Clinical Management of Bowel Endometriosis

From Diagnosis to Treatment

Simone Ferrero
Marcello Ceccaroni
Editors

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Part I

Bowel Endometriosis

1 Pathogenesis of Bowel Endometriosis

Jessica Ottolina, Ludovica Bartiromo, Matteo Schimberni, Paola Viganò, and Massimo Candiani

1.1 Definition and Epidemiology

Deep infiltrating endometriosis (DIE) is a specific entity defined by the presence of an endometriotic lesion extending more than 5 mm underneath the peritoneum, including the infiltrative forms that involve vital structures, such as the bowel, ureters, bladder, and rectovaginal lesions. The choice of 5 mm of extension was made in light of epidemiologic observation [1]. Current data are insufficient to estimate the true incidence of endometriosis causing bowel obstruction, since literature consists almost exclusively of case reports. Differences in the estimated incidence may be due to different definitions of bowel endometriosis, or may be a reflection of missed diagnosis. Furthermore, a number of women with bowel endometriosis are diagnosed with other disorders such as irritable bowel syndrome and may never actually be diagnosed with or treated for bowel endometriosis [2]. Despite this, endometriosis causing intestinal obstruction is extremely rare with reported incidence between 0.1% and 0.7% [3].

1.2 Anatomical Distribution and Classification

Intestinal endometriosis is the most common extra-pelvic site [4]. Among women with endometriosis, the reported prevalence of rectovaginal or bowel involvement ranges widely from 5% to 25%, followed by localizations of the rectum, ileum, appendix, and cecum [5, 6]. Moreover, few case reports of lesions found in the upper abdomen including the stomach and transverse colon are reported [7, 8]. Multifocality is one of the main characteristics of DIE, especially when the intestinal tract is involved. When DIE affects the recto-sigmoid, multifocal bowel lesions are observed in about 40% of patients [9]. As reported by Kavallaris et al., with regard to rectal endometriosis, multifocal involvement (defined as presence of deep lesions within 2 cm area from the main lesions) was observed in 62% of the cases while multicentric involvement (defined as a satellite deep nodule found 2 cm from the main lesions) was found in 38% of the cases [10]. Markham et al. published a classification system dividing extra-pelvic lesions into four classes: Class I: endometriosis of the gastrointestinal

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tract; Class U: endometriosis of the urinary tract; Class L: endometriosis of the lungs and thorax; and Class O: endometriosis involving all other sites. A further staging includes the classification of the lesions based on the exact location and dimension of the defect [11]. Although isolated bowel involvement can be observed, the majority of patients with bowel endometriosis show evidence of disease elsewhere [12]. Remorgida and colleagues suggested a system for staging gastrointestinal tract endometriosis correlating with patients' symptoms and based on bowel specimen. They divided the disease into four stages: stage 0, the endometriotic tissue is only affecting the peritoneum and the subserosal connective tissue (not reaching the subserous plexus); stage 1, endometriotic foci are located in the subserous fat tissue or adjacent to the neurovascular branches (subserous plexus), rarely involving the external muscle layer; stage 2, the muscular wall and the Auerbach plexus are involved; stage 3, the infiltration reaches the submucosal nervous plexus or the mucosa [13]. Most of the endometriotic lesions of the gastrointestinal tract are confined to the serosal layer and surrounding connective tissue (stage 0). According to this, diagnosis of deep gastrointestinal endometriosis can be made only when invasion of the muscularis layer is established, while deeper lesions are uncommon with only few reports of endometriosis penetrating the bowel lumen [14–16]. Lymph node involvement can be observed ranging between 26% and 42% of the cases and it seems to correlate with the size of the bowel lesion and the percentage of the intestinal wall affected by the deep nodule; its presence may contribute to postoperative recurrences [17]. The incidence of lymph node involvement may be underestimated since the definitive diagnosis is obtainable only on bowel specimens after segmental bowel resection for deep endometriosis [17–19].

1.3 Theories Surrounding Pathogenesis

Multiple theories exist regarding the pathogenesis of endometriosis, the main being the retrograde menstruation and metaplasia theories, but nowadays it is well known that the pathogenesis of the disease is complex and likely multifactorial.

1.3.1 Retrograde Menstruation

The retrograde menstruation was the first and the most commonly cited theory [20]. The "implantation" theory proposes that endometrial tissue from the uterus is shed during menstruation and transported through the fallopian tubes (retrograde menstruation), thereby gaining access to and implanting on pelvic structures, including the bowel. Numerous studies have demonstrated that reflux of endometrial cells into the peritoneal cavity is a very common physiologic condition occurring during normal menstruation in most women with patent tubes [21, 22]. Therefore, anatomic alterations of the pelvis that increase tubal reflux of menstrual endometrium should increase a woman's chance of developing endometriosis. This is supported by the evidence that incidence of endometriosis is increased in girls with genital tract obstructions that prevent the expulsion of menses into the vagina increasing the likelihood of tubal reflux [23]. However, since up to 90% of women have retrograde menstruation, most women do not develop endometriosis suggesting that additional factors are involved [24]. According to Sampson's theory, endometriotic lesions affect the recto-sigmoid starting from the serosa, invade toward the lumen of the bowel and finally infiltrate the rectal wall [20]. The pathogenetic pathway leads to superficial implantation of endometrial cells triggering a strong inflammatory stimulus. When the process involves the sigmoid or, more rarely, the cecum, a distinct, large, and hard nodule forms. This lesion most often consists of duplicated and invaginated intestinal wall with very limited endometriotic tissue. Supporting this theory, evidence showed that the bowel endometriosis is not an isolated disease and that the subserosal layer is most commonly involved, with only few reports reporting deeper involvement [16]. Another observation supporting the theory of retrograde menstruation refers to the anatomical distribution of pelvic DIE, presenting in a double asymmetry: lesions

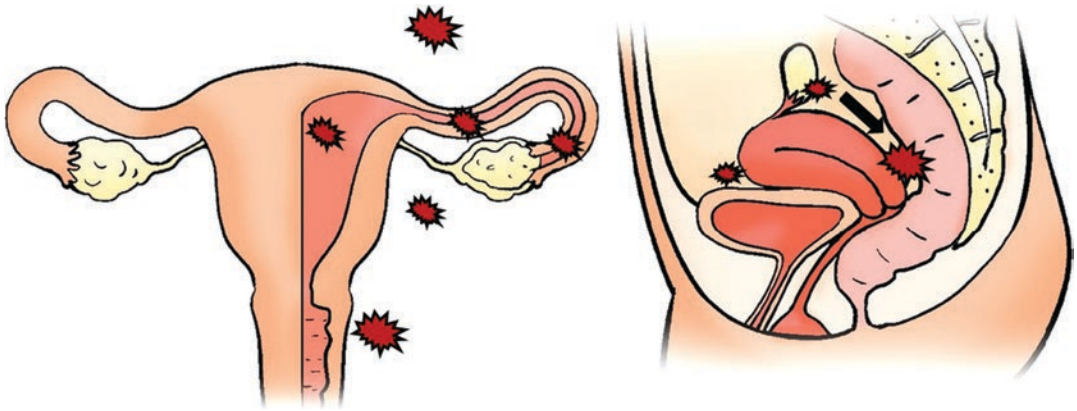

Fig. 1.1 The retrograde menstruation theory (Sampson theory)

are more frequently observed in the posterior compartment and most often located in the left side because of the gravity and the presence of the sigmoid colon on the left side close to the left adnexa [9]. This also explains why pelvic DIE lesions are more frequently observed in the low than in the high abdomen, and why intestinal lesions are preferentially located on the rectum and recto-sigmoid junction [9]. This is the so-called anatomical shelter theory. The retrograde menstruation theory is illustrated in Fig. 1.1.

1.3.2 Coelomic Metaplasia

The second theory supposed to explain the pathogenesis of endometriosis is that of "metaplasia", reported by Meyer in 1919 [25], subsequently developed as either coelomic (peritoneal) metaplasia by Gruenwald in 1942 [26] or Müllerian remnants metaplasia proposed by Donnez in 1995 [27]. The first hypothesis is based on embryologic studies demonstrating that all pelvic organs, including the endometrium, derived from cells lining the coelomic cavity. According to Donnez [27], deep lesions of the posterior cul-de-sac correspond to adenomyotic nodules originating from metaplasia of Müllerian remnants located in the rectovaginal septum, thus constituting a different entity from peritoneal endometriosis [28]. This hypothesis is based on the typical histological aspect of the different localizations and types. In fact, endometriotic rectovaginal nodules show a histological aspect similar to adenomyotic nodules: differently from peritoneal endometriosis, in which epithelial glands are surrounded systematically by endometrial-type stroma, they consist in proliferating smooth muscle cells with active glandular epithelium and scanty stroma [29]. Indeed, several authors agree that there are three different types of endometriosis based on their histological presentation, with different pathogenetic mechanisms: peritoneal, ovarian, and DIE [28]. It has to be noticed that the vast majority of fibrotic rectovaginal plaques are found in the retrocervical area [30]. The rectovaginal septum is located caudally with respect to the posterior vaginal fornix and, since the base of the posterior cul-de-sac extends to at least the level of the middle third of the posterior vaginal fornix, it may not be the real site of deep nodular endometriosis [31]. If the mullerian remnants metaplasia theory is true, the anatomy of the pouch of Douglas should be similar in women with and without the so-called "adenomyotic nodules" because these lesions, if they really originate in the rectovaginal septum, should be located extraperitoneally. On the other hand, if deep foci are a manifestation of intraperitoneal disease, the pouch of Douglas should be partially or completely obliterated in affected women. Vercellini et al. studied whether the depth and volume of the pouch of Douglas differed in patients affected by endometriosis,

with or without DIE, compared to normal controls (or patients affected by other pelvic diseases). The mean depth of the rectovaginal pouch in normal women, as measured from the upper border of the uterosacral ligaments to its base, has been demonstrated to be slightly over 5 cm [32]. All women with rectovaginal nodules had various degrees of anterior rectal displacement with adhesion to the peritoneum covering the posterior vaginal fornix: the mean depth and volume of the pouch of Douglas were significantly reduced in the deep endometriosis group, with about a one-third reduction in depth of the pouch of Douglas. No significant difference has been reported in women without deep lesions compared to controls (those with diseases other than endometriosis and those with a normal pelvis). The partial obliteration by the anterior rectal wall seems to be the cause of this apparent depth reduction and may give the false impression that nodules are subperitoneal. In other words, the authors concluded that endometriotic plaques and nodules found in the posterior vaginal fornix, cranially with respect to the rectovaginal septum may instead be a massive disease of the deepest portion of the pouch of Douglas that has been buried and excluded from the remaining pelvis by adhesions [32]. Moreover, various forms of peritoneal and ovarian disease are usually present in patients with rectovaginal endometriosis, suggesting that the pathogenesis may not be different. In this regard, Anaf et al. demonstrated (using immunochemical techniques with a monoclonal antibody against alfa-smooth muscle actin (α-SMA)) that a smooth muscle component is present in all types of endometriotic lesions but it is absent in disease-free peritoneum [33]. They hypothesize that the smooth muscle component may result from the metaplastic capacity of the mesothelium to differentiate into smooth muscle cells in response to the implanted endometrium. This metaplastic response might differ from one location to the other, thus explaining histological differences among the various forms of endometriosis [34].

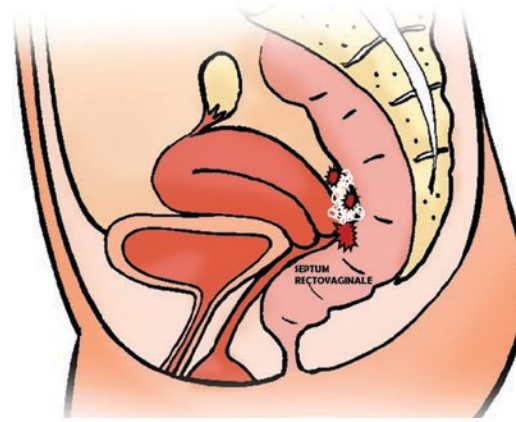

Fig. 1.2 The coelomic metaplasia (Müllerian remnants)

The coelomic metaplasia theory is illustrated in Fig. 1.2.

1.3.3 Stem Cells

The endometrial regeneration after menstrual shedding and the endometrial re-epithelialization after delivery or surgical curettage support the existence of a stem cell pool [35]. Since the endometrial basalis layer remains after the monthly menstrual shedding of the functional layer, the stem cells are thought to reside in the basalis layer of the endometrium [36]. Recently, endometrial-derived clonogenic cells (the stem cell population in the human endometrium) have been identified and proposed to be involved in the development of ectopic endometrial lesions [37]. According to Brosens et al., the neonatal uterine bleeding contains a high amount of endometrial progenitor cells [38]. Leyendecker et al. proposed that women affected by endometriosis abnormally shed the endometrial basalis tissue initiating endometriotic deposits after retrograde menstruation [39]. The possibility of an increased shedding of the stem cell from the basalis layer in patients affect by endometriosis as compared to healthy women, together with the similarity observed between ectopic lesions and the basalis layer, may support the theory of retrograde menstruation as providing an access for the endome-

trial stem cells to extrauterine structures [39]. Otherwise, these stem cells may be transported by the lymphatic or vascular pathways to ectopic sites [40]. Moreover, the fact that some of the endometrial stem cells possibly derive from the bone marrow further supports the hematogenous dissemination theory of these cells [41]. However, since stem cells are normally expected to differentiate into mature cells in concordance with the environmental niche, the supposedly multipotential endometrial stem cells in the peritoneal cavity should differentiate in peritoneal-type cells. It is possible that the deposition of endometrial tissue fragments containing both endometrial stem cells and their niche cells in the peritoneal cavity promote regeneration of endometrium-like tissue, thanks to the signals received by the stem cells from the surrounding endometrial niche cells. On the other hand, the relocation of an aberrant or committed stem cell from the endometrium to an ectopic site may also generate endometrium-like lesions. Endometrial tissue produces several chemokines and angiogenic factors causing neovascularisation in the ectopic site that ensure the establishment of these lesions [42]. Although possible, the reasons for such specific differentiation of stem cells into endometrium-like tissue remain unexplained.

1.3.4 Genetic Factors

Genetic factors probably play a role on individual's susceptibility to endometriosis [43–45]. The possibility of a familiarity for endometriosis has been recognized for several decades and concordance in twins has also been observed [43]. A study analyzing exome sequencing of DIE lesions reported somatic mutations in 79% of lesions and more specifically, mutations for the known cancer driver genes ARID1A, PIK3CA, KRAS, and PPP2R1A in 26% of lesions. The presence of cancer driver mutations in nonmalignant cells may partially explain the aggressive nature of deeply invasive lesions compared with superficial peritoneal lesions. Moreover, these mutations were only found in the epithelial cells suggesting a unique selective pressure [46].

1.4 Histopathologic Findings

1.4.1 The Profibrotic Nature of Endometriosis

In the last years, advances in knowledge regarding the histological definition of endometriosis occurred. These changes have been consistent enough to require a reconceptualization of endometriosis, which is no more considered just as the mere presence of endometrial epithelial and stromal cells in ectopic sites, involving the profibrotic nature of the disease inside its "new" definition [47]. Although the presence of endometrial cells in ectopic sites is probably the starting point in the pathogenesis of endometriosis, it has been widely demonstrated in human as well as in animal studies that endometrial stroma and glands represent only a minor component of endometriotic lesions. It has been recently emphasized the consistent presence of fibrosis and myofibroblasts in endometriotic lesions and their crucial role in the pathogenesis of the disease [33, 48, 49]. Zhang et al., proposed that endometriotic lesions consequent to the implantation of endometrial tissue are essentially wounds undergoing repeated tissue injury and repair (ReTIAR) ultimately leading to fibrosis [48]. Indeed, endometrial cells present cyclic bleeding under hormonal stimulation causing subsequent tissue repair by recruiting neutrophils and macrophages M2 to the lesions [50, 51]. These events imply the development of "leaky" blood vessels resulting in platelets extravasation, leading to an increased platelet aggregation in endometriotic lesions [52]. Activated platelets contain more than 30 important proteins involved in angiogenesis and, along with macrophages, can induce fibrosis through the release of Transforming Growth Factor beta (TGF-β1) and the induction of the TGF-β1/Smad3 signaling pathway. Recent studies in mice showed that the

STAT3 signaling pathway is a potent inducer of epithelial-mesenchymal transition (EMT), fibroblast-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM) in endometriotic epithelial and stromal cells, resulting in increased contractility, collagen deposition and ultimately in fibrosis [53, 54]. The same mechanisms have been also suggested to be involved in DIE fibrosis development. It seems that ovarian endometriosis and DIE both undergo the same cellular changes consistent with EMT, FMT, SMM, and eventually fibrosis [55]. However, recent findings from the immunohistochemistry analysis revealed that DIE is characterized by a higher production of TGF-β1 and a higher fibrotic content, with a more elevated expression of mesenchymal marker (vimentin) and but lower epithelial markers level (E-cadherin), suggesting an EMT process. Less vascularity and less platelet aggregation have been reported in DIE when compared to ovarian endometriosis [55]. Thus, the accelerated fibrosis observed in DIE might require more factors other than platelets to happen [56]. Recently, the role of oxidative stress known to be strongly present in DIE lesions has been associated with the activation of A Disintegrin and Metalloproteases (ADAM17)/Notch signaling pathway. This pathway has been suggested to have a role in the development of endometriosis and, especially, of fibrosis inducing the transcription of fibrosis-related genes and the enhanced fibroblast activation [57].

1.4.2 Histological Appearance of DIE

In accordance with these pathogenetic findings, deep endometriosis nodules (as the rectovaginal endometriotic nodules) have been already considered in the past essentially as proliferating smooth muscle cells with active glandular epithelium and scanty stroma, with a consistent similarity with adenomyotic nodule [27].

According to Donnez and coworkers this smooth muscle content pre-existed in the correspondent normal area and then was invaded by the ectopic endometrium [58]. Subsequently, other authors proposed different theories with regard to the origin of the smooth muscle cells in deep endometriosis. Van Kaam et al. [59], not only showed that all the 20 deep infiltrating endometriotic lesions studied contained fibromuscular tissue and myofibroblastic cells, but again raised reasonable doubts on the origin of this muscle content. Indeed, they demonstrated that the inoculation of human endometrium into a nude mouse could induce α-SMA expression in the surrounding murine tissue, as a consequence of a reaction of the local environment to the presence of ectopic endometrium, rather than representing the stromal differentiation toward smooth muscle cells. Despite the identification of a fibrotic component in DIE, Matsuzaki et al. [60], suggested that in patients with endometriosis, the epithelial-to-mesenchymal transition-like processes of endometrial epithelial cells, even in absence of TGF-β, was the real origin of myofibroblasts. These phenomena are probably generated by the increased stiffness (due to increased myofibroblast collagen I production) resulting in a fibrotic environment in deep disease over time [55, 61].

Proliferation of normal fibroblasts is usually tightly regulated by the presence of type I collagen. In endometriosis, deep endometriotic stromal cells can persist and are not inhibited in their growth by the surrounding fibrotic environment. Matsusaki et al. suggested that this uncontrolled growth is due to the aberrant activation of AKT and ERK pathways [62]. Unlike the other subtypes of endometriosis, DIE lesions are situated in proximity to several nerve plexus and are frequently hyperinnervated [63, 64]. Anaf and coworkers observed that deep endometriotic lesions infiltrate the large bowel wall preferentially along the nerves, even at a distance from the palpated nodule, while the mucosa is rarely and only focally involved. The most richly innervated layers of the large bowel are the most intensely involved by endometriosis, supporting a close histological relationship between endometriotic lesions of large bowel and the nerves of the large bowel wall [65]. The sensory nerves-derived neuropeptides Substance P (SP) and Calcitonin gene-

related peptide (CGRP) have been suggested to be involved in the development of endometriosis-associated fibrosis. This also provides an answer as why DIE lesions have abundant smooth muscle-like cells and more fibrosis than other lesions [56, 59, 66]. Anyway, regardless of the different hypotheses provided to explain the origin of myofibroblasts and fibrosis in endometriotic lesions, all investigators agree on the importance of this component in DIE lesions particularly and the fibromuscular component of endometriotic deep lesion seems to represent a self-amplifying event of endometriosis.

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2 Epidemiology of Bowel Endometriosis

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2.1 Introduction

Endometriosis is a disease characterized by the presence of functional endometrial-like tissue outside the uterine cavity [1]. Endometriotic lesions may have various locations: they can be found more frequently on the ovaries, the uterosacral and the large ligaments, the fallopian tubes, the pelvic peritoneum, the pouch of Douglas, the vesicouterine fold, and the bowel. Extraperitoneal locations include the uterine cervix [2–5], the bladder and the ureters [6, 7], the umbilicus [8–10], the abdominal scars after gynecological surgery [11, 12] and cesarian section [13]. Endometriosis rarely affects extra-abdominal organs such as kidneys [14–17], skin [18], central nervous system [19–21], and thoracic cavity including lung [22–24], pleura [25, 26], diaphragm [17, 25–27], and pericardium [25, 26]. The term "bowel endometriosis" is employed for indicating endometrial-like glands and stroma that infiltrate the bowel wall. Bowel endometriosis was originally described by Sampson [28] in 1922. The diagnosis of bowel endometriosis is made when infiltration needs to reach at least the muscularis propria of the bowel wall; superficial endometriotic lesion infiltrating only the intestinal serosa should be considered "peritoneal endometriosis" [29]. Intestinal endometriosis typically involves the serosa and the intestinal muscularis propria, less frequently it infiltrates the submucosa and the mucosa (Figs. 2.1 and 2.2) [30].

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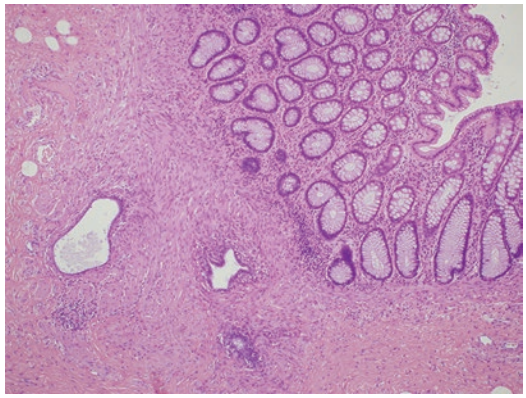

Fig. 2.1 Endometriotic nodule infiltrating the intestinal submucosa

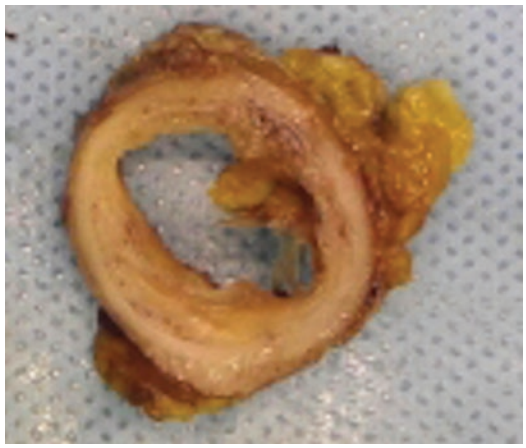

Fig. 2.2 Section of a rectal nodule excised by laparoscopic segmental resection. The nodule infiltrates the muscularis propria of the rectum

2.2 Epidemiology of Endometriosis

Several methodological issues complicate the assessment of the epidemiology of endometriosis: firstly, the need for surgery in order to establish the diagnosis affects the study of prevalence and incidence [31]; additionally, surgical confirmation may also lead to selection bias since the patients with symptomatic disease, high utilization of the medical system and comorbidities are more likely to undergo laparoscopy than the general population. Control selection is another issue: it is important to prevent the inclusion of undiagnosed cases in the control group in order to decrease the risk of misclassification and to apply to the control group every restriction applied to cases [32]. It is also very difficult to evaluate the incidence of a chronic disease like endometriosis since the delay from symptoms to diagnosis makes impossible to assess the exact onset of the disease [33].

Published studies investigated the epidemiology of endometriosis in different populations. The prevalence of endometriosis was found to be between 2% and 19% among women undergoing tubal ligation [34–41]; between 11% and 47% among those undergoing surgery because of infertility [34, 35, 39, 42–48]; between 14% and 45% among patients undergoing surgery because of pelvic pain [36, 39, 47, 49, 50]; between 50% and 70% among adolescents with severe dysmenorrhea [51], and approximately 4% among patients having routine consultation with the general practitioner [52]. Based on the prevalence of pelvic pain in the general population and the data on endometriosis diagnostic rates, it can be estimated that prevalence endometriosis of any stage in the general population is between 5% and 10% [33]. The prevalence of deep infiltrating endometriosis is estimated to be the 1% of women of reproductive age. In line with this, a recent retrospective population-based study investigated the epidemiology of endometriosis in the databases of the Maccabi Healthcare Services, a two-million-member healthcare provider representing a quarter of the Israeli population [53]. The crude point prevalence of endometriosis was 10.8 per 1000 (95% CI, 10.5–11.0); women aged 40–44 years had the highest prevalence rate (18.6 per 1000; 95% CI, 17.7–19.5); the average annual incidence rate of newly diagnosed endometriosis was 7.2 (95% CI 6.5–8.0) per 10,000 women aged 15–55 years.

A prospective observational study including 1101 patients with laparoscopic diagnosis of endometriosis investigated the distribution of endometriotic lesions [54]. The mean age of patients was 33 years. The ovary was the most frequent site of endometriotic lesions (66.94%) followed by the uterosacral ligaments (45.51%), the ovarian fossa (32.15%), the pouch of Douglas

(29.52%), and the bladder (21.25%). Deep infiltrating endometriosis was diagnosed in 14.4% of the patients and rectosigmoid endometriosis was present in 8.5% of the patients.

2.3 Epidemiology of Bowel Endometriosis

Bowel endometriosis is a rare condition and, therefore, it is impossible to estimate its exact prevalence in the general population due to the lack of major well-designed epidemiological studies. A retrospective review of 3037 patients that underwent laparotomy for endometriosis found histologically confirmed bowel lesions in 163 patients (5.4%) [55]. Another study including 1785 women surgically treated for endometriosis reported histologically confirmed bowel endometriosis in 25.4% of the patients [56].

Bowel endometriosis is estimated to be found in 8–12% women with endometriosis [57] and in 5–37% of patients with diagnosis of deep infiltrating endometriosis [29]. A retrospective study including 688 patients who underwent laparoscopy because of deep infiltrating endometriosis found that 168 women (24.4%) had bowel endometriotic lesions [58]. There are no available data in order to have a meaningful estimation of bowel endometriosis incidence also due to major changes in diagnosis and health-seeking behavior between generations. Moreover, data obtained from surgical groups are affected by referral bias [59] and lack the cohort dimension required for meaningful statistics [60].

2.3.1 Rectosigmoid Endometriosis

Bowel endometriosis develops more frequently on the left side of the abdominal cavity, even though this evidence could be biased by considering rectum involvement part of the left abdominal side whereas it could derive from endometriotic cells from the pouch of Douglas and so should be considered a midline lesion [55, 61, 62]. Due to its proximity to the fallopian tubes, the rectosigmoid is the bowel segment most commonly affected by endometriosis [62]. In fact, the sigmoid and the left tube create a pouch which facilitates implantation of endometriotic cells [61]. Rectum and rectosigmoid junction are the most common localizations, affecting up to three-quarters of the patients (10.6–75%), followed by the sigmoid colon (14.3–65%) [63]. A retrospective study including 168 women with 252 bowel endometriotic lesions found that 11.5% of the intestinal nodules were located in the lower rectum, 23.0% in the middle rectum, 18.3% in the upper rectum, and 24.2% in the sigmoid colon [58].

2.3.2 Endometriosis of the Appendix

Appendicular endometriosis (Fig. 2.3) may be asymptomatic or present as acute or chronic appendicitis, lower gastrointestinal bleeding, intestinal perforation, or intestinal obstruction as a result of intussusception of the appendix in the inferior pole of the cecum [64]. The diagnosis of appendiceal endometriosis tends to histologically do after surgical approach. Appendectomy can be performed in case of gross alterations of the appendix at intraoperative evaluation or preoperative imaging (selective appendectomy) or at the time of procedures unrelated to suspected appendiceal pathology (incidental appendectomy) [65, 66]. In the published series, the prevalence of

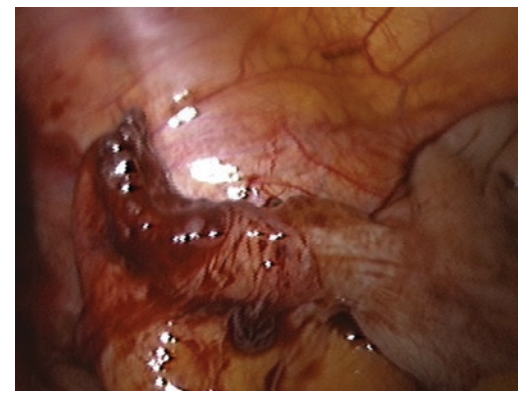

Fig. 2.3 Endometriosis of the appendix. The appendix was adherent to a right endometriotic cyst