mL.

Norethisterone (Primolut) 5 mg, twice daily, for six months is approved for use in women with endometriosis. Norethisterone

should be initiated between days one and five of the menstrual cycle.

The levonorgestrel intra-uterine device (Mirena) has been shown to be effective in managing the symptoms of endometriosis. However, this is an unapproved indication. The device is placed into the uterine cavity, usually at the onset of menstruation and may prevent endometriosis symptoms in some women, for up to five years.^{8,15}

Gonadotropin-releasing hormones

Gonadotropin-releasing hormone (GnRH) analogues are used in women with endometriosis to induce hypo-oestrogenic, medical menopause.³ They modify the release of pituitary gonadotropins through interaction with the GnRH receptor, resulting in decreased production of FSH and LH. They are typically considered if oral contraceptives or progestins are ineffective or cannot be tolerated.¹⁰ GnRH analogues are usually only prescribed in consultation with a gynaecologist.

Two GnRH analogues are available, fully subsidised, in New Zealand; goserelin acetate (implant) and leuporeolin (injection). Dosing regimens are dependent on the size of the dose, generally every 28 days or every three or six months. They are usually only used for a maximum of twelve months.

GnRH analogues are associated with several short-term adverse effects, mainly hypo-oestrogenic symptoms, including menopausal symptoms, loss of libido and emotional lability. Several long-term adverse effects may also be seen, most notably bone-mineral density loss.

Because of these adverse effects, “add-back” therapy is recommended if a GnRH analogue is continued for more than six months. Add-back therapy involves concurrently prescribing a synthetic progestin, e.g. norethisterone, plus either a bisphosphonate or oestrogen with GnRH in order to reduce the adverse effects of GnRH treatment. GnRH plus add-back treatment becomes considerably more expensive than other endometriosis treatment options.

Androgenic medicines

Androgenic medicines, e.g. danazol, were, in the past, often used to manage endometriosis due to their ability to induce a hypo-oestrogenic state.

However, the adverse effects associated with androgenic medicines are significant and generally mean that androgenic medicines are no longer prescribed other than in females for

Emerging medical treatments

Several other, new treatment options for women with endometriosis are currently being investigated. One of the primary focuses of new research is finding an effective medical treatment that does not prevent or preclude pregnancy. Medicines currently being investigated include:^{10,12}

- Metformin
- Aromatase inhibitors
- Selective progesterone receptor antagonists
- Orally-active GnRH antagonists
- Selective oestrogen receptor-beta agonists

Several other medicines, such as immunomodulators and anti-TNF-alpha agents, have been trialled but either failed to show benefit or were proven to have no benefit in randomised controlled trials.

Endometriosis and fertility

The pathophysiology of infertility in women with endometriosis is not well understood. Inflammation of the pelvic cavity, structural abnormalities, the presence of endometriomas of the ovaries, alterations of sperm-oocyte interaction and reduced endometrial receptivity are all thought to be involved.⁸

It is not possible to differentiate between those women with endometriosis who will experience reduced fertility and those who will retain normal levels of fertility, even if a laparoscopy is performed.

Surgery to ablate and excise endometriomas, adhesions and scar tissue is the most common treatment for women with endometriosis who wish to conceive, but cannot.^{2,17} Recent evidence into endometriosis treatments indicates that lipiodol (oil soluble contrast medium) flushing of the uterus, fallopian tubes and ovaries in women with endometriosis increases the rate of pregnancy, and may be considered in the setting of a specialist fertility clinic.¹⁹

Assisted fertility treatments are likely to be beneficial for most women with endometriosis who have reduced fertility.⁹

Traditionally, hormonal treatment was used in women with reduced fertility for a short period, e.g. six months, and then stopped, as it was thought that this created "rebound" fertility. However, a Cochrane review found that there is no increase in fertility after treatment with hormonal medicines for women with endometriosis.²⁰ In addition, some medicines, particularly medroxyprogesterone acetate and some androgenic agents may have lasting effects of ovulation suppression beyond the duration of treatment, although typically not more than a few months.

whom no other treatment is effective or appropriate. Adverse effects include venous thromboembolism, weight gain, voice changes, skin reactions, mood and libido changes, oedema, myalgia, acne, oily skin and hirsutism or male pattern baldness, which may be permanent.¹⁶ There is also limited evidence that androgenic medicines increase the risk of ovarian cancer.¹⁰ They should not be prescribed to women with liver disease or hyperlipidaemia. They are contraindicated in women who are pregnant as they can virilise the foetus and cause other androgenic effects.

Danazol is titrated to achieve amenorrhoea, at a dose of 200 – 800 mg, in two to four divided doses, daily (capsules are 100 mg or 200 mg). It is generally used for a maximum of six months due to adverse effects.³ Symptomatic improvement has been shown to remain up to six months after treatment is stopped.¹⁶ Patients will need to be advised to use a non-hormonal form of contraception, usually condoms, throughout treatment, and pregnancy should be excluded prior to initiating.

Surgical treatment

Surgical treatment is highly effective for symptom and pain reduction and can increase fertility in sub-fertile women.^{17,18} However, access to surgery is limited, and even when performed, recurrence rates are high: approximately 50% of women will re-develop symptoms within five years of surgery.³

The success rate of surgical treatment of endometriosis depends on the severity of the condition, its location, and the extent of the symptoms as well as the age of the patient (effectiveness is reduced in younger women). Surgery for endometriosis is divided into two strategies: surgery with preservation of fertility and surgery if fertility is not desired.

Surgery with preservation of fertility involves laparoscopy to excise or ablate all visible lesions and restore pelvic anatomy. It is the more common surgical option, which significantly reduces pain in the majority of patients and has the ability to retain, and in some cases increase, fertility in women.¹⁰ The rate of symptom recurrence is higher than with more aggressive, non-preservative techniques, however, the ability to maintain fertility outweighs this for many women.¹⁰ A prophylactic appendectomy is sometimes performed during surgery, especially if the patient presents with right-sided pain, as abnormal appendix pathology has a high prevalence in women with endometriosis.¹⁰

Radical surgery is limited to women with endometriosis who do not wish to conceive, and after all medical treatments have been unsuccessfully trialed.⁹ More aggressive surgical

options that do not preserve fertility involve hysterectomy, adnexectomy (removal of the fallopian tubes), oophorectomy (removal of the ovaries). The excision of all visible peritoneal lesions is standard alongside all aggressive treatments. Patients undergoing radical surgery should be counselled about the possibility of symptoms persisting even after complete bilateral oophorectomy and hysterectomy, and the adverse effects associated with early, medically-induced menopause. Oestrogen-replacement treatment may be required and should be discussed with the consulting surgeon.¹⁰

Complications

Long-term complications are common in women with endometriosis. Common complications are adhesion formation and ovarian failure post-surgery.

Adhesions are thought to result from the inflammation of peritoneal surfaces. The risk of this occurrence is not well known, and may be increased by surgical intervention. Sequelae may include pain, structural changes to the pelvic and reproductive organs and bowel obstruction.

Ovarian failure occurs in 2.4% of women after ablation of ovarian endometriomas, even with the less aggressive surgical interventions.¹⁰

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