Endometriosis

essentials for general practice

Part two

This Update is the second in a two-part series on endometriosis. It focuses on how endometriosis causes pain and infertility, the current treatments, and the relationship between endometriosis and malignancy.

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How does endometriosis cause pain?

THE location and severity of pain associated with endometriosis correlate poorly with the extent and location of the disease. Furthermore, the mechanisms by which endometriosis causes pain are complex and not well understood (Table 1).[1,2]

Endometriosis-related pelvic pain may result from bleeding from within endometriotic lesions before or during menses, with localised effects within the lesion itself, or a more generalised irritation of pelvic peritoneal surfaces. Increased levels of inflammatory cells and mediators found in the peritoneal fluid of patients with endometriosis may be a related to this process or may be central to the endometriosis disease process per se – in either scenario, the resultant inflammation may be responsible for the stimulation of pelvic visceral nerve nociceptors.

Endometriotic lesions may directly impact visceral nerve fibres by extrinsic compression or infiltration, which might explain why pain symptoms often correlate poorly with the actual sites of disease. Nerve entrapment is an uncommon but important cause of endometriosis pain and is due to anatomical distortion of the nerve (e.g. obturator, sciatic nerves), usually by deep fibrous nodules of endometriosis. Pain symptoms occur in the distribution of the affected nerve and may be accompanied by loss of function, e.g. muscle power.

Other types of endometriosis pain relate to abnormalities of central pain processing. Neuropathic pain is due to damage of peripheral and/or central nerve fibres and is characterised by persistent/prolonged pain after the stimulus has resolved. Although uncommon in women with endometriosis, neuropathic pain may result from damage to regenerating nerve fibres during repeat surgeries. Hyperalgesia refers to pain more severe than that expected for a given pain stimulus. Allodynia is the sensation of pain from a stimulus that does not usually produce pain.

TABLE 1. POSTULATED MECHANISMS OF ENDOMETRIOSIS-INDUCED PELVIC PAIN

Micro-haemorrhages in endometrial implants with resultant inflammation
Increased intra-peritoneal inflammatory cells and mediators in peritoneal fluid
Irritation or infiltration of pelvic visceral nerve fibres
Generation of nerve fibres in association with endometriotic lesions
Pelvic nerve entrapment, e.g. sciatic or obturator nerves
Nerve damage with resultant altered central pain processing, e.g. neuropathic pain, hyperalgesia, allodynia

How does endometriosis cause infertility?

The definition of infertility is the failure to achieve conception in a couple having regular unprotected sexual intercourse for one year. All stages of endometriosis appear to cause infertility. Numerous studies indicate that about 50% of women with endometriosis are infertile – of those women with minimal or mild disease (normal tubes and ovaries; stage I–II), 50% will be able to conceive without assistance, only 25% of women with moderate endometriosis (stage III) will be able to conceive, and very few women with severe disease (stage IV) will be able to conceive.

Despite this supporting evidence, causal links between endometriosis and infertility are controversial and may vary with the stage of disease (Table 2).[3,4]

In minimal to mild endometriosis, there is very little distortion of the pelvic anatomy but even these less-severe stages of the disease are associated with pelvic inflammation as evidenced by elevated levels of macrophages and cytokines, and other inflammatory mediators, in peritoneal fluid.

The resultant inflammatory process may affect the normal functioning of any or all of the peritoneum, ovaries, fallopian tubes and endometrium. Moderate-severe endometriosis is characterised by more extensive disease and associated more-marked pelvic inflammation, usually resulting in distortion of the pelvic anatomy by adhesions. Endometriotic ovarian cysts appear to affect egg recruitment and ovulation. The effect of these anatomical distortions on sperm transport, egg release and pick up, and embryo implantation can be readily appreciated (Figure 1).

TABLE 2. POSTULATED MECHANISMS OF ENDOMETRIOSIS-INDUCED INFERTILITY

Altered hormonal and cell-mediated immunity
Altered peritoneal fluid
Endocrine and ovulatory abnormalities
Impaired implantation
Impaired oocyte and embryo quality
Impaired fallopian tube function
Distorted pelvic anatomy

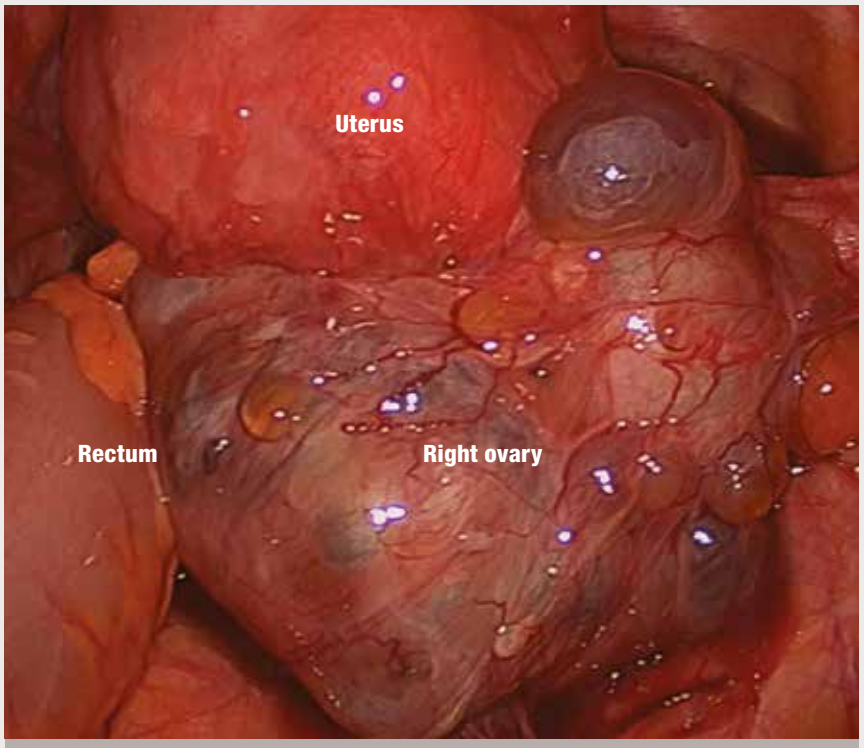

Figure 1. Severe endometriosis (stage IV) showing a large right endometrioma adherent to uterus and rectosigmoid. The left ovary and both tubes (hydrosalpinges) are adherent to the Pouch of Douglas (POD) peritoneum (not visible).

Management of pain and infertility

A. GENERAL COMMENTS

The treatment of endometriosis is based on the effect of the disease on QOL resulting from pain symptoms and/or infertility, or to exclude malignancy in a pelvic mass. While there are no robust data to support the treatment of incidentally diagnosed endometriosis to prevent the future development of pain or subfertility, the progressive nature of the disease is not in dispute.

Indeed, the American Society For Reproductive Medicine considers endometriosis "a chronic disease that requires a life-long management plan".[5] The optimal management for pain and infertility due to endometriosis is unclear, although the goal of endometriosis treatment should be to use medical treatments and lifestyle modifications when possible, and to minimise repeat surgical procedures as much as possible (Table 3).

As the diagnosis of endometriosis can only be made definitively at surgery, empirical medical treatments for pain symptoms may be undertaken – a positive clinical response is supportive of a diagnosis of endometriosis without the patient having to undergo an invasive procedure.

B. PELVIC PAIN

Non-medical therapies/lifestyle modification

Women with mild pain symptoms related to endometriosis may require no treatment. Some women may obtain relief with exercise, yoga, acupuncture and various relaxation techniques. One RCT showed that acupuncture significantly decreased pain compared to Chinese herbs. No natural products have been proven to diminish endometriosis-related pain. Nevertheless, some women may experience benefits from these treatments.[2]

Analgesia

Simple analgesia is often prescribed as a first-line treatment of endometriosis-associated pain (Table 4).[2,5] However, no adequately powered randomised controlled trials (RCTs) have been performed

TABLE 3. TREATMENT OF ENDOMETRIOSIS – GENERAL PRINCIPLES

Individualise treatment pelvic pain infertility
General approach – relieve symptoms, improve QOL
Analgesia, hormonal preparations, surgical excision/ablation, or combination therapies
Optimal managements are yet to be established
Patients whose symptoms are resistant to treatment should be referred to a chronic pain centre for ongoing management

to evaluate the efficacy of any analgesic in current use for this indication. Based on their proven efficacy in RCTs for the treatment of primary dysmenorrhoea, however, NSAIDs are commonly prescribed first-line drugs for endometriosis pain. Paracetamol is often prescribed in combination due to the additive analgesic effect. For episodes of more severe pain, codeine may be added, most conveniently in a preparation combined with paracetamol or the NSAID.

Care should be exercised when prescribing opiates for pelvic pain due to the risk of dependence. In addition, many women with moderate-severe endometriosis will have bowel symptoms, and care should be taken not to exacerbate constipation. Before prescribing analgesics, all likely side effects associated with frequent use should be discussed with the patient.

Hormonal medications

Hormonal medications used to treat endometriosis pain act by modifying the physiological oestrogen and progesterone fluctuations. Endometriosis is known to be an oestrogen-dependent condition, best illustrated by the cessation of endometriosis-related pelvic pain after the menopause.

In contrast, progesterone has a damping effect on endometriosis. For example, during pregnancy, elevated levels of progesterone are responsible for decidualisation of the endometrium; a similar effect on endometriotic deposits usually alleviates associated pelvic pain symptoms during pregnancy.

The hormonal medications used to treat endometriosis pain therefore fall into one of two categories: combined oestrogen/progestin contraceptives and progestin-only preparations which induce a pseudo-pregnancy state, and gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors which induce a pseudo-menopause state. The following hormonal medications have all been proven to decrease endometriosis-related pain but none has been consistently proven to be superior to another (Table 4).[2,5]

1. Combined oestrogen/progestin contraceptives

The combined (oestrogen and progestin) oral contraceptive pill (COCP) taken cyclically or continuously reduces endometriosis pain. The COCP is known to decrease menstrual bleeding and associated menstrual cramping – bleeding within endometriosis deposits may also be decreased, with associated decidualisation. No COCP formulation has been proven to be superior over another in reducing endometriosis pain.

Non-oral oestrogen and progestin preparations (e.g. vaginal ring, transdermal patch) may also be effective in decreasing endometriosis pain symptoms but there are no supportive data available at present. Combined oestrogen and progestin contraceptives can be used indefinitely (unless pregnancy is desired or there are contraindications). The small increased risk of venous thromboembolism is predominantly due to the oestrogen component, and the main progestin side effects include irregular spotting, weight gain and depression; the small but well-documented increased risk of breast cancer is due to the hormone combination.

2. Progestin-only preparations

Progestin-only formulations also cause decidualisation followed by atrophy of endometriotic deposits. Oral formulations, depot IM injection, subdermal implant and intrauterine device are all effective at reducing pain due to endometriosis. Long-term use of high dose oral preparations or depot injection (>6 months) is usually avoided due to concerns relating to bone density loss, especially if there are risk factors for osteoporosis. The intrauterine device and subdermal implant are suitable for long-term use (unless pregnancy is desired). The usual progesterone side effects may be associated with all preparations but the lowest systemic dose results from the intrauterine device.

3. GnRH agonists

GnRH agonists bind tightly to the GnRH receptor and dissociate slowly; the initial increase in FSH and LH secretion is followed by receptor down-regulation and reversible hypogonadism (decreased FSH and LH secretion). Ovulation is interrupted resulting in a pseudo-menopausal state. Low levels of oestrogen result in atrophy of endometriotic deposits and decreased endometriosis-related pain.

A major concern with the use of GnRH agonists is the loss of bone density and severe menopausal symptoms (including hot flushes, insomnia, dry vagina, etc). These problems can largely be ameliorated with low-dose 'add-back' oestrogen treatment without loss of efficacy of pain relief. Nevertheless, treatment is usually limited to six months. Furthermore, these drugs are expensive and are only available on the PBS for a maximum of six months.

4. Aromatase inhibitors

Aromatase inhibitors block the conversion of androgens to oestrogens, producing a pseudo-menopausal state. These drugs reduce pain associated with deeply infiltrating endometriosis that persists despite treatment with other available hormonal treatments and/or surgical excision.

Prolonged use of aromatase inhibitors is associated with significant bone density loss, and menopausal symptoms may be severe. In addition, high levels of FSH (due to the low oestrogen levels) cause the development of multifollicular cystic ovaries – hence, aromatase inhibitors must be used with either GnRH agonists or oestrogen/progestin contraceptives so that follicular development is also inhibited. The severity of side effects associated with aromatase inhibitor limit the utility of this drug class.

Neuromodulators

Various classes of neuromodulator drugs (e.g. low-dose amitriptyline, gabapentin) may be of benefit in the management of intractable neuropathic pain resulting from endometriosis.

Surgery

Surgical management of endometriosis is usually undertaken after failure of medical treatments to relieve pain symptoms. Appropriate preoperative counselling regarding surgical options is essential. Initial surgical management is generally conservative with preservation of the uterus and as much ovarian tissue as possible (as preservation of reproductive potential is generally a priority). All endometriosis deposits should otherwise be treated. The patient should have realistic expectations - that endometriosis is an incurable condition and that repeat surgical procedures may be necessary if symptoms return.

Indeed, even with the best surgical treatment of endometriosis, the need for a repeat surgery for recurrent pain symptoms is up to 30% after five years.[6] Depending on the need for preservation of fertility, the repeat surgery may be conservative or definitive, the latter involving treatment of all visible endometriosis plus removal of the uterus and fallopian tubes with or without preservation of one or both ovaries.

Surgical management of endometriosis has been shown in several RCTs to decrease pain symptoms for all stages of the disease.[2,6] Endometriosis surgery performed by laparotomy or laparoscopy appear to be equally effective in treating pain due to endometriosis. However, laparoscopy is the preferred technique for all the advantages associated with minimally invasive surgery, namely, less postoperative pain, shorter hospital stay, shorter recovery time, better cosmetic result and decreased overall cost.

It is important to appreciate that surgical treatment of endometriosis should aim to treat all visible disease, and that even a small amount of residual disease left in situ may cause significant pain. All generalist

TABLE 4. NON-SURGICAL TREATMENT OF ENDOMETRIOSIS PAIN

Non-medical/lifestyle modification
Analgesia (commonly used drug combinations)
NSAID
NSAID + paracetamol
NSAID + paracetamol + codeine
Hormonal medications
COCP (cyclic or continuous)
Progestins
Oral
Parenteral
Depo-Provera (IM depot)
Implanon (sub-dermal implant)
Intrauterine
Mirena
GnRH agonists (e.g. Zoladex, Synarel)
Aromatase inhibitors (e.g. Femara)
Neuromodulators (e.g. amitriptyline)

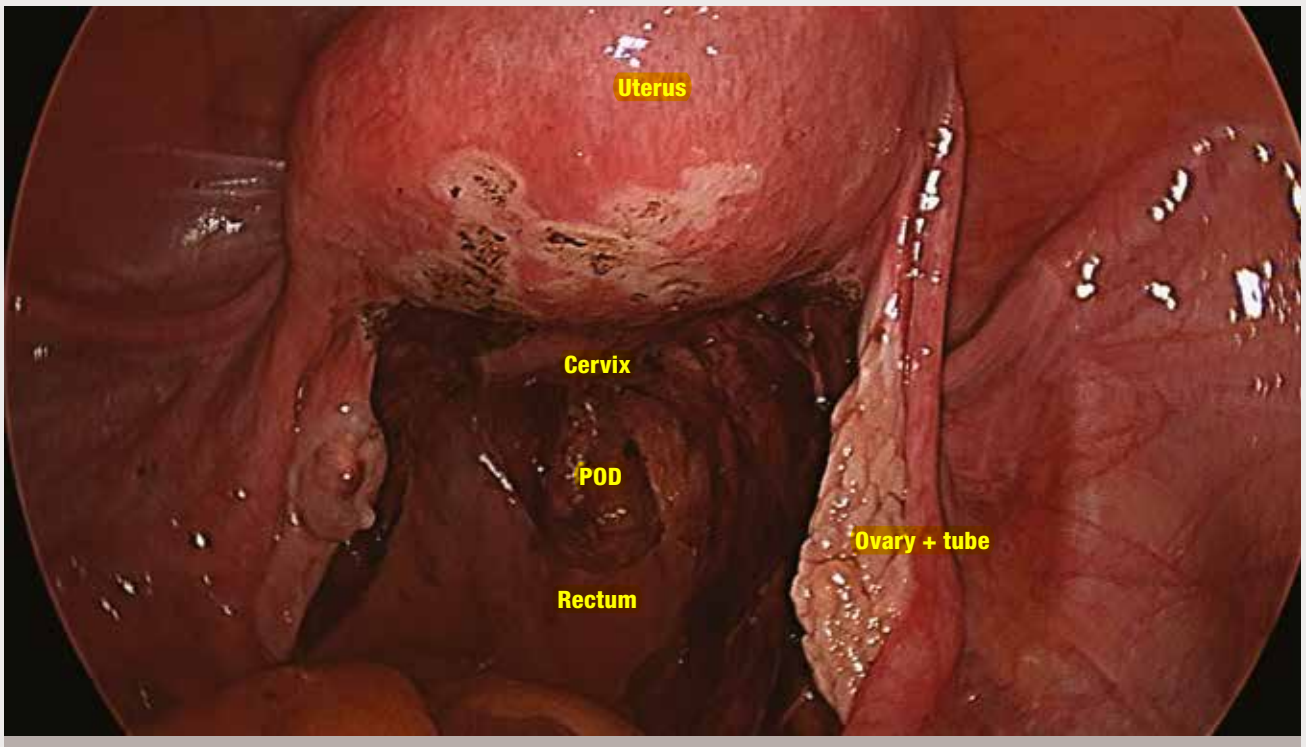

Figure 2. Post-surgery image showing ablated superficial endometriosis on the surface of the uterus, and areas of peritoneum affected by endometriosis excision on the pelvic side walls and Pouch of Douglas (POD) endometriosis.

gynaecologists are trained to perform laparoscopy, but if the extent/stage/site(s) of endometriosis found at diagnostic laparoscopy is beyond the level of the individual's expertise, it is appropriate to halt the surgery and refer the patient to a tertiary endometriosis centre to maximise the surgical outcome.

Both ablation and excision of superficial peritoneal endometriosis deposits are associated with improvement in pain symptoms, although excision is most likely to be the treatment of choice for deeper deposits (Figure 2).[7]

Furthermore, while ablation of discrete deposits of endometriosis is relatively simple, ablation of superficial peritoneal endometriosis over underlying structures may not be safe (Figure 3), and ablation of diffuse disease over a wide expanse of peritoneum is not feasible (Figure 4).

Ovarian endometriomas result from invagination of the ovarian germinal epithelium and underlying cortex caused by haemorrhage from superficial endometriosis – the 'chocolate' found in these cysts is predominantly cellular debris from degraded blood. Surgical excision of the cyst is more effective at relieving pain than cyst drainage and diathermy of visible endometriosis; furthermore, endometrioma recurrence is less with cyst excision. As ovarian cortex is removed during cystectomy, however, it may be better to perform drainage and ablation if ovarian reserve is more important to the patient than the risk endometrioma recurrence (Figure 5).

Surgical excision of deeply infiltrating endometriosis is effective in treating pain, but the rate of intra- and post-operative complication rates are high (2% and 14%, respectively).[2] Hence, it is generally recommended that deeply infiltrating endometriosis is managed by surgeons who have undergone advanced training in this type of complex surgery, preferably within a multidisciplinary centre with access to surgeons from other specialties.

Definitive surgery for endometriosis pain usually involves hysterectomy with removal of the ovaries, as well as treatment of all visible superficial and deep deposits of endometriosis. If the patient's age is remote from the likely age of menopause, preservation of one or both ovaries may be appropriate (or exogenous oestrogen may be prescribed) to protect bone density. The patient should be counselled that ovarian, peripheral or exogenous oestrogen might stimulate residual endometriosis. For this reason, patients should be counselled that definitive surgery is effective for the treatment of endometriosis pain, but that pain symptoms will persist in a small proportion of women.[6]

Combined hormonal and surgical therapy

There is no evidence to support the use of either pre- or post-surgical hormones to improve pain outcomes. Intra-vaginal progestogen or COCP for at least 18–24 months postoperatively appears to have a role in the secondary prevention of endometriosis-related dysmenorrhoea.[2,5]

C. INFERTILITY

General comments

In women undergoing laparoscopy for tubal ligation, the reported frequency of endometriosis may be as low as 4%, whereas about 50% of women undergoing diagnostic laparoscopy for infertility have endometriosis.

There is no dispute that all stages of endometriosis can affect fertility, or that surgical treatment of endometriosis seems to increase the likelihood of conception for all stages of the disease. There is no robust evidence that endometriosis causes miscarriage or has other deleterious effects on pregnancy. Hence, while conceiving can be a problem for women with endometriosis, once pregnant the outlook is generally optimistic.

Non-medical therapies

There is no evidence that any alternative or complementary therapies, or supplements will positively impact on the endometriosis-related infertility.[2]

Hormonal medications

Prior suppression of ovulation with hormonal medications has no impact on endometriosis-related infertility.

Hormonal medications may be used with good effect for treatment of pain related to endometriosis, however, while women are awaiting surgery or an assisted reproductive technology (ART).[2,8]

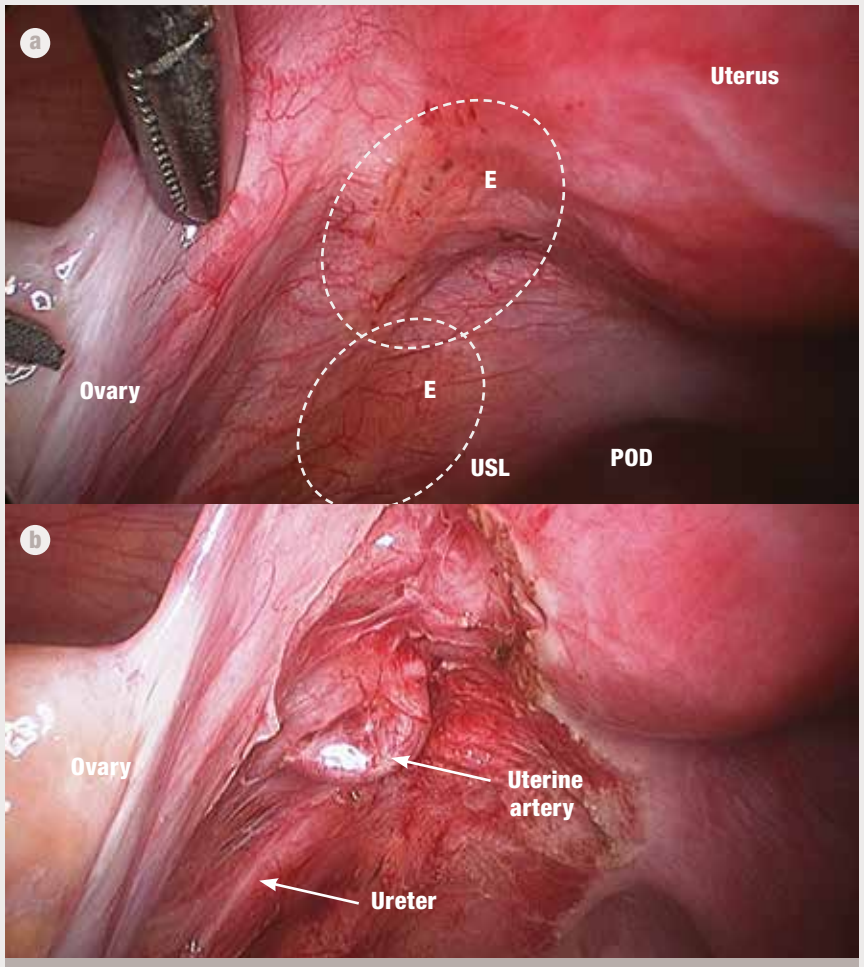

Figure 3a. Diffuse superficial endometriosis (E) over left pelvic side wall and uterine isthmus (USL: uterosacral ligament; POD: Pouch of Douglas).
Figure 3b. Post-excision of diseased peritoneum which was overlying the ureter and uterine artery.

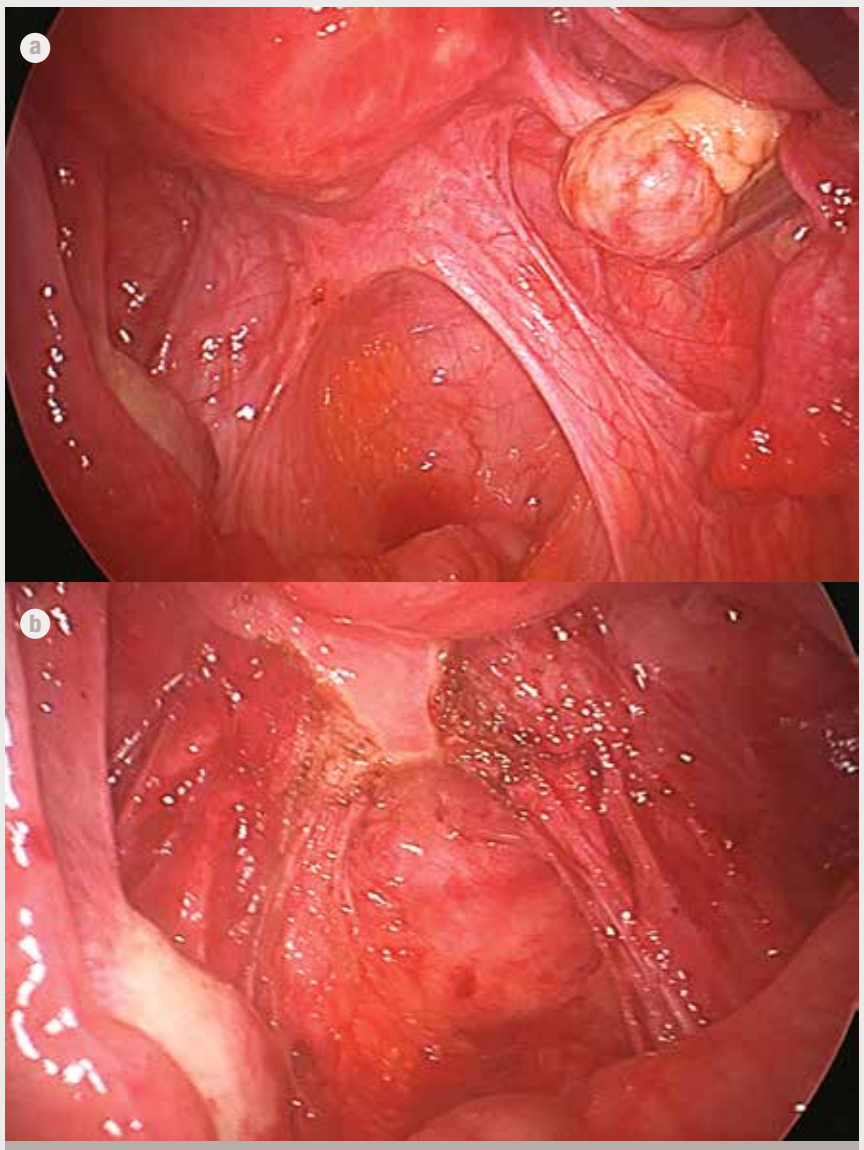

Figure 4. Widespread pelvic endometriosis (of varied appearance): a) Pre-resection; b) Post-resection.

Key points

- Endometriosis is incurable (without a pelvic clearance) but it can be managed effectively in the majority of cases.
- Treatment for endometriosis is undertaken when pain and/or infertility symptoms significantly impact on the patient's quality of life (QOL).
- It is appropriate to commence medical management presumptively in patients whose history, symptoms and examination are consistent with endometriosis.
- Refer patients with pain symptoms resistant to analgesia or hormonal treatments for laparoscopy.
- Surgical management of endometriosis improves pain symptoms and fertility for all stages of the disease.
- Surgical management of endometriosis can only be considered complete if all visible disease has been treated by excision or ablation as symptoms may persist if residual disease is left in situ.
- Always consider a history of sexual, physical or psychological abuse in women with chronic pelvic pain (especially if the symptoms are unresponsive to treatment) – don't miss the opportunity to ask the question!
- Patients with symptoms unresponsive to treatment should be referred to a chronic pain clinic for long-term follow-up and support, and given information on support groups – it is imperative that women with chronic pelvic pain are not left devoid of hope.

Surgery

The principles of surgical management of endometriosis are essentially the same whether the symptom is pain, infertility or both. That is, the restoration of normal anatomy with adhesiolysis, treatment of superficial and deep peritoneal deposits and treatment of ovarian endometriomas.

Data from RCTs on women with minimal-mild endometriosis (stage I/II) indicate that surgical treatment appears to be more effective than diagnostic laparoscopy at increasing fertility. The superior mode of treatment (excision versus ablation) is yet to be determined. Data from several cohort studies on women with moderate-severe endometriosis (stage III/IV) indicate that crude pregnancy rates are significantly improved with surgery compared to expectant management (moderate disease: 57–69% versus 33%; severe disease: 52–68% versus 0%). Hence, surgical treatment of endometriosis appears to improve fertility for all stages of the disease.[2,8,9]

Spontaneous pregnancy rates in women with endometriomas are higher after surgical excision of the cyst wall as opposed to cyst drainage with diathermy of visible endometriosis. Excisional surgery should only be undertaken after discussion with the patient, however, as excision of the cyst wall is likely to impact more on ovarian reserve (Figure 5).[2,8,9]

Assisted reproductive technology (ART)

For women with minimal-mild endometriosis (stage I/II), fertility is improved with ovarian stimulation with gonadotrophins plus intrauterine insemination (IUI) compared to expectant management, and with ovarian stimulation with gonadotrophins plus IUI compared to IUI alone.

Data on the effect of endometriosis (all stages) on pregnancy rates after ART are inconsistent.

In vitro fertilisation/intra-cytoplasmic sperm injection (IVF/ICSI) is a good option for women with endometriosis-related infertility, especially if there is associated male or tubal factor.

Combination therapy

A number of combination therapies have been used to improve pregnancy rates.[2,8]

For example:

- In infertile patients with minimal-mild endometriosis, ART performed within six months after surgical treatment improves pregnancy rates to those achieved in patients with unexplained infertility.
- Surgical management of minimal/mild endometriosis prior to ART may improve live pregnancy rates

Importantly, ART performed after surgical treatment of endometriosis does not appear to cause disease recurrence (Figure 5).

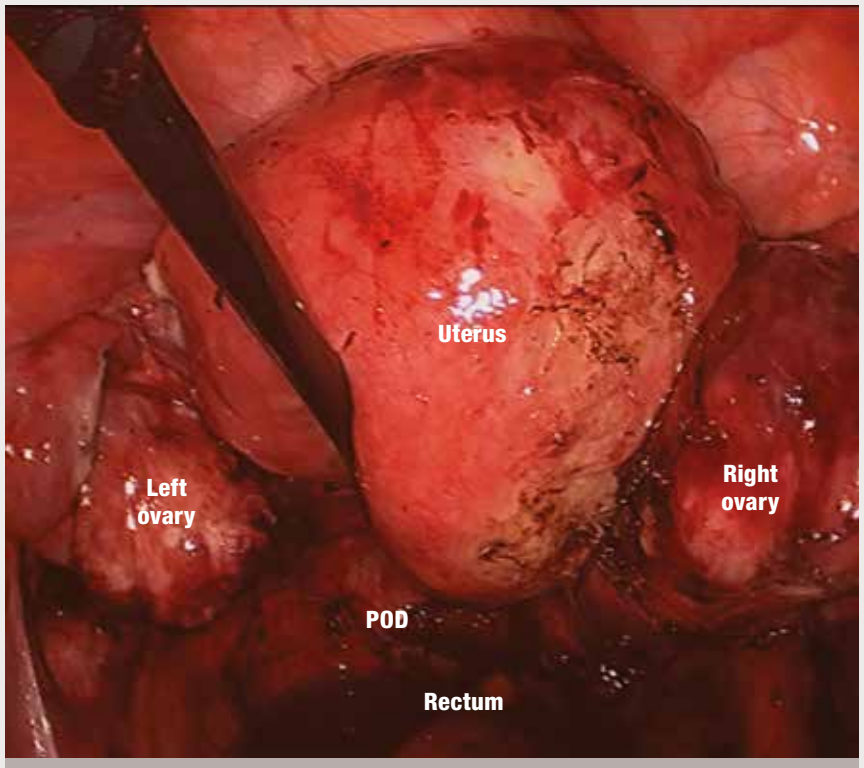

Figure 5. Post-surgical image of the pelvis shown in Figure 1. Surgery was performed prior to undergoing IVF to treat significant pain symptoms and to normalise pelvic anatomy: restoration of the Pouch of Douglas (POD), drainage of bilateral endometriomas (concomitant cystectomy was not performed as ovarian reserve was already decreased), and bilateral salpingectomies (as toxic fluid from blocked tubes can drain into the uterine cavity and adversely affect IVF outcomes).

The association between endometriosis and ovarian cancer

Faced with a diagnosis of endometriosis, most patients will enquire about the associated risk of malignancy. The perceived risk of malignancy may be the reason for a decision to proceed to surgery rather than a trial of conservative or medical therapy.

The increased risk of ovarian cancer, in particular endometrioid and clear ovarian carcinoma, in patients with ovarian endometriosis is now well established. Consistent data on the proposed association between endometriosis and the development of other malignancies (e.g. breast cancer, melanoma, non-Hodgkin's lymphoma, cervical cancer and endometrial cancer), however, are inconclusive. The reported prevalence of ovarian cancer in association with endometriosis varies widely but is probably less than 1%.[10] Although thought to be likely, a causal link between endometriosis and the development of ovarian cancer has yet to be confirmed.

The main risk factors for ovarian cancer are well known and are related to increased lifetime number of ovulations: early menarche, late menopause, non-users of the COCP, no breast feeding, and low parity. These are similar to the risk factors for endometriosis, which also include short and heavy menstrual cycles, both likely to be associated with increased retrograde menstruation. Despite the association between endometriosis and endometrioid and clear ovarian carcinoma, endometriosis is generally considered to be a benign condition. Nevertheless, endometriosis shares some characteristics of malignant processes including the development of local and distant deposits of disease with the potential to invade adjacent tissues.

There is no accepted ovarian cancer-screening regimen for women with or without endometriosis. In women with significant pain symptoms or subfertility, the decision to proceed with surgical management of endometriosis is generally straightforward, based on the deleterious effect on quality of life. A conundrum for the general practitioner is, however, the correct advice to give asymptomatic women about whether to proceed with surgical management of ovarian endometriosis.

Risk factors for the development of ovarian cancer in women already diagnosed with ovarian endometriosis appear to include the severity of endometriosis per se, large endometriomas (greater than 9cm in diameter), and age greater than 45 years (especially if postmenopausal). So how should a woman with a small and asymptomatic endometrioma be counselled? In the absence of ultrasound findings suspicious for malignancy, it may be appropriate to monitor the ovarian cyst with serial pelvic ultrasound scans and serum CA-125 levels. Serum CA-125 is a non-specific marker of many causes of inflammation within the peritoneal cavity, including ovarian cancer and endometriosis, although the level is usually much lower in the latter.

If the ultrasound appearance of the cyst does not change significantly and the CA-125 level is stable (or in normal range) it may be acceptable to the patient to not proceed with ovarian cystectomy or oophorectomy.

However, the patient must be informed that neither of these investigations rule out a diagnosis of ovarian malignancy, which is only possible with histopathology obtained from a surgical specimen. While ovarian endometrioma cystectomy is associated with a smaller recurrence rate than ablative techniques, ovarian malignancy may develop in any recurrent endometrioma. COCP use does not result in endometrioma resolution without associated surgical resection, but this medical treatment appears to prevent recurrence of endometriomas (and possible ovarian cancer) relative to non-users.

Closer surveillance may be of benefit in patients who have previously undergone endometriosis resection of which epithelial atypia was confirmed in the surgical specimens (1–2% of cases), possibly be a precursor of malignancy.

Conclusion

Endometriosis is a common condition but the majority of affected women are unaware they have the disease. The time to diagnosis of endometriosis after the onset of symptoms is many years, primarily because of the incorrect belief that severe pelvic pain in women is normal, and also because the diagnosis cannot be made with an invasive surgical procedure. Less-invasive diagnostic tests for endometriosis would probably decrease the time to diagnosis, and research in this area on native endometrial biopsies and serum biomarkers is promising, hopefully the way of the future.

While endometriosis is not curable without a pelvic clearance, newly diagnosed patients should be reassured that in most cases the disease can be managed effectively. Women with pain resistant to available medical and surgical treatments should be referred to a chronic pain clinic for long-term follow-up and support.

Endometriosis support groups may also play an important role. Women with infertility associated with endometriosis should be reassured that most will be able to conceive with surgical treatment and/or ART.

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