Diagnosis and management of endometriosis

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Diagnosis of endometriosis can be difficult but there are steps GPs can take to help achieve early identification and treatment of the condition.

Endometriosis is a common inflammatory condition affecting approximately 5–10 per cent of women during their reproductive phase. However, in certain subgroups such as women suffering from subfertility or chronic pelvic pain the prevalence can be significantly higher. Endometriosis is a complex disease arising from the interplay between multiple genetic and environmental factors. For example, twin studies have shown increased concordance in monozygotic twins when compared to dizygotic twins. It is estimated that about 51 per cent of the variation in endometriosis risk is heritable.

Endometriosis is defined as the presence of endometrium-like tissue, ie glandular endometrial and stromal cells, outside the uterine cavity. Endometriotic lesions are almost exclusively found in the pelvis. Rare locations include the diaphragm, caesarean section scars and the pleural space. Many clinicians and researchers subcategorise pelvic endometriosis into three entities: superficial peritoneal lesions (see Figure 1), ovarian endometriotic (“chocolate”) cysts (see Figure 2) and deep, infiltrating disease (see Figure 3), which often involves fibrotic changes in the bowel, bladder and/or vagina. Various staging systems exist for endometriosis.

The revised American Fertility Society Score (rAFS) takes into account the extent of peritoneal disease, adhesions and the presence and size of ovarian endometriotic cysts. The only scoring system that has reproducibly been a predictor of spontaneous pregnancy rates is the Endometriosis Fertility Index. It takes various factors into account including a least function score of bilateral fallopian tubes, fimbriae and ovaries, the extent of endometriosis, the age of the woman and previous pregnancies. However, no sufficient correlation exists between the location of disease or any staging system and the quality and extent of clinical symptoms, prompting current research into better characterisation and classification of endometriosis.

Symptoms

While endometriosis can be asymptomatic in some cases, many women suffer from significant symptoms and/or subfertility. Such symptoms include dysmenorrhea, non-cyclical abdominal pain, deep dyspareunia, dyschezia, dysuria and chronic fatigue. These can start as early as at menarche and last past menopause, espe-
cially if the woman has scar tissue or adhesions from the disease and/or pelvic surgery. Endometriosis can be a debilitating condition that has a profound effect on the quality of a woman’s life, causing untold misery and pain over many years. As such, endometriosis can also have a profound effect on partners, friends and families of affected women and on society in general. Recent studies suggest that the costs associated with endometriosis are similar to those inflicted by other chronic diseases such as diabetes, rheumatoid arthritis and Crohn’s disease. They clearly have been identified in more than 90 per cent undergoing laparoscopic surgery at the time of menarche. However, retrograde menstruation may be a physiological phenomenon, as such cells have been identified in more than 90 per cent undergoing laparoscopic surgery at the time of menstruation. They also seem to play a central role in the pathophysiology. Another theory describes the process of metaplasia of existing tissue/cells. However, as only circumstantial evidence currently exists, the exact process of endometriosis development remains unclear.

**Pathogenesis**

While the exact cause of the development of the disease remains elusive, it is commonly believed that in the majority of cases endometriotic lesions develop after retrograde menstruation where endometrial cells and/or pieces of tissue are washed into the abdominal cavity, attach to the peritoneum, invade the mesothelial cell layer and acquire a blood supply from the surrounding tissue. However, retrograde menstruation may be a physiological phenomenon, as such cells have been identified in more than 90 per cent undergoing laparoscopic surgery at the time of menstruation. Therefore, other factors such as overexpression of various adhesion molecules, digestive enzymes and angiogenic factors might contribute to disease establishment and development. An impaired immune system, in particular macrophages and T cells, also seem to play a central role in the pathophysiology. Another theory describes the process of metaplasia of existing tissue/cells. However, as only circumstantial evidence currently exists, the exact process of endometriosis development remains unclear.

**Diagnosis**

Although many studies have been performed to date, no clinically suitable biomarkers exist. This is possibly partially attributable to the heterogeneity of endometriosis and the fact that data are collected and processed methods may be able to identify biomarkers in the future. Clinical symptoms as outlined above are commonly found in patients suffering from endometriosis, but are unspecific. Imaging techniques such as a transvaginal ultrasound scan or magnetic resonance imaging (MRI) can identify ovarian endometriomas and possibly deep infiltrating disease, but usually fail to detect peritoneal lesions. Therefore, a laparoscopy with histological verification remains the gold standard to diagnose or exclude the disease. Although this is a common and well-established procedure, it is still not free of the risk of morbidity and even mortality. As no non-invasive method exists to diagnose most forms of endometriosis reliably, the average time between the onset of symptoms and the diagnosis ranges between eight to ten years.

**Managing symptoms**

The course of progression of the condition is still not fully understood. In women enrolled in the placebo or sham surgery arm of endometriosis trials who had a second look laparoscopy at the end of the study, the extent of disease increased in a third of patients, whilst there was no change or even regression in about two-thirds of patients. However, the numbers of women enrolled was small (140 total) and no data was available on whether this correlated with symptoms. At present it is impossible to predict how endometriosis will develop in an individual patient.
While it is likely that most women with endometriosis have clinical symptoms, endometriosis may be an incidental finding in others. There is no known benefit in treating asymptomatic endometriosis.\textsuperscript{17} In general, women need to be counselled about the risks and benefits of treatment. Therefore, an informed decision on whether and how to treat should be made by the patient possibly together with her partner. This decision should be based on various factors such as the pros and cons of treatment, the presence, quality or absence of symptoms and should take into account her personal circumstances and history (see Figure 4).

**Endometriosis patients with subfertility**

If fertility is an acute issue for the patient then hormonal therapy should be avoided due to the contraceptive nature of the drugs used.\textsuperscript{17} The only exception might be the prolonged ovarian down-regulation prior to an IVF cycle as small studies suggest improved pregnancy rates compared to standard IVF.\textsuperscript{21} However, larger, randomised prospective studies are yet to confirm this.

Symptomatic endometriosis patients undergoing laparoscopy for fertility investigation might benefit from surgical treatment of the disease. However, approximately 24 women with minimal or mild disease need to undergo this procedure to create one extra spontaneous pregnancy.\textsuperscript{22} For moderate to severe disease spontaneous pregnancy rates of 57–69 per cent and 52–68 per cent, respectively, have been described, suggesting a benefit of surgical treatment compared to no treatment.\textsuperscript{23,24} It should be stressed that surgical therapy for severe endometriosis can be associated with significantly higher complication rates and should ideally only be performed in centres with sufficient expertise.\textsuperscript{25}

Alternatively, women may choose to undergo medically assisted reproduction (MAR), which includes techniques such as intrauterine insemination (IUI) and in vitro fertilisation (IVF). A systematic review comparing intrauterine insemination and ovarian hyperstimulation to no treatment did not reveal any improvement in outcome. However, two large randomised control trials (RCTs) on the use of ovarian stimulation with intrauterine insemination in subfertile women with minimal or mild endometriosis showed significantly better pregnancy rates. The evidence from these studies suggests that ovarian hyperstimulation using gonadotrophins with intrauterine insemination is better than no treatment or intrauterine insemination alone for these women.\textsuperscript{17}

The data for or against the benefit of IVF in patients with endometriosis is still unclear. A systematic review, which included 2377 cycles from 22 studies, suggested that IVF success rates are reduced in endometriosis patients with moderate to severe disease compared to women with tubal factor infertility.\textsuperscript{26} However, no significant difference was found in women with minimal and mild disease. The European Society of Human Reproduction and Embryology (ESHRE) guidelines caution these findings as the dates of the included studies ranged from 1980 – 1999 when different drug regimen and culture techniques were used compared to today. Also, no difference was found in large national IVF registries such as the Human Fertilisation and Embryology Authority (HFEA) and the Society for Assisted Reproductive Technology (SART).\textsuperscript{17} Surgeons need to keep in mind the effect of ovarian surgery on the follicle pool as studies have demonstrated a reduction in antimüllerian (AMH) and increases in follicle-stimulating hormone (FSH) levels after surgical treatment of ovarian endometriomas.\textsuperscript{27}

**Endometriosis patients with pain**

Women who are suffering from pain symptoms and who are not trying to conceive in the immediate future could either be treated surgically or medically. Only one study directly compared both treatment approaches.\textsuperscript{28} Interestingly, surgery reduced pain scores quicker than medical treatment with a progestogen. However, no difference was seen after 12 months of treatment and in women with non-rectovaginal disease, hormone treatment was superior to surgery after 12 months.

Endometriosis is an oestrogen driven condition. As such most medical therapies aim to reduce oestrogen levels or minimise the oestrogenic effects on ectopic endometrium. Many studies have demonstrated the benefit of hormonal treatment for endometriosis-associated pain symptoms.\textsuperscript{29} Currently, the most popular approaches are:

- Combined oral contraceptive pill (COCP)
- Progestogen-only pill
- Depot medroxyprogesterone acetate
- Levonorgestrel-releasing IUD (Mirena)
- Subcutaneous progestogen-releasing implant
- Gonadotrophin-releasing hormone (GnRH) agonist

Many of these drugs have been shown to be effective without a significant benefit of any particular preparation. The main differences are the price and the side-effect profile, which should be taken into account when counselling a patient. There is no enhanced indication to use a GnRH agonist with a less favourable side-effect profile over eg a progestogen for severe disease. Women with a predominant dysmenorrhea component might
benefit from the IUD, possibly because of concomitant adenomyosis. Intramuscular or subcutaneous injections of GnRH agonists result in a significant decrease in circulating oestrogen levels often leading to menopausal symptoms such as hot flushes, headaches, sleeplessness and mood disturbances. Three months of treatment are equally effective as six months. Unfortunately, long-term effects such as a chronic reduction in bone mass limit their single use to six months. No data exists about potential benefits or risks if the GnRH agonist is discontinued for some time. The concomitant use of low-dose HRT helps to alleviate the symptoms and reduces the risks of osteoporosis. This approach is based on the threshold theory, which suggests that endometriosis is only activated beyond a certain threshold of oestrogen while bone density can be maintained even at low oestrogen levels. Again, data about long-term use of a GnRH agonist together with HRT is lacking. In general, the choice of medication should depend on patient preference, risk factors and side-effects as well as previous experience with hormone therapy.

Years ago danazol, a derivative of the synthetic steroid ethisterone, was widely used in the treatment of endometriosis and was usually the standard control in treatment studies. Nowadays, it is hardly used due to its androgenic side-effects and is not available in many countries. Aromatase inhibitors have recently been trialled as a targeted treatment approach

![Figure 4. Recommended management of endometriosis](image-url)
in endometriosis. This is based on the finding that endometriotic tissue overexpresses P450 aromatase, the enzyme responsible for the conversion of androgens into oestrogens, mainly estradiol, which can stimulate further lesion growth. However, despite the fact that they have been shown to be somewhat effective, aromatase inhibitors are not frequently used due to their relatively poor side-effect profile. Other drugs such as GnRH antagonists, which can be given orally as opposed to the monthly or three-monthly injections of GnRH agonists, the anti-progestogen gestrinone or progesterone-receptor modulators are currently being tested for their efficacy in clinical trials.

Conclusion
Endometriosis is a common, inflammatory condition affecting approximately 176 million women worldwide as well as their partners and families. Current non-invasive tests fail to identify peritoneal disease and only laparoscopic identification coupled with histological verification of endometriotic tissue are reliable diagnostic tools. However, empirical treatment is justified in many suspected cases. Treatment options include surgical removal, evaporation or burning of the ectopic tissue, or medical suppression/alteration of endogenous oestrogen levels. The choice of treatment depends on the clinical and personal situation of the patient and costs; possible contra-indications and side-effects should be taken into account when a therapy suggestion is made.

References


Declaration of interest
None to declare.

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