ABSTRACT:

Deeply infiltrating endometriosis (DIE) includes rectovaginal lesions as well as infiltrative forms that involve vital structures such as bowel, ureters, and bladder that might greatly alter the quality of life because of severe pain at menstruation and intercourse, and pose particularly difficult surgical problems. It is diagnosed in 20% of women with endometriosis.

The vast body of evidence available in the literature strongly supports the implantation theory in DIE pathogenesis.

Although hormonal treatment is efficient with respect to the pain, surgery is the treatment of reference in this context. The complexity and morbidity associated with the surgical procedures must be considerate. Great importance must be given to complete and balanced counseling, as awareness of the real possibilities of different treatments will enhance the patient’s collaboration.

It appears to be increasingly clear that DIE will be best treated in a multidisciplinary center.

INTRODUCTION

Endometriosis is an estrogen-dependent inflammatory disease and its defining feature is the presence of endometrium–like tissue in sites outside the endometrial cavity and uterine musculature. These ectopic endometrial implants are usually located in pelvis, but can occur nearly anywhere in the body.

The three clinically distinct forms of endometriosis are endometriotic implants on the surface of the pelvic peritoneum and ovaries (peritoneal endometriosis), ovarian cysts lined by endometrioid mucosa (endometriomas), and deeply infiltrating endometriosis (DIE).\(^1\)

DIE includes rectovaginal lesions as well as infiltrative forms that involve vital structures such as bowel, ureters, and bladder, which might greatly alter the quality of life because of severe pain at menstruation and intercourse, and pose particularly difficult surgical problems.\(^2\)

In the present paper, the anatomic and pathologic evidence regarding the pathogenesis of infiltrating endometriosis is described. This constitutes the basis for the development of a classification of deep disease. Despite extensive research, the optimal management of endometriosis is unclear. This paper will review medical and surgical options for treating women with DIE.

PREVALENCE

The overall true prevalence of endometriosis is unknown, primarily because surgery is the only reliable method for diagnosis and generally is not performed on women without symptoms or physical findings that strongly suggest the possibility. The prevalence of asymptomatic endometriosis is approximately 4% in women having surgery for elective sterilization. Most estimates of prevalence of endometriosis have ranged between 5 and 20% among women with pelvic pain and between 20% and 40% among infertile women; a general prevalence ranging between 3% and 10% in reproductive-aged women is likely.\(^3\)
DIE is diagnosed in 20% of women with endometriosis. Moreover, bowel endometriosis is found in 5% to 12% of patients with endometriosis.\textsuperscript{4}

**PATHOGENESIS**

The etiology and pathology of the disease has been argued about since the first detailed pathologic description in 1860 by Karl Freiherr von Rokitansky. Despite the passage of time and extensive investigation, the exact pathogenesis of this enigmatic disorder remains unknown.

Two physiopathological hypotheses are the most often proposed to explain the pathogenesis of endometriosis. The first theory is that of retrograde menstruation in which the lesions would be secondary to implantation and proliferation of regurgitated endometrial cells in an ectopic situation (Sampson, 1927). The second theory is that of metaplasia (Meyer, 1919), either of the celomic metaplasia or Mullerian remnants metaplasia.\textsuperscript{5}

**Retrograde Menstruation**

Initially proposed by Sampson in the 1920s, the theory of retrograde menstruation is both intuitively attractive and supported by multiple lines of scientific evidence, although no single mechanism can explain all cases of endometriosis. According to this theory, ectopic endometrium is sloughed via patent fallopian tubes into the peritoneal cavity during menstruation. Indeed, the universality of this phenomenon is supported by the finding of menstrual blood in the peritoneal fluid of up to 90% of healthy women with patent fallopian tubes undergoing laparoscopy during the perimenstrual period of the cycle.\textsuperscript{6} Further support for this etiology is derived from studies of obstructed or compromised outflow tracts. In adolescent girls with congenital outflow obstruction, the prevalence of endometriosis is high. The viability of the retrogradely menstruated endometrial cells is of paramount importance for the plausibility of the transplantation theory. This has been most elegantly addressed by the experiments of Ridley and Edwards.

The anatomic distribution of endometriotic lesions also favors the retrograde menstruation theory. Superficial implants are more often located in the posterior compartment of the pelvis and in the left hemipelvis. Primary and recurrent ovarian endometriomas are significantly more often located on the left ovary in contrast to the distribution of non endometriotic benign ovarian cysts, which do not display a predilection for sidedness.

**DIE pathogenesis**

A large observational study\textsuperscript{6} suggest that the anatomical distribution of pelvic DIE lesions presents a double asymmetry. Pelvic DIE lesions are more frequently observed in the posterior pelvic compartment and are most often located on the left side. Furthermore, abdominal DIE lesions are far less frequent than pelvic DIE lesions, and unlike these, they are most often located in the right side of the abdominal cavity (appendix and ileocaecum junction).

All these observations plead in favour of the theory of regurgitation and the importance of peritoneal flow patterns in DIE pathogenesis. With the patient standing erect, under the effect of gravity, menstrual blood reflux accumulates in the bottom of the Pouch of Douglas, which is the most dependant portion of the abdomino-pelvic cavity.

The effect of gravity also explains why pelvic DIE lesions are more frequently observed than abdominal DIE lesions and why intestinal DIE lesions are preferentially located on the rectum and the recto-sigmoid junction. The far lower frequency of deep bladder endometriosis compared with uterosacral ligament, vaginal and rectal DIE can be explained by the anatomy, because the lower limit of the vesico-uterine pouch is located well above the lower limit of the pouch of Douglas, which lies opposite the middle third of the posterior vaginal wall.

The more the uterus is retroverted, which makes it easier for the peritoneal liquid to flow from the anterior compartment towards the posterior compartment, the more the DIE lesions will be found posteriorly.\textsuperscript{7}

The anatomical differences between left and right hemipelvis, because of the presence of the sigmoid colon on the left, could explain why pelvic DIE lesions (as superficial and ovarian lesions) are observed more frequently on the left pelvic side wall. The close anatomical relationship between the sigmoid colon and the left adnexa forms a barrier to pelvic diffusion of menstrual blood reflux, resulting in an anatomical situation that could encourage adhesions and growth of regurgitated endometrial cells on the left pelvic side wall.

Results of research into the flow of peritoneal fluid support the hypothesis that peritoneal liquid plays a part, together with regurgitated endometrial cells, in DIE pathogenesis. Four predominant sites have been identified for the preferential, repeated or arrested flow of peritoneal fluid: (i) the pelvic cavity and especially the Pouch of Douglas; (ii) the right lower quadrant at the termination of the small bowel mesentery (caecum and ileocaecum junction); (iii) the superior aspect of the sigmoid mesocolon; and (iv) the right paracolic gutter (Meyers, 1973). Just as for superficial lesion, the anatomical distribution of DIE
Several studies have indicated that endometriosis is a complex disorder that involves the peritoneal cavity. At stage I, endometriotic lesions are stratifying patients by the spherical nature of endometriotic cells and for developing a secondary microenvironment for implantation. Greater exposure to progesterone may be diverse manifestations of a disease with a single origin i.e., regurgitated endometrium. Peritoneal, ovarian, and deep endometriosis may be diverse manifestations of a disease with a single origin i.e., regurgitated endometrium.

Molecular mechanisms

Though retrograde menstruation explains the physical displacement of endometrial fragments into the peritoneal cavity, additional steps are necessary for the development of implants. It is the propensity for implantation that best accounts for the disparity between the 90% prevalence of retrograde menstruation and the nearly 10% prevalence of the disease.

One of two mechanisms could explain the successful implantation of refluxed endometrium onto the peritoneal surface: molecular defects or immunologic abnormalities (or both). In endometriosis, the eutopic endometrium exhibits multiple subtle but biologically important molecular abnormalities, including the activation of oncogenic pathways (e.g., the Wingless-type MMTV integration site family member Wnt or the rat sarcoma viral oncogene homologue Ras) or biosynthetic cascades favoring increased production of estrogen, cytokines, prostaglandins, and metalloproteinases. When the eutopic endometrium, biologically distinct tissue, attaches to mesothelial cells, the magnitude of the molecular abnormalities is amplified drastically, enhancing the survival of the implant. A possible second mechanism of implant survival entails a failure of the immune system to clear implants from the peritoneal surface. Both mechanisms may contribute to the development of endometriosis.

CLASSIFICATION OF DEEP ENDOMETRIOSIS

Based on different pathogenetic hypotheses, several schemes have been proposed to classify deep endometriosis, but further data are needed to demonstrate their validity and reliability.

It seems instinctive to include deep endometriosis in stage 4 of the revised American Society for Reproductive Medicine (ASRM) classification. However, infiltrative forms are not specifically addressed in the ASRM scheme, which was devised mainly with the object of stratifying patients with different reproductive prognoses.

Koninckx and Martin were the first to define deep endometriosis. They distinguished posterior cul-de-sac and rectovaginal lesions in three different subgroups: type I, conically shaped, developed from infiltration; type II, deeply located, covered by extensive adhesions, probably formed by retraction; and type III, the most severe, one or more spherical nodules located in the rectovaginal septum with the largest dimension under the peritoneum, possibly to be considered as adenomyosis externa.

Adamany classified specifically retrocervical endometriosis in four stages according to extent of the disease. At stage I, endometriotic lesions are confined to the rectovaginal cellular tissue in the area of the vaginal vault. At stage II, endometriotic tissue
invades the cervix and penetrates the vaginal wall, causing fibrosis and small cyst formation. At stage III, lesions spread into the uterosacral ligaments and the rectal serosa. At stage IV, the rectal wall, rectosigmoid zone, and rectouterine peritoneum are completely involved, and the rectouterine pouch is totally obliterated.

Martin and Batt differentiated among retrocervical, rectovaginal pouch, and rectovaginal septum endometriosis. Retrocervical endometriosis includes lesions in the anterior aspect of the Douglas pouch, posterior vaginal fornix, and retroperitoneal area behind or beneath the cervix with no rectal involvement. In rectovaginal endometriosis, rectal and vaginal walls, as well as both vaginal and rectal aspects of the posterior cul-de-sac are involved. Rectovaginal septum endometriosis refers to isolated, true subperitoneal lesions without continuity with Douglas pouch lesions. According to the proponents of this scheme, it is difficult to determine true rectovaginal septum involvement, also because rectovaginal and rectovaginal septum lesions may be associated.

Most recently a classification system for deep endometriosis based on the anatomical location of the lesion with a recommended preferred surgical treatment for each location has been developed.12-13

DIE: PATHOLOGY AND SITES OF INVOLVEMENT

Martin et al., (1989) and later Cornillie et al. (1990) suggested that endometriosis should be classified according to the depth of invasion into superficial (<1 mm), intermediate (2±4 mm), deep (>5 mm) and very deep (>10 mm).12

DIE is defined by the presence of endometrial implants, fibrosis and muscular hyperplasia under the peritoneum, and can involve, in descending order of frequency, the uterosacral ligaments, the rectosigmoid colon, the vagina and the bladder.7

Rectovaginal endometriosis accounts for 5% to 10% of women with endometriosis and is characterised by the presence of palpable endometriotic nodules deep in the connective tissue of the pelvis, which show profound fibrosis and fibromuscular hyperplasia.14

Multilocularity is a major characteristic of DIE lesions.13

RECTOVAGINAL ENDOMETRIOSIS: CONFUSION ABOUT NAMES

Cullen’s original name for deep pelvic disease was adenomyoma of the rectovaginal septum (Cullen, 1920).12 It is now recognized that endometriosis only rarely involves the true rectovaginal septum and much more frequently involves the overlying rectovaginal pouch.9. A variety of other descriptions has been used to describe the anatomical location of these lesions and includes cul-de-sac endometriosis (Martin et al., 1989), obliteration of the cul-de-sac (Redwine, 1991) and rectocervical endometriosis (Adamyan et al., 1993; Perry et al., 1995). These three terms were combined to produce an anatomically precise but hardly concise cul-de-sac obliteration secondary to retrocervical deep fibrotic endometriosis (Reich et al., 1991).

Other terms that have also been used include pelvic wall-infiltrating endometriosis (Khare et al., 1996), rectovaginal septum adenomyotic nodules (Donnez et al., 1997), retroperitoneal adenomyosis (Donnez, 2001) and rectovaginal endometriosis (Kavallaris et al., 2003). From this review it is not immediately obvious what these lesions should be called or how we should describe their locations.12

CLINICAL FEATURES OF DIE

Endometriosis exhibits a broad spectrum of clinical manifestations: can be asymptomatic, being incidentally discovered at laparoscopy or postmortem examination;7 or a disorder of such severity that the sufferer’s quality of life is destroyed.12 DIE is known as a severe and painful modality of disease.15

A causal association between severe dysmenorrhoea and endometriosis is very probable. This association is independent of the macroscopic type of the lesions (superficial endometriosis, cystic ovarian endometriosis or DIE) or their anatomical locations and may be related to recurrent cyclic micro-bleeding in the implants. Endometriosis-related adhesions may also cause severe dysmenorrhoea.

However, pelvic pain may be more common in women with deep, infiltrating implants. There are histological and physiopathological arguments for the responsibility of DIE in severe chronic pelvic pain symptoms. DIE-related pain may be in relation with compression or infiltration of nerves in the subperitoneal pelvic space by the implants.16 The intensity of pain in woman with DIE correlates well with the depth and volume of infiltration.3

The painful symptoms caused by DIE present particular characteristics, being specific to involvement of precise anatomical locations (severe deep dyspareunia, painful defecation) or organs (functional urinary tract signs, bowel signs). They can thus be described as location indicating pain.

There is a clear-cut relationship between posterior DIE and deep dyspareunia, painful defecation during menses with involvement of the posterior wall of the vagina, non-cyclic pelvic pain and functional bowel signs with bowel involvement and functional urinary tract signs with involvement of the
bladder. A prospective study, based on patients operated by laparoscopy for chronic pelvic pain, demonstrated that painful defecation during menses and severe dyspareunia were specifically connected to DIE involving the posterior area compared to the other diagnoses (other macroscopic type of endometriosis or non-endometriosis diagnosis).16

DIE and deep dyspareunia

When dyspareunia is referred to the rectum or lower sacrococcygeal area, it suggests rectovaginal or uterosacral ligament involvement. In particular, several studies correlated deep dyspareunia with the presence of endometriosis of the uterosacral ligaments. This correlation is consistent with the presence of a considerable amount of nerve tissue within the uterosacral ligaments; dyspareunia may be related to the stimulation of pain fibers by traction of scarred inelastic tissues and by pressure on endometriotic nodules embedded in fibrotic tissues.

Dyspareunia has been associated with a negative attitude toward sexuality, anxiety and avoidance of intercourse. Women with dyspareunia, not surprisingly, have lower frequency of intercourse and lower levels of desire and arousal and experience fewer orgasms.17

Gastrointestinal involvement in DIE

Bowel endometriosis is found in 5% to 12% of patients with endometriosis and colorectum represents 90% of all bowel locations.4

Symptoms range from rectal bleeding, urgency, pelvic pain, severe dyschezia, bowel cramping and alteration in bowel habit from diarrhea to obstruction of the colon.18 Symptoms usually occur cyclically at or about the time of menstruation. Intestinal endometriosis should be suspected in women of childbearing age who present with gastrointestinal symptoms and a history of endometriosis.6

Malignant change in colonic endometriosis has been documented. The rate of progression is unknown but is uncommon.12

Genitourinary involvement in DIE

The urinary tract is involved in 1% to 4% of women with endometriosis of which around 90% involve the bladder. Patient presentation in vesical endometriosis is quite variable, and symptoms may consist of suprapubic discomfort, pelvic pain, dysmenorrheal, dysuria, urinary frequency, urgency, microscopic hematuria, and even cyclical gross hematuria.6

Malignant transformation of bladder endometriosis although rare has been described repeatedly and must represent a risk if bladder lesions remain untreated.12 Ureteral endometriosis is uncommon, with an incidence of less than 0.1% of all cases of endometriosis. Obstructive uropathy that may lead to renal cortical atrophy and severe loss of renal function can occur with this type of lesion.6

DIAGNOSIS OF DIE

Endometriosis remains difficult to diagnose, with a delay of 8-11 years between first report of symptoms and recognition of disease.19

Unfortunately, the substantial advances in our understanding of the pathogenesis of endometriosis have not yet provided any reliable noninvasive alternative to laparoscopy for diagnosis of the disease.3

Physical examination

In endometriosis physical examination of the external genitalia is typically normal. Occasionally, speculum examination may reveal typical blue-colored implants or red proliferative lesions that bleed on contact, both usually in the posterior fornix. Whereas disease in women with DIE involving the rectovaginal septum is frequently palpable, it is much less often visible, and in many there is no remarkable findings.3

Analysis of the findings on vaginal examination in symptomatic patients with presumed endometriosis suggests that palpable induration or nodules in the posterior vaginal fornix and/or along the uterosacral ligaments appears to be pathognomonic signs of deep endometriosis.12 These lesions are tender and pressure reproduces symptoms. The predictive positive value of such tenderness predicting endometriosis is between 76 and 79% and this rises to 83% with a specificity of 92% if focal tenderness is located only in the uterosacral ligaments and cul de sac.

The accuracy of these findings is further increased if the examination is performed during menstruation. Deep invasive endometriosis is frequently associated with ovarian endometriosis. The co-existence of these two conditions further improves the reliability of the clinical diagnosis.

In summary, the presence or absence of palpable nodular or infiltrative lesions is related to the location and depth of the lesions and reflects the severity of the pain and the risks of severe complications.12

Imaging studies

Physical examination has a limited capacity to
diagnose and quantify DIE and transvaginal, transrectal or rectal endoscopic sonography as well as magnetic resonance imaging (MRI) has all been recommended for its diagnosis and for determining its location.20

The significant role of MRI in the diagnosis of endometriosis is related to the identification of intermingled lesions in the presence of adhesions, and also the demonstration and evaluation of sub-peritoneal lesions extent in cases where these lesion cannot be visualized by laparoscopy, with accuracy, sensitivity and specificity > 90% for deep endometriosis.

In patients with deep pelvic endometriosis, clinical and sonographic results may be normal or poorly elucidative, difficulting the diagnosis determination. In these cases, MRI is essential for an accurate differential diagnosis. Because of its multiplanar capacity and excellent tissue characterization, MRI plays an essential role in the preoperative evaluation of patients with deep pelvic endometriosis.21

**Serum CA 125**

Although women with endometriosis often have high (greater than 35 IU/mL) serum CA 125 concentrations, serum CA 125 is not a sensitive indicator of the disease. However, knowledge of an elevated preoperative CA 125 concentration may be useful for selecting women who are at high risk for bowel injury because of dense pelvic adhesions and thus most likely to benefit from preoperative bowel preparation.3,7

**Laparoscopy**

Progestins should be considered as first-line medical treatment for temporary pain relief.22

**Conservative surgical treatment of DIE**

In most cases of severely infiltrating disease, surgery is the treatment of reference.13 Surgical treatment is effective for relieving pelvic pain, dyspareunia, and painful defecation.2

In general, deep endometriotic lesions should not always be treated just because they are there. Intestinal and ureteral foci that cause progressive stenosis constitute indisputable reasons for operating. Otherwise, surgery for asymptomatic DIE should not be considered mandatory in all cases. The results of treatment for a benign condition such as endometriosis are functional, and surgical indications should be based mainly on symptoms and nonresponse to medical therapies.22

The location of the DIE lesions must dictate the choice of operating technique. In multifocal cases, several surgical procedures must be associated. For bladder DIE, the standard treatment is partial cystectomy which can be performed by operative laparoscopy. For DIE infiltrating the uterosacral ligaments, it has been shown that laparoscopic surgical resection is efficient. For vaginal DIE, numerous authors have demonstrated that operative laparoscopy is efficient using various techniques (electrosurgery, sharp dissection or laser CO2; exclusively laparoscopic procedure or laparoscopically assisted vaginal surgery).

The different topographical location of uterosacral ligaments and vaginal DIE requires specific operating techniques. Lesions strictly located on the uterosacral ligaments require, in the majority of patients, ureterolysis without associated exeresis of the upper part of the posterior vaginal wall. In cases of isolated vaginal DIE, dissection of the latero-rectal fossae is necessary in >80% of cases and exeresis of the upper part of the posterior vaginal wall is

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TREATMENT OF DIE

**Medical treatment of DIE**

It is well established that hormonal drugs do not cure endometriosis but only induce temporary quiescence of active lesions and that in most cases of advanced disease, surgery is the final solution. However, there are several situations in which medical treatments are still useful. Some women who have already undergone several operations might prefer to avoid further surgery but need pain relief, and others may want only to postpone surgery because of study, work, or family problems. Furthermore, drugs may be chosen as an alternative to surgery in the rare very difficult cases in which the risks of morbidity and complications outweigh the benefits of a radical operation.

Long-term pain relief is the main objective, and great care should be paid to the choice of drug. DIE has been treated successfully with danazol, gonadotropin-releasing hormone analogs, progestins, and estrogen-progestin combinations.
essential. The reason for this is that vaginal DIE most often does not infiltrate the rectovaginal septum which is located lower down but rather the upper third of the posterior vaginal wall.15

The question of operative technique is far more complex when the digestive tract is involved. Surgery for rectovaginal endometriosis can be complex and challenging and often involves a multidisciplinary team. There are several approaches to be considered, from shaving the disease off the rectal wall to carrying out an excision of the anterior rectal wall or a segmental excision of the rectum; none of which has been accepted as “best” practice. All these procedures can be carried out by either a laparoscopic, combined or open approach.18

In women with advanced symptomatic disease in whom medical and conservative surgical treatment fails, radical surgical treatment (hysterectomy and bilateral salpingo-oophorectomy) merits serious consideration and discussion.3

DIE complications and recurrences

Surgery for deep endometriosis is associated with a relatively high risk of postoperative complications, such as de-novo or worsening voiding dysfunction and rectovaginal fistula.2

Endometriosis is a nonmalignant disease that usually affects young women with high expectations in terms of conception and quality of life. In these circumstances, intraoperative and postoperative complications are perceived and tolerated with difficulty, and incapacitating pain recurrence and persistent infertility are particularly frustrating. A thorough preoperative diagnostic investigation and careful detailed counseling are of major importance. Involvement of the intestinal and urologic systems should be known in advance, to schedule intraoperative consultation, if necessary, and to inform the woman about the type of surgery required and its potential sequelae. This will also help patients and their families understand the clinical severity of the condition, and balance the risks and benefits of the proposed treatments. In particular, as the chances of pregnancy after surgery may be limited, an alternative solution might be chosen such as in vitro fertilization or adoption. Awareness of the real possibilities of different treatments will enhance the patient’s collaboration.22

Recurrence or persistence of endometriosis after treatment is one of the most vexing problems of gynecology and is based on the known unpredictability of the disease. Endometriosis recurrence rates vary from 2% to 47%. The highest recurrence rate is documented for deep infiltrative endometriosis, based on difficulties in estimating the real borders of the infiltrate, as well as the conscious rejection of more aggressive approaches to removal of the lesions, which are located near vital organs.23

The surgeon should be aware of the biopsychosocial nature of the disease: “the surgeon who only thinks, for instance, to eradicate the lesions of endometriosis, and who does not consider all living of the patient will often have few successes and many recurrences. The key to taking good charge is therefore to act on both aspects: psychological and physical” (Rodolphe Maheux, World Endometriosis Association).24

THE FUTURE...

New developments in fiber optic endoscopes with diameters less than 1 mm have enabled a gynecologist to diagnose and stage the disease in an office setting under local anesthesia, possibly at earlier stages.23

The development of “Centers of Excellence” for the overall management of severe endometriosis has been advocated in recent publications. Working in conjunction with colorectal and urological surgeons and through the use of multidisciplinary team meetings appropriate case selection can be made to ensure that the correct skill base is present for curative surgery.14

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