JEPPD Journal of Endometriosis and Pelvic Pain Disorders

Review

Journal of Endometriosis and Pelvic Pain Disorders
1–8

DOI: 10.1177/2284026519841520
journals.sagepub.com/home/pev
SAGE

Management of women affected by endometriosis: Are we stepping forward?

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Abstract

Endometriosis is an estrogen-dependent chronic disease defined by the presence of endometrial-like tissue, glands and stroma in ectopic areas. Among all the pathogenic theories proposed to explain the origin of the disease, a pivotal role for immune, hormonal, and epigenetic disbalances have been hypothesized. Endometriosis affects up to 10%–15% of women in reproductive age and represents one of the most common gynecological causes of severe pelvic pain. The main symptoms reported by patients are dysmenorrhea and deep dyspareunia. Although the histological confirmation has been commonly considered mandatory, to date the possibility offered by the improvement in imagining techniques allows to make a proper diagnosis of the disease in most of the cases. Medical therapy represents only a symptomatic treatment and not the definitive solution. The aim of the hormonal therapy is to abolish the menstrual flow using progestin, oral contraceptives, and gonadotropin-releasing hormone agonists to reduce pelvic pain. Surgical treatment consisting of laparoscopy has the goal of abolishing pain and may be conservative or radical in nature depending on the patients' desire of spontaneous conception in the future. Radical surgery seems to be associated with a higher percentage of pain relief as well as higher recurrence rates. Due to the worldwide acceptance and the ongoing evolution of minimally invasive surgery to treat both benign and malignant diseases, future investigations may be conducted to consider this approach to save the function of all the organs involved by the disease and to reduce post-operative discomfort and psychological impact.

Keywords

Endometriosis, infertility, dysmenorrhea, pathogenesis, treatment, minimally invasive surgery

Date received: 16 January 2019; accepted: 11 March 2019

Etiology and epidemiology

Endometriosis is an estrogen-dependent chronic disease, characterized by the presence of endometrial-like tissue, glands and stroma outside the uterine cavity. It represents one of the most common gynecological diseases and is characterized by progressive and invasive growth, response to hormonal stimulation, and tendency to recurrence.[1] Due to the direct correlation of the endometriosis implants growth with the ovarian steroids production, the disease

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affects most severely women between ages of 25–35 years.[2] Moreover, it has been estimated that endometriosis affects up to 10%–15% of women in reproductive-age, with a 0.1% annual incidence in women aged 15–49 years.[3,4] Several theories have been proposed to explain the etiology of endometriosis, but the retrograde menstruation represents the one most accepted worldwide. Other hypothesis such as coelomic metaplasia and metastatic spread may also play an important role in pathogenesis of endometriosis.[5] However, although the etiology of the disease is still unclear, immune, hormonal, and epigenetic disbalances may all play a pivotal role. Recent studies underlined the possibility of a crucial effect of the dysregulation of the epigenetic and immune system in this condition, with particular emphasis to the alteration of the peritoneal homeostasis creating a permissive environment for the progression of the disease. This last fact is related to the failure of scavenging mechanisms, promoting the reduction of the apoptosis of endometriotic cells,[6,7] to the recruitment of the peripheral mononuclear cells and to the secretion of inflammatory cytokines and chemokines in early phases and of angiogenic and fibrogenic cytokines in the late stages of the disease.[8,9] Moreover, recent evidence suggests the possibility of involvement of the Natural Killer T (NKT)'s action[10] and the tumor necrosis factor-α (TNF-α)/tumor necrosis factor receptors (TNFRs) system with the ability to trigger opposite cellular signal as proliferation or death, underlying the simultaneous existence of both inflammatory and reparative phenomena in endometriosis.[11] Oxidative stress and reactive oxygen species (ROS) may also contribute to the pathogenesis of disease through the activation of macrophages aggravating the inflammatory conditions in affected women by the increased production of pro-inflammatory mediators such as apolipoproteins and peroxides.[12] Finally, a pathogenic role for bone marrow-derived stem cells (BMDSCs) have been hypothesized in particular for extra pelvic endometriosis due to the ability of stem cells to migrate through peripheral circulation, causing thus endometriosis in remote sites.[13] A unifying theory for the pathogenesis of endometriosis has been recently proposed, but successive studies are still necessary to better understand how all the pathogenic hypothesis could be linked.[14]

Signs and symptoms

Endometriosis lesions are classified peritoneal/superficial endometriosis, ovarian cysts, and deep infiltrating endometriosis. Peritoneal/superficial endometriosis is commonly found on the peritoneal surface of the rectovaginal space: retro-cervical area, utero-sacral ligaments, and the recto-sigmoid region of the colon. Endometriotic foci can also be found on scars of the abdominal wall, on the bladder and ureters, the last part of the ileum, the cecum, and appendix. Ovarian cysts, also known as ovarian endometrioma, may represent the celomic metaplasia development expression of invaginated epithelial inclusions due to the involvement of unknown growth factors. Deep infiltrating endometriosis consists in the presence of adenomyotic nodules in the rectovaginal septum. This formation seems to be the result of metaplastic changes of müllerian rests in the endometriotic glands involving the rectovaginal septum creating a striking proliferation of the smooth muscle similar to the aspect of endometrial adenomyosis.[15] As far as uterine adenomyosis is concerned, it seems to be characterized by the presence of heterotopic endometrial glands and stroma in the intramural muscular layer of the uterus.[16] However, nowadays, it is considered as a distinct entity from endometriosis that cannot be explained by regurgitation and implantation of endometrial elements but as a phenotype of a more profound disorder characterized by impaired cellular responses to ovarian sex steroids throughout the reproductive tract.[17]

Endometriosis, rarely, spreads to extra-abdominal organs such as the pericardium, diaphragm, lungs, lower limbs, and central nervous system (CNS). However, a rare form of thoracic endometriosis syndrome is described in literature characterized by the presence of functioning endometrial tissue in lung parenchyma airways and pleura, associated with a high percentage of infertility.[18] Endometriosis has traditionally been included among the most important causes of chronic pelvic pain in women of reproductive age.[19] The presentation of endometriosis may include abnormal menstrual bleeding (including metrorrhagia and menorrhagia) or can be completely asymptomatic. However, the most common clinical manifestations are dysmenorrhea, dyspareunia, and chronic non-menstrual pain. Numerous controversies are reported about the association between endometriosis extension, type, and severity of pain.[20] However, some clinical studies have shown that dysmenorrhea and deep dyspareunia are more frequently associated with advanced endometriosis than early disease: in these cases, it was reported that laparoscopic surgery could offer improvement in most symptomatic patients.[21] The most common clinical expressions of thoracic endometriosis are catamenial pneumothorax, hemothorax, hemoptysis, chest pain, and lung nodules. The catamenial character of these symptoms is related to the menstrual cycle.[22,23] The intestine involvement manifestations are represented by rectal bleeding with pain, cramping, and the alternating constipation and diarrhea.[24–26]

Ureteral endometriosis may still remain asymptomatic; however, it can lead to signs of urinary tract obstruction such as hydroureter and hydronephrosis until the involvement of renal function that usually occurs when ureteral endometriosis is presented bilaterally (although this condition represents a rare complication).[27,28] Finally, one of the most important endometriosis complication is the reduction of fertility, and although the disease affects about 5% of the general population, its prevalence can reach up to 30% in infertile women. Infertility in women affected by

endometriosis is due to several conditions such as painful intercourse, endocrine dysfunction related to luteinic phase defect, distorted pelvic anatomy supporting the relationship in advanced stages of endometriosis with the pelvic adhesions, dysfunction of the pelvic immune system, and inflammatory peritoneal environment with alteration of peritoneal homeostasis.[29–31]

Diagnosis

Although the confirmatory diagnosis of endometriosis is only performed with histologic exam after a biopsy during laparoscopic inspection,[32] clinical history and physical exam consistent with the disease can help the clinicians to do a primary diagnosis of endometriosis. The pelvic examination consists of the palpation of pelvis areas that may be involved by endometriotic infiltrations, taking into account the eventual presence of abnormalities, such as pelvic masses, nodules of uterosacral ligaments (USLs), tenderness in the uterine area, adnexal area, and posterior fornix. The pelvic examination should be accompanied by the request of the doctor to describe the symptoms, including the location of the pain and when it occurs. Pelvic pain is not a specific symptom, since it is also related to several other diseases such as pelvic adhesions, urologic, or gastrointestinal disorders, in these cases a differential diagnosis is required.[33] Pelvic transvaginal ultrasound (TVS) scan is performed to visualize uterine cavity and endometrium as well as to detect the typical aspect of the ovarian endometrioma, reporting also high sensitivity, specificity, and accuracy in diagnosis of deep retrocervical and rectosigmoid endometriosis cases.[34]

When a big pelvic mass is found, the integration of transvaginal along with the transabdominal ultrasounds helps to better understand the anatomical involvement of the nearby organs. Imaging such as magnetic resonance and computed tomography can help to characterize the pelvic masses and to discover extra-pelvic foci. Magnetic resonance imaging (MRI) has a high diagnostic performance for detection of endometrioma especially on T1-weighted images with or without fat suppression.[35] Moreover, it is reported that thin-section oblique axial T2-weighted imaging may enhance the success of conventional MRI for assessment of USL endometriosis.[36] Other evidences suggested a crucial role of MRI for the detection of deep pelvic endometriosis especially for lesions localized to the vagina and rectovaginal septum when integrated with opacification of the vagina and rectum.[37] In the same view, although the diagnosis of ovarian endometrioma, vaginal, and rectovaginal endometriosis are reliable at ultrasound, MRI, covering the entire pelvis, may represent a valid option to diagnose "all-in-one" the lesions and exactly set the disease limits when a consistent clinical suspicion of deep pelvic endometriosis exists. In addition, MRI is also considered useful to point out preoperatively those lesions that may be hidden by adhesions at surgery.[38] Finally, a recent systematic review and meta-analysis reported that the diagnostic performance of TVS and MRI is similar for detecting deep infiltrative endometriosis involving rectosigmoid, USLs, and rectovaginal septum.[39]

Women affected by endometriosis may show altered levels of CA-125, and inflammatory cytokines, angiogenic and growth factors, but none of the biochemical alterations have been proven to be a specific marker for the diagnosis of endometriosis. Among the main symptoms and signs, infertility affects up to 50% of women affected by endometriosis and may require the use of assisted reproduction techniques. Several approaches of assisted reproductive techniques (ART) have been proposed to treat endometriosis patients with infertility but recent evidence suggests the use of an integrated approach (surgery, assisted reproductive technology or both) as gold standard treatment for endometriosis associated infertility in carefully selected patients.[40] Moreover, the personalization of the therapy during ART in terms of procedures, start dosage of gonadotropins during the stimulation protocols,[41] dehydroepiandrosterone (DHEA) supplementation[42] and luteal phase ovarian stimulation[43] supplementation in poor ovarian responders, myo-inositol supplementation for male gametes,[44] and preimplantation methods as endometrial scratch[45,46] may represent a start point to reach positive effects on fertility. Finally, endometriosis alone[47] or associated with chronic pelvic pain[48–50] or infertility[51] have a severe impact on both psychological well-being and sexuality[52,53] with the high risk of development of severe psychological and psychiatric disturbances such as anger, anxiety, and major depression.[54–57] Moreover, higher levels of anxiety characterize women with endometriosis,[58] especially when they approach for ART for the first time or became pregnant by ART requiring, thus, the psychologist or psychiatric support.[59–62]

Medical treatments

As far as the chronic inflammatory diseases are concerned, the medical therapy in women with endometriosis should be a long-term treatment able to realize the suppression of symptoms without any drug interruption. Moreover, medical therapy represents only a symptomatic treatment and not the definitive solution to endometriosis lesions that may persist despite different medications, dosages, and duration of the therapy.[63,64] Although there is no clear evidence about the superiority of one treatment over the others, hormonal treatments represent the first line of choice in several cases of patients affected by endometriosis. Among hormonal therapy, gonadotropin-releasing hormone (GnRH) agonists have been proposed as effective treatments against associated-endometriosis pain,[65] but although the high effectiveness, they showed a scarce compliance due to their hypoestrogenic effect. The hypoestrogenic environment is related to mood

instability, vasomotor symptoms, genital hypotrophy, and osteopenia. GnRH agonists may be associated with add-back therapy consisting of tibolone (2.5 mg per day orally) or a bone-sparing progestin such as norethisterone acetate (5 mg per day orally), which have both been successfully used[66,67] but is suggested in selected women unresponsive to progestins or at high surgical risk. Danazol and gestrinone create a hyperandrogenic environment and oral contraceptives including progestins create a hyperprogestogenic environment which are other choices of medical treatments of endometriosis. Both drugs have been found not suitable for prolonged treatments[63] in order of their association with hyperandrogenic adverse effects such as seborrhoea, hypertrichosis, and weight gain and negative effect of increasing serum low-density lipoprotein (LDL) concentration, except for low dose Danazol which is used vaginally.[68] Low dose combined oral contraceptives are candidate as the best medical chronic treatment in terms of long-term pain control, compliance, and safety.[64–66] Administration of oral contraceptives consists of the continuous regimen in order of creating a hormonal balance able to induce the decidualization and subsequent atrophy of the eutopic endometrium and of the endometriosis implants. Moreover, the efficacy of oral contraceptives may help to decrease the retrograde menstruation. Although different administrations of progestins are available, such as subcutaneous, intramuscular, intrauterine, and vaginal,[64–66] norethisterone acetate and dienogest used orally represents the first line of choice and are supported by the most available evidences. The key point of endometriosis treatment with oral contraceptive or progestins is the continuative regimen of the therapy maintaining the drug steady state, reducing the episodes of bleeding per year and avoiding the endometriosis cell proliferation.[69] In case of severe dysmenorrhoea, oral contraceptives in continuous administrations represent the first-choice therapy with aim to totally abolish the cycle bleeding. The alternative to oral contraceptive is the insertion of the levonorgestrel intrauterine device which is able to decrease the flow in a high percentage of patients with endometriosis.[64,66,67,70] This treatment should be reserved for women without fertility desire in a short period of time and may be used as adjuvant treatment after surgery.[70,71] In addition, recent evidence suggests an effective role for the etonogestrel implants in reducing pelvic pain and improving quality of life and sexual function in women patients with ovarian cysts of suspected endometriotic origin.[72] Finally, the deep dyspareunia benefits from the use of progestin oral administration with a satisfactory relief of pain in absence of rectovaginal lesions, norethisterone acetate seems to have better results than surgery.[73] Although patients may benefit from these medications in cases of pelvic pain, the same may not be said in case of endometriosis-associated infertility. Hormonal medical therapy, in fact, should be discouraged in patients with endometriosis and desire to conceive with the only exception for patients undergoing in vitro fertilization (IVF) that should benefit from the use of GnRH agonist or oral contraceptives before ART.[51,74–76] The issue of post-operative medical treatment of endometriosis has been extensively investigated and there was no evidence of benefit with post-surgical medical treatment.[77]

Surgical approach

Surgical treatments in women with endometriosis represent an effective alternative to the medical approach. The choice between the two alternatives depends on the patient's anatomical involvement by the disease such as the presence of ovarian endometrioma and lesions invading adjacent organs such as bowel, bladder, appendix, or ureter creating thus urogenital and intestinal stenosis.[78] Moreover, when the dyspareunia afflicts patients without any possibility of solving the symptom, probably the reason is the presence of rectovaginal deep plaques, and in these cases, patients are candidates for surgery. Considering that hormonal therapy, which interferes with spontaneous ovulation, is not indicated in case of desire of natural conceiving, a fertility sparing surgical approach may be encouraged in women with pelvic pain but searching for a spontaneous pregnancy, similarly to what occurs in reproductive-age young women affected by early stage of endometrial cancer with desire of conceiving.[79–81] Endometriosis conservative surgical management has the goal of restoring normal anatomy and relieving pain. This approach may involve removal of ovarian endometriomas, adhesiolysis, interruption of nerve pathways, and excision of lesions invading adjacent organs. Although the surgical approach may help to relieve pain temporarily,[82,83] it unfortunately may lead to several complications depending on the type of lesion removed. Women with severely painful endometriosis and without desire of pregnancy may be candidate to hysterectomy with bilateral salpingectomy as well as parametrial and deep lesions resection. This intervention has been reported to solve the dysmenorrhoea and deep dyspareunia. However, the choice to leave ovary in situ is associated with the possibility of pain persistence related to the continued production of estrogen increased by the still presence of endometriotic implants in non-radical treatment. The alternative of bilateral oophorectomy should be considered in women suffering significant symptoms including pain despite conservative treatment with no desire of future pregnancies. In this case, an appropriate hormonal replacement therapy should be proposed to avoid hyperplasia of residual endometrial implants exposed to estrogen. To date, the use of minimally invasive surgical techniques represent a valid option to treat several benign [84–87] and malignant gynecological diseases.[80,88–90] In this scenario, the preferred surgical route for management of endometriosis is considered laparoscopy. The laparoscopic approach offers a greater visualization, reduced post-operative

discomfort, a shorter patient recovery, and a quicker return to normal activity with respect to laparotomy.[91] Moreover, in order of the precision required for the endometriosis interventions and of the potential impact of surgical treatment on women's physical, sexual, and emotional function, it is important that the surgical approach be reserved for surgeons with experience or advanced training, especially in patients with invasive endometriosis.[92] Endometriosis surgery is a required surgical skill which should focus on the complete resection because it has been shown that complete resection is mandatory in order to prevent recurrences and alleviate the associated symptoms.[93] Finally, benefiting from the ongoing evolution of minimally invasive surgery,[94–96] future investigations should be conducted to use this approach to save the function of all the organs involved by the disease.

Conclusion

Endometriosis is a gynecological proliferation characterized by progressive and invasive growth affecting up to 10%–15% of women in reproductive-age and representing one of the most common cause of severe pelvic pain. To date, the hormonal medical treatment is reserved for patients with low to moderate pain, deep dyspareunia in absence of rectovaginal lesions, and to patients that should benefit from this therapy before ART. Laparoscopic surgical treatment, conservative or radical has the goal to abolish pain and is reserved, respectively, to those women desiring a spontaneous pregnancy and to those without any future desire of conceiving. However, surgical treatment may have an important impact on women's physical, sexual and emotional function, so it is important that the surgical approach be performed by surgeons with advanced training to reduce the risk of severe complications. The aim for the future is to replace the invasive surgery with less invasive approach, already used to treat both benign and malignant gynecological diseases, to better preserve the function of all the organs involved by the disease and to reduce, the post-operative discomfort, time to return to normal activity and psychological impact in women suffering from endometriosis.

Acknowledgements

The Authors alone are responsible for the content and writing of the article.

Author contributions

F.D.G. wrote the article draft; M.C.C. and P.G. screened the literature and included appropriate data; M.S., E.K., P.T., D.A.Y., and A.M.-B. reviewed and edited the article, providing insightful suggestions; and A.B. and A.S.L. provided direction and guidance throughout the preparation of this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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