REVIEW

CORRESPONDENCE: J Biko| Email: drbiko@icloud.com

Endometriosis: An overview

J Biko
Department of Obstetrics & Gynaecology, Reproductive unit, University of Pretoria, Pretoria, South Africa

Keywords: Dysmenorrhea, chronic pelvic pain, infertility, progesterone resistance

INTRODUCTION

Endometriosis is a chronic disease that require a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures. Instead of assessing endometriosis on the day of diagnosis, gynaecologists should preferably consider the patient's "endometriosis life".[1]

It is a chronic inflammatory, hormonal, immune, systemic and heterogenous disease with three different phenotypes: superficial, ovarian and deep. The clinical hallmarks of symptomatic endometriosis are chronic pelvic pain and infertility.

The prevalence of endometriosis in the general female population is estimated to be 2% - 10% and up to 50% in patients with infertility. Despite the high prevalence, there is a diagnostic delay of 8 -12 years from onset of symptoms to the eventually diagnosis.[2] This delay in diagnosis, is probably one of the reasons that many patients are only diagnosed when they present with advanced stage endometriosis. Adolescent girls with severe period pains are amongst the most frequently misdiagnosed group of patients.

Although it is defined as the presence of endometrial glands and stroma outside the uterine cavity, laparoscopy and histological confirmation of endometrial glands and stroma are no longer the gold standard for diagnosing endometriosis.[2] The diagnosis can be made, and treatment commenced based on history and clinical findings only.

Pathophysiology of endometriosis

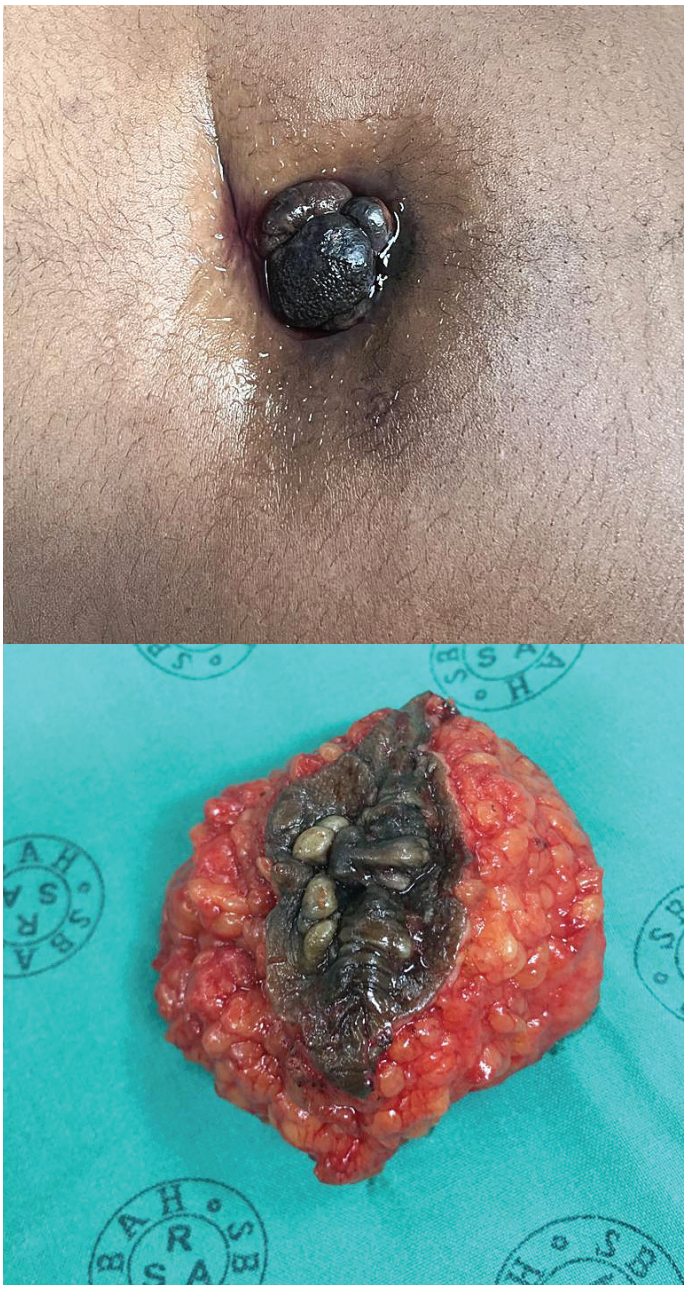
Endometriotic tissue arise from the eutopic located intracavitary endometrium. Oligoclones of endometrial glandular epithelial cells with somatic mutations and attached stromal cells may give rise to endometriosis if they travel to the peritoneal surfaces via retrograde menstruation and/or become entrapped in the myometrium to give rise to adenomyosis.[3] The endometrial cell population within the endometriotic tissue, possess survival and growth capabilities conferred by the somatic epithelial mutations and epigenetic abnormalities of the stromal cells. These epigenic defects give rise to excessive local oestrogen biosynthesis by aromatase and abnormal oestrogen action. These patients also have deficient progesterone receptor expression resulting in progesterone resistance.

Extra pelvic endometriosis

Extra pelvic endometriosis refers to endometriotic lesions implanted outside the pelvic cavity. These include lesions in the gastrointestinal system, diaphragm, pulmonary system, umbilical lesions and skin lesion on surgical scars. The diagnosis of extra pelvic endometriosis is further delayed by the atypical location of symptoms. The rectum and sigmoid colon are the most common GIT sites of endometriosis with the appendix involved in 5 – 20% 0f cases.[4] Endometriosis within the chest involving the lung parenchyma, pleural surfaces or diaphragm present with atypical symptoms such as haemoptysis, haemothorax and catamenial pneumothorax (thoracic endometriosis syndrome). A high index of suspicion is required to make an early diagnosis.

Primary umbilical endometriosis is an uncommon form of extra pelvic endometriosis where the disease is confined to the umbilicus only. These patients present with cyclical umbilical bleeding and pain.

Figure 1.: Primary umbilical endometriosis



Diagnosis

Historically, the diagnosis of endometriosis was based on visual inspection of the lesions at laparoscopy with histological confirmation of the presence of endometrial glandular cells and stroma. This unfortunately resulted in many unnecessary laparoscopic procedures simply to confirm the diagnosis.

The current opinion is that the diagnosis of endometriosis should be considered in individuals presenting with the following cyclical and noncyclical signs and symptoms: dysmenorrhea, deep dyspareunia, dysuria, dyschezia, painful rectal bleeding, haematuria, shoulder tip pain, catamenial pneumothorax, cyclical cough/haemoptysis, chest pain, cyclical scar swelling and pain and infertility.[2]

A thorough clinical examination, including a digital examination were appropriate, should be done to exclude the presence of palpable endometriotic nodules and a transvaginal ultrasound (were appropriate) should be done determine the presence of endometrioma, adenomyosis and endometriotic nodules.

Endometriosis associated pain.

Pain is one of the predominant clinical features of endometriosis. The pain symptoms include, cyclical period pains, deep dyspareunia, noncyclical pain and dyschezia.

Pain relies on the existence of sensory transduction pathways linking peripheral stimuli to the spinal cord for processing and the brain for perception. However, endometrial fragments do not have an intrinsic sensory nerve supply. For endometrial lesions to induce chronic pelvic pain, the development of new sensory nerves to convey these signals need to occur. Studies have now shown that once endometrial fragments adhere to a peritoneal location and become lesions, they undergo a process of neuroangiogenesis.[5] This formation new nerves and blood vessels plays an essential role in the development and progression of endometriosis associated chronic pelvic pain.

There is now a significant body of literature demonstrating that chronic pelvic pain, regardless of the cause, is associated with alterations in brain function, particularly about the processing of pain and other sensory information.[6] In another small study, Hanna Grundstrom et al, showed widespread alterations in pain thresholds of women with persistent pelvic pain that are indicative of central sensitization.[7]

Current evidence demonstrates that chronic pelvic pain, whilst perceived as a peripheral (pelvic) condition, is in fact associated with significant central changes when compared with healthy pain-free women. These findings support the use of adjunctive medication targeting the central nervous system (such as amitriptyline, duloxitine and gabapentin.[8]

Endometriosis – associated pain arises due to initial local inflammatory and nociceptive events and develops as a product of peripheral sensitization, central sensitization and cross- organ sensitization. This pain often coexists with and is further complicated by other pelvic pain syndromes such as irritable bowel syndrome and bladder pain syndrome.[9]

Management of endometriosis pain

NSAIDs

Non-steroidal anti-inflammatory drugs are widely used for symptomatic treatment of pelvic pain. Long – term use is associated with bowel side effects.

Progestins

The ASRM recommends progestins as first line therapy for the management of endometriosis associated pain. Studies have shown similar efficacy of Dienogest to the GnRh-analogues but with a better tolerability. The 3- monthly injection of Medroxyprogesterone acetate has been shown to be effective but also very economical with less bone loss when compared to GnRH- agonists. MPA is also regarded as first line management of endometriosis by ESHRE. Other recommended progestins include the Levonorgestrel intrauterine system.

Combined oral contraceptive pills.

The oral contraceptive pill is widely used to treat dysmenorrhea. They have been shown to be superior to placebo in the management of dysmenorrhea.

Gonadotropin releasing hormone analogues.

The use of GnRH analogues should be reserved for patients who did not respond to first line therapy. Add back therapy with Progestin – only or progestin with low dose oestrogen should be given at the commencement of GnRH therapy to reduce the hypooestrogenic side effects.

Other drugs

Other drugs such as aromatase inhibitors and Danazol have been shown to reduce pain but they are either not FDA approved or their side effect profile is unacceptable.

Adjunctive therapy

Medication such as amitriptyline and duloxitine, that modulates the nervous system should be considered in patients with chronic pelvic pain

Laparoscopic surgery should only be offered to patients who do not respond to medical management and those with advanced stage endometriosis wishing to conceive. Endometriosis surgery is very challenging and is associated with significant morbidity. It is best done in a center with an experienced multidisciplinary team. Patients must be adequately counselled about the possible side effects of the surgery. It is important to note that surgery does not reduce pain in 20 – 28% of patients,[10] and that up to 60% of patients will require a repeat laparoscopy in 5 years.

Endometriosis associate infertility

Although endometriosis impairs reproduction, it does not usually completely prevent pregnancy. Ovulation induction with timed intercourse or intrauterine insemination, assisted reproductive techniques and surgery in selected cases, do enhance the chances of conception.

The mechanisms underlying endometriosis related infertility are not completely known. In cases of advanced endometriosis (ASRM stage 3 and 4), anatomical changes of the reproductive tract such as peritubal and periovarian adhesions as well as pelvic distortions are implicated as limiting factors which would impair oocyte capture by the fimbriae, its passage through the fallopian tubes as well as gamete interaction.[11] In patients with minimal to mild disease, fertility impairment is thought to be due to inflammatory changes in the peritoneal cavity and follicular environment, sperm function, abnormal endometrial receptivity and possibly progesterone resistance.

Patients with minimal to mild endometriosis could be offered controlled ovarian stimulation whilst patient with

advanced endometriosis will require either surgery or assisted reproduction technology to conceive.

Obstetric complications of endometriosis

Pregnant patients diagnosed with endometriosis should regarded as high risk and should preferably be referred to a tertiary Centre. Available evidence has shown that endometriosis was an independent risk factor for preterm birth, miscarriages, placenta praevia, small for gestational age and caesarean delivery.[12]

Bo Y. Park et al showed that women with pregnancies complicated by endometriosis were 2.4 times more likely to develop severe maternal morbidity than those who did not have endometriosis. These patients had a higher risk of developing disseminated intravascular coagulation (aOR, 2.46; 95% CI, 1.65 – 3.66), heart failure (aOR, 2.58; 95% CI, 1.69 – 3.94), pulmonary oedema (aOR 3.02; 95% CI, 1.11 – 8.17), blood transfusion (aOR, 2.17; 95% CI, 1.75 – 2.68) and hysterectomy (aOR 2.46; 95% CI, 1.58 – 3.85). These risks of severe maternal morbidity were higher with vaginal delivery than caesarean delivery.[13]

Deep invasive endometriosis is a risk factor for spontaneous haemoperitoneum during pregnancy and is associated with surgical complications during caesarean delivery.[14]

CONCLUSION

Endometriosis is a common but frequently misdiagnosed condition that has a negative impact on the quality of life of patients. Early diagnosis and treatment will prevent the various neurological sequelae such as peripheral sensitization, central sensitization and cross sensitization which are very difficult to manage. Adolescent girls with dysmenorrhea that affect their schooling, should be given medical treatment for endometriosis without laparoscopic confirmation. After conceiving, patients with endometriosis should be referred to, and managed at a high-risk Obstetrics unit as they are prone to develop severe morbidity.

REFERENCES

1. *Chapron C, Marcellin L, Borghese B and Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev Endocrinol, November 2019, volume 15 (11): 666 – 682.*
2. *Becker C, Bokor A, et al. ESHRE guideline: endometriosis. Human Reprod Open, 2022, issue 2*
3. *Serdar E.B, Sule Y et al. Fertility and sterility. May 2023; volume 119, Issue 5: 746 – 750*
4. *Jubanyik K.J and Cpmite F. Extrapelvic endometriosis. Obstetrics and Gynaecology Clinics of North America. June 1997, Volume 24, issue 2: 411 – 440.*
5. *Maddern J. Grundy L, Castro J and Brierley S. Pain in endometriosis. Front. Cell. Neurosci, 06 October 2020, Volume 14*
6. *Tracey I, Bushnell M.C. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? Journal of Pain 2009, Volume 10: 1113 – 1120.*
7. *Grundstrom H, Gerdie B, Alehagen S, Bertero C, Arendt-Nielsen L and Kjolhede P. Reduced pain thresholds and signs of sensitization in women with persistent pelvic pain and suspected endometriosis. Acta Obstetrica et Gynecologica Scandinavica. 25 November 2018*
8. *Brawn J, Morotti M, Zondervan T.T, Becker C.M, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. Human Reproduction, October 2014; Volume 20, issue 5: 737 – 747.*
9. *McNamara H.C, Frawley H.C, Donoghue J et al. peripheral, Central, and Cross Sensitization in Endometriosis – Associated Pain and Comorbid pain Syndromes. Frontiers in Reproductive Health, 2021, Volume 3.*
10. *0. Abbott J, Hawe J, Hunter D, et al.: Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. Fertil Steril. 2004;82(4):878–84.*
11. *Da Broi M.G, Ferriani R.A and Navarro P.A. Ethiopathogenic mechanisms of endometriosis- related infertility. JBRA Assist Reprod, Juky -Sept 2019; volume 23 (3): 273 – 280.*
12. *Zullu F, Spagnolo E, Saccone G et al. Endometriosis and obstetrics complications: a systematic review and a meta-analysis. Fertility and Sterility 2017; 108: 667 – 72.*
13. *Park B.Y, Yao R, Rossi J, Lee A. Severe maternal morbidity associated with endometriosis: a population-based, retrospective cohort study. Fertility and Sterility 2023, Volume 120 (2): 360 – 368.*
14. *Vercellini P, Vigano P, Bandini V et al. Association of endometriosis and adenomyosis with pregnancy and infertility. Fertility and Sterility. May 2023, Volume 119, (5): 727 – 740.*