

ORIGINAL RESEARCH

## Endometriosis: Unveiling the contemporary issues in diagnosis and treatment

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### Summary

Endometriosis is characterized by the presence of ectopic endometrial-like tissue in extra-uterine sites which may induce chronic inflammatory reaction, scar tissue, and adhesions that may distort the pelvic anatomy. The true prevalence of the disease is not known. The disease usually affects women of the reproductive age group and is most typically diagnosed in women aged between 25 and 30 years. Some of the factors which increase the risk of disease include early menarche, shorter menstrual cycles and nulliparity. The symptoms are often non-specific making diagnosis difficult with resultant delays in initiation of appropriate therapy. However, chronic cyclical or non-cyclical pelvic pain with or without menstrual abnormality is common. This review describes the various management options in endometriosis with emphasis on the effective medical and surgical interventions which are useful in the developing world.

*Key words: Chronic inflammation; Endometrium; Non-Steroidal Anti-Inflammatory Drugs; Nulliparity; Oestrogen; Pelvic pain*

### Introduction

Endometriosis is a common oestrogen-dependent disorder which can result in substantial morbidity, including pelvic pain and infertility. It is defined by the presence of ectopic endometrial-like tissue (glands and stroma) in extra-uterine sites usually within the pelvis and rarely the lungs, which may induce chronic inflammatory reaction, scar tissue, and adhesions which may distort a woman's pelvic anatomy. It is a common condition with a diverse clinical course that is highly variable and unpredictable.<sup>[1]</sup>

### Epidemiology

The true prevalence of the disease is not known. However, the UK General Practice Research

Database suggests a prevalence of 1.5% in women of reproductive age.<sup>[2]</sup> The prevalence of endometriosis is notably higher in women undergoing laparoscopy for investigation of pelvic pain and has been to vary between 23-80%.<sup>[3]</sup> In a Scottish study, 6% of the women undergoing sterilization had the visible disease while 21% of those women being investigated for infertility and 15% for pelvic pain had endometriosis.<sup>[4]</sup>

### Incidence in Sub-Saharan Africa

Endometriosis has been extensively studied among the white populations with very few studies carried out among African women. The disorder was for long believed to be uncommon among blacks. Somigliana *et al.*, in their study documented a prevalence of visible lesions at surgery among

women with clinical and ultrasound diagnosis of disease of 0.2%.<sup>[5]</sup> In Nigeria, prevalence rates between 0.9% and 20% had been documented by other authors at laparoscopy for infertility and pelvic pain.<sup>[6, 7]</sup> Fawole *et al.*, in a recent study, however, documented a prevalence rate of 48.1%.<sup>[8]</sup>

Endometriosis usually affects women of the reproductive age group and is most typically diagnosed in women aged between 25 and 30 years. Factors which may increase the risk of the disease include early menarche, shorter menstrual cycles and nulliparity. Pregnancy, use of oral contraceptives, current habit of smoking and high body mass index are associated with reduced risk of disease. It has no racial discrimination, but the incidence has been found to increase by 7-10 folds among first degree relatives.<sup>[2,3,9]</sup>

### Aetio-pathogenesis

The definitive aetio-pathogenesis of endometriosis is yet to be fully known. However, a generally accepted theory is that of retrograde menstruation with normal endometrial tissues implanted on pelvic peritoneum and organs. There are associated inflammatory reactions in response to local mediators, including cytokines, growth factors and prostaglandins. Although, retrograde menstruation is seen in a majority of women, only a small percentage develops the disease. This has been attributed to a failure of normal clearance mechanisms secondary to a defective immune defense system in susceptible women.<sup>[1]</sup> Other theories, including coelomic metaplasia or the transformation of Mullerian tissue remnants, direct implantation at surgery, lymphatic and vascular metastases of normal endometrial tissues, genetic and immunological factors have been used to explain the possible cause of the disease.<sup>[1, 4]</sup> Therefore, endometriosis may result from an interplay of different factors. Whatever the underlying mechanism is, it is evident that the symptoms and disease progression vary considerably among patients with a poor correlation between laparoscopic appearances and clinical symptoms seen.<sup>[1]</sup>

Endometriosis may occur as a peritoneal disease

where it appears as superficial lesions with an appearance which varies from red implants, polypoid lesion, clear vesicles or "powder-burns" or "gunshot" deposits. Cystic ovarian endometriosis is suggested to arise initially as superficial inflammatory lesions in the ovarian cortex, which subsequently invert and invaginate to form retention cysts. These cysts may be multiple and very large and may interfere with fertility by formation of adhesions and distortion of the Fallopian tubes. Deep endometriosis may occur as nodules which extend beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder and the ureters. Dense adhesions involving the rectum may occur and result in partial and total obliteration of the pouch of Douglas.

### Clinical Presentation

The disease may be asymptomatic in some women with incidental findings on evaluation for other gynaecological conditions. The commonest presentation of endometriosis is chronic cyclical or non-cyclical pelvic pain, with or without menstrual abnormality, chronic fatigue, deep dyspareunia and subfertility. Symptoms are often non-specific thereby, making diagnosis difficult with resultant delays in initiation of therapy or referral for appropriate therapy. Endometriosis may also be confused with other conditions like pelvic inflammatory disease and irritable bowel syndrome. Deep endometriosis may present as dyschezia and dysuria and or haematuria with involvement of the bowel or bladder respectively.<sup>[3]</sup>

### Management

Although a definitive diagnosis can only be made histologically at the time of surgery, evidence of endometriosis from a woman's clinical history may lead to symptomatic medical management. Women who suffer from much severe disease, failed medical therapy, or who desire fertility may benefit from surgical intervention. The management goal varies with disease severity and the patient's desire. Current approaches in the therapeutic management of endometriosis are aimed at treating symptoms of pain and infertility,

while targeting disease progression and preventing recurrence.<sup>[1]</sup>

Physical examination has poor sensitivity and specificity in the diagnosis of endometriosis as no abnormal findings may be demonstrated in some patients. Bimanual pelvic examination may help facilitate diagnosis.<sup>[10]</sup> Speculum examination of the posterior vaginal fornix may show some lesions. Transvaginal ultrasound (TVS) of the pelvis may detect endometriomas or deep seated deposits in the rectosigmoid. Magnetic Resonance Imaging (MRI) has no advantage over TVS in the routine assessment of disease, but may be useful for investigating deep seated diseases. Laparoscopy is regarded as the gold standard for the diagnosis of endometriosis, but it is an invasive procedure and not without risks. A systematic review of findings at laparoscopy concluded that although the procedure is highly accurate in excluding the disease, its usefulness becomes limited in the absence of histology. Laparoscopy has more predictive value with moderate to severe disease.<sup>[11]</sup>

The extent or stage of disease has been described using the American Fertility Society (AFS) classification. Scores can be used for the assessment of the extent of disease, but its usefulness is limited by its poor correlation with the pain symptom. CA-125 measurement is not helpful in diagnosis as it is elevated in so many other conditions. Treatment options should be individualized and is dependent on the age of the patient, size and extent of disease, severity of symptoms, desire for fertility and the outcome of previous therapy. The options include: conservative management of minimal or mild disease, medical therapy and surgery.

### ***Medical management of pelvic pain associated with endometriosis***

Medical management of endometriosis varies depending on the patient's age, symptoms, and extent of the disease, reproductive goals, treatment risks, drug tolerability, side effects and cost considerations. The goals of medical management of endometriosis are pain control and the suppression of estrogen production. Hormone therapy (HT) is aimed at inducing amenorrhea with

a resultant relatively hypoestrogenic environment which will inhibit endometrial growth and promote regression of the disease.<sup>[10]</sup> The therapeutic goals are to prevent disease recurrence, preserve fertility and reduce operative intervention. The main disadvantage of this approach is that the symptoms recur once therapy is discontinued. In addition, hormonal therapy is not appropriate for women considering pregnancy as it delays, rather than, enhance fertility.<sup>[10]</sup>

The scope of medical therapy available and used over the years include the Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), combined oral contraceptives (COCPs), progestogens, levonorgestrel-releasing intrauterine device (LNG-IUS), GnRH antagonists, aromatase inhibitors, selective estrogen-receptor modulators (SERM), progesterone antagonist, androgens, selective progesterone receptor modulators, angiogenesis inhibitors, and immunomodulatory drugs.

NSAIDs are non-hormonal and are particularly useful in the management of pelvic pain related to the disease especially among women trying to conceive. COCPs are also effective in dysmenorrhea and also help in the suppression and reduction of menstrual flow. Both continuous administration and cyclical administration are effective. However, continuous rather cyclical therapy may be preferable for pain management. They are also ideal for long term use.<sup>[1]</sup>

Progestogens have direct anti-proliferative effects on endometriotic deposits. This leads to decidualization and eventual atrophy. Both oral (medroxyprogesterone acetate 30mg, desogestrel 75mcg or dienogest, 2mg daily) and injectable (Depo-Provera 150mg-3monthly) forms are effective and were found to be comparable with GnRH analogues.<sup>[12]</sup> A common side effect associated with progestogens is breakthrough bleeding which occurs in about 33% of cases and which is often not dose dependent. Based on the findings of a systematic review, continuous oral or depot progestogen can be used in the management of pelvic pain associated with endometriosis, although this could be limited by its side effects.<sup>[12]</sup>

The LNG-IUS acts locally on the endometrium. Although the exact mechanism of action of the LNG-IUD is unclear, Lockart and co-workers in their study<sup>[13]</sup> suggested that the LNG-IUS delivers significant amounts of Levonorgestrel into the peritoneal cavity, thus explaining its local effect on the endometriotic implants which may be mediated through estrogen and progesterone receptors, most probably inducing decidualization. A systematic review compared the effects of LNG-IUS with that of GnRH agonists and found no significant difference in the pain score after six months. It was also found that following laparoscopic treatment of endometriosis, the use of LNG-IUS reduced the incidence of recurrence of dysmenorrhoea compared with no other treatment after 12 months.<sup>[14]</sup>

GnRH agonists act by downregulating the pituitary receptors with a resultant inhibition of production of gonadotropins, thus suppressing ovarian function and atrophy of endometriotic deposits. Both intra-nasal and intra-dermal applications are effective. The effectiveness of GnRH agonists is comparable to LNG-IUS and Danazol in the treatment of pelvic pain associated with endometriosis. However, its setback stems from its hypoestrogenic effects and the cost.<sup>[15]</sup> The use of GnRH agonist for longer than six months will require additional therapy with low dose continuous combined hormone replacement therapy with or without Tibolone to combat bone loss.

Treatment with NSAIDS and COCPS could be the first line approach in the absence of specific indications for laparoscopy with the use of LNG-IUS or continuous progestogens if oestrogenic preparations are contraindicated or give rise to intolerable side effects. GnRH is preferred to androgenic preparations as an alternative when initial therapy fails.<sup>[10]</sup> In certain cases, pain may be resistant to both NSAIDS and hormonal therapy. There is some evidence that neuropathic and central sensitization may be a component of endometriosis-associated pelvic pain. To this end, the use of tricyclic antidepressants like amitriptyline and gabapentin, an antiepileptic drug has been suggested for pain management.<sup>[1]</sup>

Hormonal treatment for subfertility associated with endometriosis has not been shown to improve the chances of natural conception.<sup>[24]</sup> The odds ratio for pregnancy following ovulation suppression versus placebo or no treatment in a meta-analysis was 0.79 (95% CI 0.54 - 1.14) and 0.80 (95% CI 0.51 - 1.24), respectively. Clearly, treatment can do more harm than good because of the lost opportunity to conceive. In more advanced disease, there is no evidence of an effect on natural conception, but there may be a role for hormonal treatment as an adjunct to assisted conception. A meta-analysis, involving a small number of subjects, has shown that the administration of a GnRH agonist for three to six months prior to *in-vitro* fertilization (IVF) in women with endometriosis increased the odds of clinical pregnancy fourfold.<sup>[25]</sup> This strategy can be particularly helpful for a woman who also has severe pain to help relieve her symptom prior to IVF.

#### *Surgical management of endometriosis-related pain*

Surgery can be an initial step in the diagnosis and treatment of endometriosis. In general, local excision of endometriosis is associated with good short-term outcomes, but, a high re-operative rate.<sup>[16]</sup> In contrast, hysterectomy with conservation of the ovary is associated with a low re-operation rate.<sup>[16]</sup>

The indications for surgical management of endometriosis include: severe incapacitating pain with significant functional impairment, severe, advanced disease associated with anatomic distortion of pelvic organs, endometriomas, a failure of expectant or medical management, rupture of endometriomas, obstructive uropathy or bowel obstruction.

Endometriomas do not usually resolve with medical treatment of endometriosis. Laparoscopic excision is the best mode of treatment. It is associated with improved chances of spontaneous pregnancy compared with cyst drainage or coagulation in women with subfertility.<sup>[10]</sup> A major setback is the observed association of significant reduction in ovarian reserve evidenced by decreased serum levels of anti-Mullerian hormone, especially when the cyst is large or bilateral.<sup>[17]</sup>

A systematic review of five trials reported a significant benefit from laparoscopic surgery for endometriosis-related pelvic pain.<sup>[18]</sup> Surgical excision or ablation at the time of initial laparoscopy is cost-effective for pain management and may improve pregnancy rates in women with ASRM stage I or II endometriosis. It is thus advocated that, the procedure be carried out by a gynaecologist with the necessary skills and should be preceded by appropriate preoperative assessment, counseling and consent.<sup>[10]</sup> Laparoscopic uterine nerve ablation (LUNA) and pre-sacral neurectomy (PSN) are additional laparoscopic procedures for the management of chronic pelvic pain associated with endometriosis. A direct comparison of the two techniques was done in a study which showed better outcomes for PSN in the management of dysmenorrhoea. However, it had significantly worse side effects, including constipation and urinary urgency, and was more technically demanding.<sup>[19]</sup> Laparoscopic resection of deep infiltrating lesions or advanced disease may be effective in relieving chronic pelvic pain. However, it requires advanced laparoscopic surgical expertise and may involve a multidisciplinary approach in cases involving excision or resection of rectal, bladder or ureteric lesions. Open laparotomy may be required in these advanced cases.<sup>[3, 10]</sup> In some instances adjunctive medical therapy using COCPS or LNG-IUS may be beneficial for long term therapeutic effects and prevention of recurrence in women who are not interested in fertility.<sup>[10]</sup> When endometriosis occurs in rare sites like surgical scars on the abdomen, umbilicus, cervix and lungs, treatment is better achieved with surgical excision as they not respond well to medical therapy.

Hysterectomy is a definitive surgical management of endometriosis in women who have completed childbearing. It may be combined with bilateral salpingo-oophorectomy. However, it is required that women be counseled prior to surgery that, hysterectomy may not be curative. Hormone replacement therapy is required following bilateral oophorectomy. The oestrogen-progestogen combination is recommended because of the small risk of reactivation of small or remnant lesions if oestrogen alone is used.<sup>[10]</sup>

## Conclusion

Endometriosis is a problem common in women in the reproductive age group and symptom relief is essential for most affected women. An array of treatment measures has evolved over the years, including conservative, medical and surgical options. The choice of therapy should be individualized based on age, extent of disease, reproductive goal, treatment risk, side effects and cost. Adjunctive laparoscopic surgical therapy with LUNA and PNS are found to be valuable in the management of endometriosis. Post-operative hormonal treatment is beneficial to the prevention of recurrence. Surgery improves fertility compared to medical treatment and assisted reproduction may improve the outcome following prior down-regulation with GnRH.

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**Conflict of Interest:** None

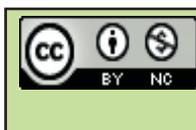
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