Endometriosis

The optimal management of endometriosis remains controversial.

N T MATEBESE, ***MB ChB, Dip Obs (SA), FCOG (SA), MMed***
Senior Specialist, Department of Obstetrics and Gynaecology, Groote Schuur Hospital, Cape Town
Dr Matebese works mainly in the field of reproductive medicine. She is a committee member of the South African Menopause Society and is registered with the Health Professions Council of South Africa as a subspecialist in reproductive medicine.
E-mail: tamtam.matebese@uct.ac.za

Endometriosis is a benign disease defined as the presence of endometrial glands and stroma outside the uterus. Its pathogenesis and optimal management remain controversial, and its true prevalence is unknown. Endometriosis can be debilitating and can affect the psychosocial functioning of women. It is estimated to occur in 1 - 7% of women undergoing bilateral tubal ligation, in 12 - 32% of women in the reproductive age group undergoing laparoscopy for pelvic pain, and in about 20 - 40% of infertile women.[1]

Pathogenesis

The development of endometriosis is highly dependent on ovarian steroids, in particular oestrogen and progesterone. Several theories have been postulated with regard to the pathogenesis, including retrograde menstruation, coelomic metaplasia, lymphatic or vascular spread and direct transplantation of endometrial cells during surgery.[2] The main focus of this review is the management of endometriosis; hence the above theories are not discussed in detail. There appears to be a genetic predisposition to its development, as a woman has a 7% chance of developing the disease if it is present in a first-degree relative.[3] Increased local production of oestrogen has been shown to occur in ectopic endometrium. This is due to the abnormal expression of the aromatase enzyme in ectopic endometrium, which leads to the conversion of androgens to oestrogen.[2] Alterations in both humoral and cellular immunity have been described in women with endometriosis. Natural killer cell activity is reduced and abnormal macrophages are produced, which secrete cytokines and growth factors that promote the proliferation of ectopic endometrium.[3]

Endometriosis is estimated to occur in 1 - 7% of women undergoing bilateral tubal ligation, in 12 - 32% of women in the reproductive age group undergoing laparoscopy for pelvic pain, and in about 20 - 40% of infertile women.

Signs and symptoms

The clinical presentation is variable. Symptoms include pelvic pain, dysmenorrhoea, deep dyspareunia, subfertility and abnormal uterine bleeding. A small percentage of women are asymptomatic. Symptoms of extrapelvic disease can occur, such as cyclical urinary or bowel symptoms. Clinical findings are often variable and have a poor predictive value. These include a fixed retroverted uterus, tender adnexal masses, tenderness or nodularity of the uterosacral ligaments, nodules in the rectovaginal septum, and rarely blue or red lesions in the posterior vaginal fornix.[4]

Diagnosis

- Transvaginal ultrasound is useful for the diagnosis of endometriomas (masses consisting of endometrial tissue and blood) – 90% sensitivity.[4]
- Magnetic resonance imaging is superior to transvaginal ultrasound for the diagnosis of endometriomas and small peritoneal endometriotic lesions, with a 70% sensitivity for disease documented histopathologically.[4]
- Laparoscopy and biopsy with histological confirmation of endometriosis is the preferred method for diagnosis of the condition.[5] Endometriotic implants, however, have a variable range of appearance at laparoscopy, including red flamed lesions, dark pigmented lesions, clear vesicles, and white scarring. This variability in appearance of endometriotic lesions increases the likelihood of observational error; the experience of the surgeon is therefore important for correct laparoscopic diagnosis. Deep infiltrating endometriosis is not readily apparent at laparoscopy, thus posing another diagnostic difficulty. There is now evidence for therapeutic trial for the diagnosis of endometriosis.

Classification

The classification of endometriosis was introduced by the American Society for Reproductive Medicine in 1979 and revised in 1996.[6] A point score is assigned, based on the size, depth and location of endometriotic implants and adhesions. Endometriosis is classified as minimal, mild, moderate or severe. Minimal endometriosis refers to the presence of isolated endometriotic lesions and no significant adhesions. Severe endometriosis refers to the presence of multiple superficial and deep endometriotic lesions, large endometriomas and dense adhesions.[6] There is, however, no correlation between the extent of disease and symptoms.

Treatment

The optimal management of endometriosis is unclear. There are no studies comparing medical versus surgical treatment. The main aims of treatment are therefore to relieve symptoms of pain and

infertility and to treat endometriomas. Available treatment options include medical, surgical and combination therapy. Medical treatment is mainly for the management of pain associated with endometriosis.

Medical treatment

A summary of endometriosis treatment is given in Table I.

Analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain associated with endometriosis. This treatment is based on a few randomised controlled trials demonstrating their effectiveness in the treatment of primary dysmenorrhoea. There are no large randomised trials demonstrating their effectiveness for the treatment of pain associated with endometriosis. NSAIDs are however widely used owing to their low side-effect profile and lower cost compared with other medical treatment options.

The main aims of treatment are therefore to relieve symptoms of pain and infertility and to treat endometriomas.

The combined oral contraceptive (COC) pill

The COC pill has been demonstrated to be effective in relieving pain associated with minimal or mild endometriosis. Its mechanism of action is by decidualisation and atrophy of endometrial tissue. In a randomised controlled trial by Vercellini *et al.* comparing a gonadotrophin-releasing hormone (goserelin) with the pill for relief of pain associated with endometriosis, both treatments were equally effective in significantly reducing pain.[7] Goserelin was, however, associated with better relief of dyspareunia than the pill.[7] The pill can be given in a cyclical or continuous manner, with the latter method providing better pain control.

Progestogens

Progestogens are effective for the treatment of pelvic pain associated with endometriosis. They also induce decidualisation and atrophy of the endometriotic tissue and inhibit gonadotrophin secretion, with resultant reduction in the production of ovarian hormones. Medroxyprogesterone acetate and norethindrone acetate are both commonly used for the treatment of pain in endometriosis. Medroxyprogesterone acetate has been shown in randomised controlled trials to be of similar efficacy as gonadotrophin-releasing agonists and danazol.[8] It can be administered orally (10 mg three times a day,) or intramuscularly (150 mg every 3 months). The use of progestogens is limited by side-effects, including weight gain, irregular bleeding, and mood changes (mainly depression). Long-term use of medroxyprogesterone acetate is also associated with bone loss. The levonorgestrel intrauterine device (Mirena) has been shown to be effective for the treatment of dysmenorrhoea and pain associated with endometriosis.[9] Use of the Mirena for the treatment of endometriosis has not been approved by the FDA.

Gonadotrophin-releasing hormone agonists (GnRH agonists)

GnRH agonists are effective for the treatment of pain associated with moderate to severe endometriosis.[8] They bind to GnRH receptors for extended intervals, with resultant downregulation of the pituitary gland, resulting in decreased production of gonadotrophins and ovarian hormones. The initial use of GnRH agonists is limited to 6 months because of hypo-oestrogenic side-effects, the most important side-effect being bone loss. However, the side-effects are reduced with add-back therapy with a progestogen or a combination of oestrogen and progestogen. This is based on the 'oestrogen threshold hypothesis', which suggests that the amount of oestrogen and/or progesterone necessary to prevent hot flushes or bone loss is less than that which would stimulate endometriosis. GnRH agonists can be administered twice daily via a calibrated nasal spray, by injection of a short-acting daily dose, or by a depot formulation given every 1 - 3 months.

Danazol

Danazol is a 17α-ethinyltestosterone derivative that acts by inhibiting steroidogenesis and by increasing free testosterone levels. This drug has been shown in a *Cochrane Database Systematic Review* to be effective for the treatment of pain associated with mild to moderate endometriosis.[10] Danazol is given orally (400 - 800 mg daily). Its use is limited to 6 months owing to androgenic side-effects. Women need to be counselled well about these side-effects, as voice change is irreversible.

Gestrinone

Gestrinone is a 19-notestosterone derivative with antiprogestinic, anti-oestrogenic and androgenic effects. Its mechanism of action is by inhibiting steroidogenesis and by inducing a progestational withdrawal effect at the level of the endometrium. Gestrinone has been shown to be as effective as danazol and GnRH agonists in relieving pain symptoms in endometriosis.[11] It is administered orally in a dose of 2.5 - 10 mg twice or three times a week. Its use is limited by side-effects, including weight gain, hirsutism, seborrhoea and acne.

Women need to be counselled well about androgenic side-effects, as voice change is irreversible.

Experimental medical treatments

Several medical treatments are still being investigated for endometriosis. These drugs include the aromatase inhibitors, mefipristone, selective oestrogen-receptor modulators, selective progesterone-receptor modulators, GnRH antagonists, pentoxyfylline and drugs that inhibit the effects of tumour necrosis factor, α-matrix metalloproteinase, and angiogenesis. These drugs have not been approved by the FDA for the treatment of endometriosis and therefore should not be used as definitive treatment.

Surgery can be performed for restoring normal anatomy in women with endometriosis who wish to be fertile.

Surgical treatment

Surgical treatment of endometriosis is reserved for patients with severe incapacitating symptoms who do not respond to medical treatment, for those who cannot tolerate medical treatment owing to side-effects, for those with endometriomas, and for those with symptoms and signs of urinary or bowel obstruction. Surgery can be performed for restoring normal anatomy in women with endometriosis who wish to be fertile. The modalities of surgery include laparoscopy and laparotomy. There is better visualisation of endometrial lesions with laparoscopy compared with laparotomy. The latter is therefore reserved for women

Table I. Summary of endometriosis treatment

Medical treatment	
NSAIDs	Widely used, although no trials demonstrating efficacy
Combined oral contraceptive pill	Effective in relieving pain in mild to moderate endometriosis
Progestogens	Effective in relieving pelvic pain
GnRH agonists	Effective in relieving pain in mild to moderate endometriosis, but treatment limited to 6 months because of hypo-oestrogenic side-effects, particularly bone loss
Danazol	Effective in pain relief for mild to moderate disease, but treatment limited to 6 months because of androgenic side-effects. Warn women that voice change is irreversible
Gestrinone	Effective in pain relief, but treatment limited by side-effects of weight gain, hirsutism, seborrhoea and acne
Surgical treatment	Reserved for women with servere intractable pain not responding to medical treatment

with extensive disease. The methods of ablation of endometriotic implants include cauterisation, laser, and excision. There are no randomised controlled trials evaluating the comparative efficacies of these ablative methods. The recurrence rate of endometriosis after laparoscopy and ablation is about 40% in 10 years.[12]

The only guaranteed treatment for adenomyosis is total abdominal hysterectomy.

Laparoscopic uterine nerve ablation (LUNA) was initially thought to significantly reduce pain in women with endometriosis. A large, randomised controlled trial showed no significant reduction in patients who had LUNA compared with those who only had ablation of visible endometrial implants.[13] The procedure has been shown to be associated with uterine prolapse and risk of ureteric injuries.[14] Presacral neurectomy involves interruption of the sympathetic supply to the uterus at the level of the superior hypogastric plexus and is associated with an increased risk of bleeding. It should only be performed by experienced surgeons.

Women who do not respond to ablation therapy and who do not wish to have more children should be treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. They should receive hormone therapy for prevention of oestrogen-deficiency symptoms, importantly bone loss. Continuous combined oestrogen-progestogen treatment is recommended despite the absence of a uterus in order to reduce the recurrence rate associated with unopposed oestrogen.

Management of endometriomas and adenomyosis

Endometriomas are best managed surgically, as those more than 1 cm are unlikely to resolve with medical therapy. Cystectomy with stripping of the cyst wall followed by coagulation or laser vaporisation of the inner side-wall is the recommended method of surgery. Drainage and cauterisation of the endometrioma is not recommended owing to the high recurrence rate associated with this procedure.

The only guaranteed treatment for adenomyosis is total abdominal hysterectomy. There is limited evidence to suggest that the Mirena is useful in the treatment of pain symptoms associated with adenomyosis.[9] Uterine artery embolisation has been shown to decrease pain symptoms of endometriosis; however, evidence for its use is also limited.[15]

Rectovaginal septum endometriosis

Extensive surgery is frequently required for the treatment of rectovaginal septum endometriosis. Dissection and exposure of the anterior rectum is often necessary with resection of nodular disease. A portion of the posterior vagina is often excised, and rarely a short segment of the rectum. This procedure should be performed by experienced surgeons.

Infertility

Endometriosis affects 40% of infertile couples where normal semen parameters, ovulation and patent fallopian tubes are present. Excision and ablation with restoration of normal anatomy during diagnostic laparoscopy improve fertility. Medical treatment after surgery does not improve fertility. The best chance for spontaneous conception is 6 - 18 months after surgery. If pregnancy does not occur after this time period, assisted reproductive techniques are recommended. These include ovulation induction and intra-uterine insemination in women with minimal to mild endometriosis and *in vitro* fertilisation in those with severe disease.

References

1. Missmer SA, Hankison SE, Spiegelman D, *et al.* Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric and lifestyle factors. *Am J Epidemiol* 2004; 160: 784.
2. Bulun SE. Endometriosis. *N Engl J Med* 2009; 360: 268.
3. Lebovic DI, Muller MD, Taylor RN. Immunology of endometriosis. *Fertil Steril* 2001; 75: 1.
4. Abrao MS, Goncalves MO, Dias JA, *et al.* Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. *Hum Reprod* 2007; 22: 3092.
5. Kennedy S, Bergqvist A, Chapron C, *et al.* ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2007; 22: 3021.
6. Cains M, Donnes JG, Guzick DS, *et al.* Revised American Society for Reproductive Medicine Classification of Endometriosis, 1996. *Fertil Steril* 1997; 60: 952.
7. Vercellini P, Frontino G, De Giorgi O, *et al.* A gonodotropin-releasing hormone agonist versus a low dose oral contraceptive for pelvic pain associated with endometriosis. *Fertil Steril* 1993; 60: 75.
8. Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxy progesterone acetate versus leuprolide acetate in treatment of endometriosis associated pain. *Hum Reprod* 2006; 21: 248.
9. Vercellini P, Frontino G, De Giorgi O, *et al.* Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. *Fertil Steril* 2003; 80: 305.
10. Selak V, Farquhar C, Prentice A, *et al.* Danazol for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev* 2007: CD 000068.
11. Prentice A, Deary AJ, Bland E. Progestagens and antiprogestagens for pain associated with endometriosis. *Cochrane Database Syst Rev* 2000(2): CD002122.

12. Wheeler JM, Malinak LP. Recurrent endometriosis: Incidence, management and prognosis. *Am J Obstet Gynecol* 1983; 146: 247.
13. Vercellini P, Aimi G, Busacca M, *et al.* Laparoscopic uterosacral ligament resection for dysmenorrhoea associated with endometriosis: Results of a randomised, control trial. *Fertil Steril* 2003; 80: 310.
14. Davis GD. Uterine prolapse after laparoscopic uterosacral transaction in nulliparous airborne trainees: A report of three cases. *J Reprod Med* 1996; 41: 279.
15. Pelage JP, Jacob D, Fazel A, *et al.* Midterm results of uterine artery embolization for symptomatic adenomyosis: Initial experience. *Radiology* 2005; 234: 948.

In a nutshell

- Other causes for pelvic pain should always be excluded, including bowel and urinary pathology.
- There is no evidence to suggest that one form of medical treatment is superior to the other.
- The choice of medical treatment should be based on side-effects, cost and availability of medication.
- Ablation and excision of endometriotic implants at diagnostic laparoscopy improve pain symptoms and fertility.
- Medical treatment of endometriosis does not improve fertility.
- Endometriomas are best treated by cystectomy with stripping of the cyst capsule, followed by ablation of the inner cyst wall.
- There are some experimental drugs that in future might alter the treatment of endometriosis.
- More research is needed to further understand the pathogenesis and treatment of endometriosis.

Single Suture

Speed kills

Analysis of road fatalities in the USA provides yet more evidence that speed kills. Federal speed limit controls were altered in 1987 and again in 1995, allowing individual states to set their own limits. All states raised their limits, but at different times and to different extents. Overall, there has been a 3% increase in fatalities since 1995, with the largest increases in those states and on those roads where speed limits were raised most.

Friedman LS, *et al. Am J Public Health* 2009; 99: 1626-1631.