Endometriosis
essentials for general practice

This Update is the first in a two-part series on endometriosis. It covers the epidemiology, pathogenesis, symptoms, signs and diagnosis of endometriosis.

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Introduction

ENDOMETRIOSIS is defined as the presence of endometrial glands and stroma in locations outside the uterine cavity. It is a common, benign, chronic disease in women of reproductive age.

The pathogenesis is the commonest cause of chronic pelvic pain (CPP) in women, and is the cause in 10–15% of infertile couples. If endometriosis is not diagnosed in a timely fashion, and treated appropriately, there is the potential for many years of suffering for those with the disease.

Endometriosis is also a major drain on the health budget due to diminished quality of life (QOL), missed days away from school or work, associated medical and surgical treatments and the chronic nature of the disease. Similar to patients with other chronic conditions, sufferers of endometriosis (and their families and friends), often access information via various means, including the internet and self-help groups, and look to medical practitioners for guidance regarding treatment options.

Epidemiology

Endometriosis can only be diagnosed by visualisation at surgery with histological confirmation, so it is not surprising that there is wide variation on the prevalence of endometriosis in population-based studies.

Overall, the disease appears to affect about 5–10% of women. However, in adolescent girls or women undergoing laparoscopy for investigation of dysmenorrhoea or infertility, respectively, the prevalence is closer to 50%. In women undergoing laparoscopy for pelvic pain symptoms, the prevalence is as high as 80%. Many women with endometriosis are, however, asymptomatic.

The pathogenesis of endometriosis is most commonly thought to involve the process of retrograde menstruation (Table 1), and the disease is known to be oestrogen-dependent. Consequently, many of the epidemiological risk factors for endometriosis are related to these factors.

Pathogenesis

Endometriosis is an oestrogen-dependent condition – it occurs rarely prior to the menarche and becomes quiescent after natural or surgical menopause. Endometriosis has been found in all parts of the body – no single mechanism of pathogenesis from the many proposed hypotheses can explain this observation (Table 1).

The most widely accepted mechanism for the development of endometriosis is the implantation theory, where retrograde flow of the menstrual fluid via the fallopian tubes allows passage of viable endometrial cells to the peritoneal cavity from which endometriosis deposits develop. Evidence to support this mechanism includes the following:

- Endometriosis is generally confined to gravity-dependent areas (i.e. within the pelvis)
- In primate studies where the cervical canal is surgically closed to prevent normal menstrual flow, development of endometriosis is inevitable
- Studies on women with mothers or sisters with endometriosis have consistently shown an increased risk of endometriosis.
- Smoking has been found to reduce the risk of endometriosis.
- Infertility also increases the risk of endometriosis.
- Environmental exposure to dioxin has been associated with the development of endometriosis.
- Studies on women with mothers or sisters with endometriosis have consistently shown an increased risk of endometriosis.

Table 1. Pathogenesis of Endometriosis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
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<tbody>
<tr>
<td>Implantation theory</td>
<td>Endometriosis develops from endometrial cells that are transferred to distant parts of the body through the fallopian tubes.</td>
</tr>
<tr>
<td>Mullerian rest theory</td>
<td>Endometriosis develops from endometrial cells that are transferred to wounds during surgical procedures.</td>
</tr>
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Diagnosis

The average time to diagnosis for women with pelvic pain due to endometriosis is eight years. This delay in diagnosis may due to a combination of factors.

Most women are conditioned to believe that a degree of cyclical pelvic pain is normal. Furthermore, each individual has a different pain threshold and range of pain-coping mechanisms. Therefore, it is difficult for women suffering from pelvic pain to objectively gauge when they should seek medical advice.

Furthermore, in a study of women undergoing laparoscopy for indications other than pelvic pain, 30% had elevated visual analogue scores for dysmenorrhoea, non-menstrual pelvic pain, dyschezia and dyspareunia.

Overall, however, the pain scores were less than for women with endometriosis and, unlike those with endometriosis, these women did not have decreased QOL.1 Irrespective, these data confirm that many ‘normal women’ experience significant cyclical pelvic pain.

The diagnosis of endometriosis may also be delayed because other common causes of pelvic pain such as pelvic inflammatory disease (PID) and irritable bowel syndrome (IBS) share many of the symptoms of endometriosis.

There is some evidence that these may in fact be comorbid conditions,1 hence many women with endometriosis may first undergo treatments for PID and IBS. Treatment failure should therefore trigger exclusion of endometriosis as the cause of pelvic pain. A detailed history and physical examination may provide information suggestive of a diagnosis of endometriosis. Imaging and biomarkers are rarely useful. A successful trial of analgesia or hormonal preparations may support the diagnosis.

The lack of a non-invasive diagnostic investigation for endometriosis, however, is probably the main reason for the delay in its diagnosis. Indeed, endometriosis can only be diagnosed by visualisation of deposits during surgery with histopathological confirmation.

In addition, the macroscopic appearance of endometriosis takes many forms and the diagnosis can be easily missed. Hence, diagnostic accuracy is dependent upon the location, extent and type of lesions as well as the surgeon’s training and experience.
Pathology

Endometriosis is essentially ectopic endometrium, microscopically similar to eutopic endometrium, in that it contains endometrial glands and stroma. Macrophages laden with haemosiderin are also commonly observed. At least two or three of these findings are required to confirm a diagnosis of endometriosis. More recently, nerve fibres have been found in the curettage biopsies of eutopic endometrium of women with endometriosis, a finding that is extremely rare in women without the disease; nerve fibres commonly found in deposits of endometriosis may be a related phenomenon.7

A view of the female pelvis obtained at laparoscopy is shown in Figure 1. Consistent with the implantation theory, endometriosis is primarily a disease of the pelvis due to the effects of gravity in determining site(s) of implantation. Consequently, the organs commonly affected by endometriosis include the peritoneum of the pelvic side walls, anterior cul-de-sac (overlying the bladder) and posterior cul-de-sac (Pouch of Douglas; overlying the vagina and rectum), the fallopian tubes, ovaries and uterus, the uterosacral ligaments, sigmoid colon and appendix.

The macroscopic appearances of endometriosis deposits within the pelvis are widely varied. The appearance will vary with the type, extent and age of the lesions. Peritoneal lesions are generally superficial but may extend into the retroperitoneal space and affect adjacent organs (e.g. the ureter). Superficial peritoneal deposits may be single or scattered throughout the pelvis. Lesions may be several millimetres in diameter or involve wider areas of peritoneum with only subtle changes indicating where the boundary between normal and abnormal tissue lies.

Peritoneal endometriosis is generally thought to arise from retrograde menstruation and the various stages of the disease have very different appearances:

a) red lesions are the first stage where newly attached endometrial cells undergo proliferation, neovascularisation and partial shedding (similar to eutopic endometrium)

b) black lesions (‘powder burn’) represent a later stage where vascularisation is decreased and scarring encloses the implant which accumulates cellular debris (similar to an ovarian endometrioma)

c) white lesions are the final stage in the process where fibrosis has devascularised the implant, now probably quiescent (Figure 2).

The peritoneum may also exhibit more subtle changes: bizarre vessels, small cystic lesions filled with clear fluid and haemosiderin staining. The peritoneum itself may be translucent, thin and fragile, sometimes with a characteristic ‘punched out’ appearance, or ‘fenestration’ (Figure 3). Fibrosis may result in discrete nodules or generalised thickening of the peritoneum (Figure 4).

Ovarian endometriosis may be confined to superficial deposits on the surface of the ovary, either derived from coelomic metaplasia or implantation (Table 1). Bleeding from the functional endometrial cells within these deposits may invaginate the ovarian cortex giving rise to an endometrioma or ‘chocolate cyst’ (endometriomas are pseudocysts, not having a true cyst wall). This is an important consideration in the surgical management of endometriomas — the aim of minimising disease recurrence, best achieved with excision of the cyst wall (ovarian cortex), has to be balanced against the potential loss of reproductive potential due to the loss of ovarian tissue.

DIE generally refers to endometriosis located beneath the peritoneum of the Pouch of Douglas. This disease probably arises either from metaplasia of Mullerian remnants or from the retrocervix itself. The nodule is microscopically similar to adenomyosis, having a prominent fibromuscular component, and the endometrial component does not function like eutopic endometrium. Rectovaginal endometriosis is the commonest form of DIE and is responsible for Pouch of Douglas obliteration where the rectum may become adherent to the upper vagina (the rectovaginal septum usually only extends to the mid-vagina) and cervix (Figure 5). Rectovaginal endometriosis may be associated with full- or partial-thickness nodules invading through the vagina and/or rectosigmoid.

Adhesions tend to be associated with moderate-severe endometriosis. Initially filmy, adhesions may become organised into thickened fibrotic bands. The ovaries can become fixed to their respective pelvic side walls, and the rectosigmoid may become fixed onto to the adnexa and/or uterus. In severe cases, all the pelvic structures may become adherent to one another, resulting in the so-called ‘frozen pelvis’ (Figure 6).
Staging

The most commonly used staging system for endometriosis is that of the American Society of Reproductive Medicine (ASRM) where the disease is assessed as minimal, mild, moderate or severe according to the extent and depth of peritoneal deposits, the presence of ovarian disease, the extent of adhesions and distortion of the pelvic anatomy. This classification is designed to predict the likelihood of conception after treatment for endometriosis, and its applicability for treatment of pelvic pain has been questioned. In fact, the correlation between the stage of endometriosis and the severity of pain symptoms is generally poor.

Many women with minimal disease have severe pain and disrupted QOL, while some women with severe disease have minimal symptoms and/or good QOL.

Clinical evaluation

Although endometriosis can only be diagnosed by surgery or visualisation of the disease with histopathological confirmation, a detailed history of the presenting symptoms, thorough pelvic examination and the prudent use of investigations can rule out or, conversely, heighten suspicion of a diagnosis of endometriosis in many cases.

A) PRESENTING SYMPTOMS

Many women with endometriosis are asymptomatic and the disease will generally only be diagnosed in these patients when undergoing abdominal surgery for another indication. Sometimes an ovarian endometrioma is found incidentally on pelvic ultrasound. The presenting symptoms for women with endometriosis fall into two predominant categories, chronic pelvic pain (CPP) and infertility (Table 2). In addition, women with endometriosis often have decreased QOL scores related to either or both of these symptoms.

Chronic pelvic pain

The pain symptoms associated with endometriosis may vary with the menstrual cycle or there may be no association (Table 2). The classical endometriosis pain symptoms include painful periods (dysmenorrhea), non-menstrual pelvic pain, painful intercourse (dyspareunia), painful bowel movements (dyschezia) and painful urination (dysuria).12

Dysmenorrhea often begins several days prior to menses and is often associated with premenstrual spotting. It is usually worst on days 1–2 (as for women without endometriosis, but more severe) and persists for a variable time, sometimes for several days after menses. The pain is often described as intense, unbearable, cramping, gnawing, crushing and pressing; the pain is most commonly located centrally in the lower abdomen, lower back and deep pelvic area, and may be referred to the thighs, loin, groin, rectal area or umbilicus.7 Contrary to primary dysmenorrhea, the menstrual

pelvic pain due to endometriosis usually develops one or two years after the menarche. Non-menstrual pelvic pain may be episodic or relatively constant with exacerbations with no specific features — sharp or dull, localised or generally throughout the pelvis. This type of pelvic pain probably results from chronic inflammation and fibrosis resulting from long-standing disease.

Dyspareunia is typically deep and central, and usually worse with menses. The pain is usually worse with deep penetrating positions position although the patient may not recognise this because deep positions are avoided. Therefore, the following question should be posed: Are certain positions avoided because they are more uncomfortable? The pain can be sharp or dull and may occur during or after intercourse. Sometimes pain with penetration may be prominent (superficial dyspareunia, with or without deep dyspareunia) and is due to voluntary or involuntary pelvic floor muscle spasm. Pain with intercourse can be so severe that apparently the presenting symptom. Endometriosis causing dyspareunia is usually found in the Pouch of Douglas or uterosacral ligaments. Endometriosis often presents with dyschezia, often described as a burning pain in the rectum; the pain is usually worse with menses. Other gastrointestinal symptoms include alternating constipation and diarrhea, bloating (often with associated abdominal discomfort) and PR bleeding with menses. Consequently, endometriosis should be suspected in any female IBS patient with chronic abdominopelvic pain who has failed medical management, particularly those with classical symptoms of endometriosis and/or a positive family history (Table 3). Endometriosis deposits causing bowel symptoms are usually found in the Pouch of Douglas although not necessarily in direct contact with, or invading the bowel wall.

Endometriosis may also present with dysuria, usually worse during menses,

<table>
<thead>
<tr>
<th>TABLE 2. COMMON ENDOMETRIOSIS SYMPTOMS</th>
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<tbody>
<tr>
<td>Pelvic pain</td>
</tr>
<tr>
<td>• Dysmenorrhea</td>
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<tr>
<td>• Non-menstrual pelvic pain</td>
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<tr>
<td>• Dyspareunia (deep and/or superficial)</td>
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<tr>
<td>• Dyschezia</td>
</tr>
<tr>
<td>• Dysuria</td>
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<tr>
<td>Other gastrointestinal symptoms: PR bleeding*, cyclical bloating, alternating bowel habit</td>
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<tr>
<td>Other urological symptoms: haematuria*, urinary frequency and urgency</td>
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<tr>
<td>Infertility</td>
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*Usually with and/or worse with menses

<table>
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<tr>
<th>TABLE 3. COMPARISON OF IBS AND ENDOMETRIOSIS</th>
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<tr>
<td>IBS</td>
</tr>
<tr>
<td>Prevalence</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Time to diagnosis</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gynaecological symptoms</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
</tr>
<tr>
<td>? in the majority</td>
</tr>
<tr>
<td>Exacerbation with menstrual cycle</td>
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<tr>
<td>Nearly always</td>
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<tr>
<th>TABLE 4. ENDOMETRIOSIS FINDINGS AT PHYSICAL EXAMINATION</th>
</tr>
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<tbody>
<tr>
<td>• May be normal</td>
</tr>
<tr>
<td>• A pelvic mass may be palpable abnormally</td>
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<tr>
<td>• Tender and tense pelvic floor muscles</td>
</tr>
<tr>
<td>• Tender and thickened uterosacral ligaments</td>
</tr>
<tr>
<td>• Tenderness and nodularity in Pouch of Douglas</td>
</tr>
<tr>
<td>• Tender adnexal mass, fixed to sidewall or uterus</td>
</tr>
<tr>
<td>• Fixed retroverted uterus</td>
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Infertility

Patients with endometriosis may present with primary or secondary infertility. There may be no associated pain symptoms characteristic of endometriosis, or pain symptoms may be prominent. However, the stage of disease may only be determined at laparoscopy, so a lack of pain symptoms does not rule out the diagnosis or imply minimal-mild endometriosis. The dilemma in the otherwise asymptomatic infertile patient is whether to refer for laparoscopy or in vitro fertilisation. A comprehensive infertility screen should be performed prior to either option. 1

Quality of life

Numerous randomised controlled trials consistently show that patients with endometriosis have decreased QOL. Hence, the opportunity to specifically address this aspect of the impact of endometriosis should not be missed.

B) ABDOMINOPELVIC EXAMINATION

Physical examination findings consistent with a diagnosis of endometriosis may be found at both routine gynaecological review, as well as consultation for evaluation of pain and/or infertility symptoms (Table 4). Hence, a thorough abdominopelvic examination should always be performed in both scenarios.

Examination findings will vary according to the site and size of implants and, probably, the extent of the associated inflammatory process. It is important to recognise that a normal examination does not rule out a diagnosis of endometriosis. Occasionally a large endometrioma or ‘frozen pelvis’ may be palpable abdominally.

The pelvic floor muscles may be tense and tender due to voluntary or involuntary spasm. The uterosacral ligaments, normally prominent, may be thickened and tender (the lateral borders of the Pouch of Douglas). A nodule may be palpable in the Pouch of Douglas, and may be visible on speculum examination in the posterior fornix as a blue-black cystic lesion, usually indicative of severe endometriosis.

The uterus is usually quite mobile – a fixed, retroverted uterus is suggestive of severe endometriosis.

A tender and enlarged ovary, often fixed to the uterus or pelvic sidewall, usually indicates an endometrioma and severe disease.

A rectal examination should be performed in patients with prominent bowel symptoms (especially PR bleeding) or deep dyspareunia to exclude a full-thickness endometriosis nodule (Figure 7).

C) INVESTIGATIONS

In general, investigations are of limited use in the diagnosis of endometriosis.

Imaging studies

Transvaginal ultrasound (TVUS) is the imaging modality of choice for many benign and malignant gynaecological conditions, including endometriosis. However, TVUS cannot visualise peritoneal disease and a ‘normal’ examination does not exclude a diagnosis of endometriosis. TVUS may be useful to assess the ovaries for endometriomas that have a characteristic ‘ground glass’ appearance, although the observation itself is not diagnostic. Bladder nodules can also be detected in some cases.

Indirect evidence to support a diagnosis of endometriosis may be obtained using the ultrasound probe to assess organs for tenderness and organ fixation.

Overall, however, TVUS is poor at assessing the stage of disease. More specialised transvaginal ultrasound techniques are in development to assess the posterior fornix, Pouch of Douglas, rectosigmoid and rectovaginal septum for severe endometriosis. For example, a technique developed in Australia uses the uses dynamic real-time TVUS to assess the ‘sliding sign’ – a diagnosis of obliterated Pouch of Douglas is suspected if the rectosigmoid does not slide freely against the upper vagina and uterus; in addition, assessment of rectosigmoid nodule position, size and depth of invasion into the bowel wall is being trialled. 2

For rectovaginal endometriosis and deep-infiltrating infiltrating endometriosis in other areas, magnetic resonance imaging (MRI) can provide valuable information regarding the relationship of nodules to adjacent organs such as the uterus, rectosigmoid, bladder, ureters and major pelvic nerves. In general, however, the cost/benefit of MRI precludes its use for this indication except in rare circumstances (e.g. sciatic nerve endometriosis).

Biomarkers

Serum CA-125 is a non-specific biomarker that is elevated in many benign and malignant inflammatory intra-peritoneal processes. The CA-125 level is either normal or slightly elevated in endometriosis and is of little diagnostic use. CA-125 may be useful for deciding whether to perform surgery for an endometrioma – a normal or slightly elevated level suggests a benign process but patients need to be made aware that malignancy can only be excluded by tissue histopathology. Suspicious features on TVUS should always be followed up as endometriomas have been associated with epithelial ovarian cancer (see Part 2 of this Update).

Colonoscopy

This should be performed for all patients with a history of PR bleeding (irrespective of its relationship to menses, Figure 7).

Infertility screen

If not already performed, a woman presenting with infertility (and her partner) should undergo tests to exclude other causes of infertility.

Conclusion

Women with CPP commonly consult a GP, and endometriosis is the commonest cause of CPP. Endometriosis is also a common cause of infertility. If a diagnosis of endometriosis is suspected based on clinical review, the patient should be offered treatment for her symptoms. Remember, the main precipitant for the patient seeking your help may be the effect of endometriosis on her QOL. Part 2 of this Update focuses on how endometriosis causes pain and infertility, the current treatments for associated pain and infertility, and the relationship between endometriosis and malignancy.

References at medobs.com.au

See Dr Lyons’ Opinion, page 20.