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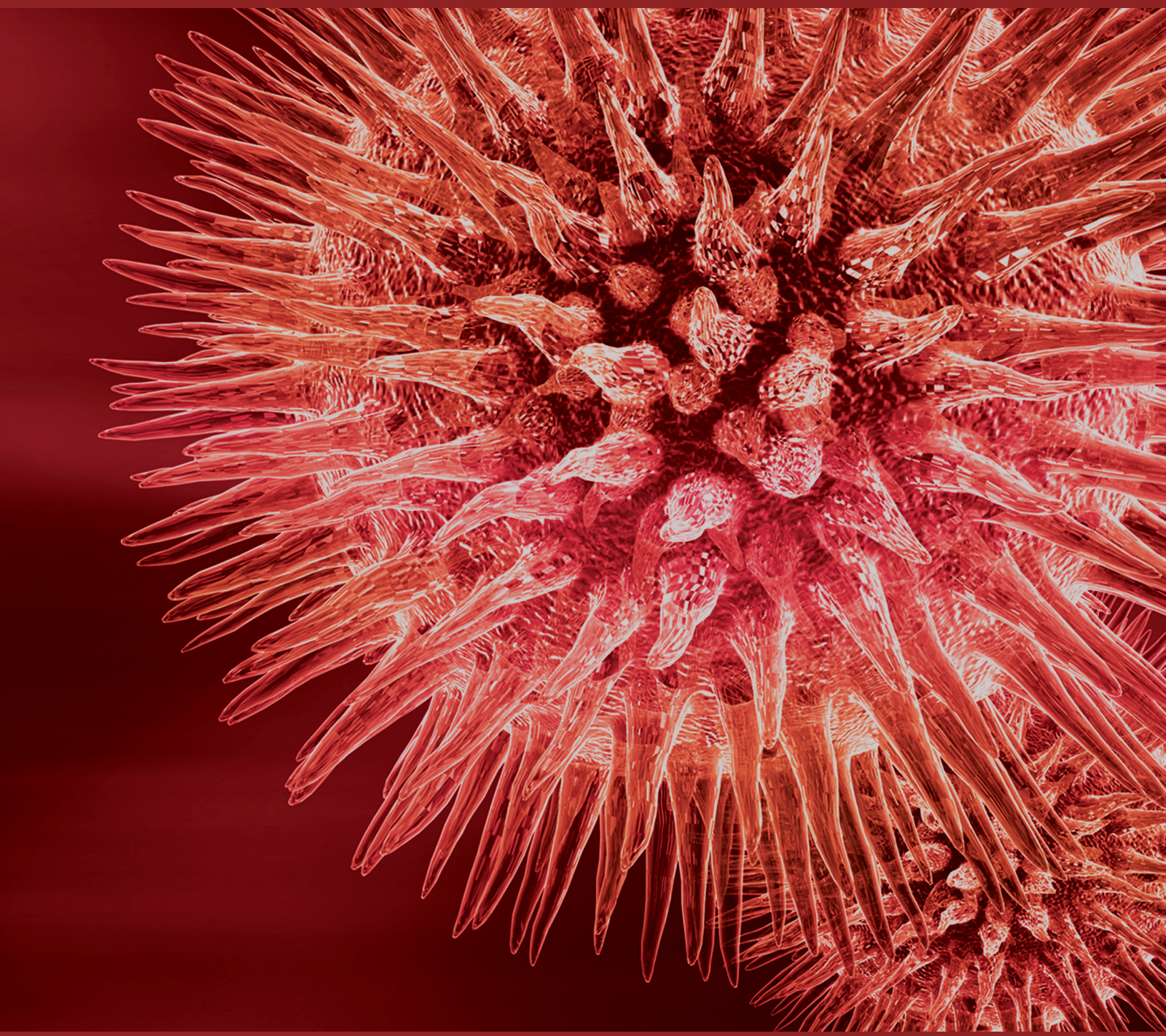
The Impact of Endometriosis on the Health of Women 2016

Guest Editors: Liselotte Mettler, Dietmar Schmidt, and Peter Maher



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Editorial

The Impact of Endometriosis on the Health of Women 2016

Liselotte Mettler,[1] Dietmar Schmidt,[2] and Peter Maher[3]

[1]*Department of Obstetrics and Gynecology, University Clinics of Schleswig-Holstein, Arnold Heller Strasse 3/24, 24105 Kiel, Germany*
[2]*Institute of Pathology, Gereonstr. 14a, 41747 Viersen, Germany*
[3]*Department of Endosurgery, Mercy Hospital for Women, Heidelberg, VIC 3084, Australia*

Correspondence should be addressed to Liselotte Mettler; profmettler@gmx.de

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Originally described already more than 300 years ago endometriosis is an estrogen-dependent, chronic, inflammatory disease prevalent worldwide in 10–30% of women of reproductive age and beyond. Characterized by the growth of endometrium-like tissue in aberrant locations outside of the uterus, it is responsible for symptoms including chronic pelvic pain, inflammation, dysmenorrhea, dyspareunia, and subfertility that degrade quality of life of women significantly. In Germany the direct and indirect economic cost of endometriosis amount annually to 1.5 billion dollars, which today equalizes euros and this is elevated to 20 billion dollars/euros in the United States [1].

The awareness of endometriosis and adenomyosis in patients and doctors has changed and is continuously updated. The aim of this special issue in 2016 is to focus on several features in endometriosis, their research in particular molecular aspects as well as their clinical applications for surgical excisional treatment and for deliveries, and certain aspects of infertility. We have selected six papers, of which 2/3 deal with basic research aspects, and the other third highlights the clinical management and treatment of this enigmatic but not malignant disease.

In the first review article I. Jeung et al. deal with the decreased cytotoxicity of peripheral and peritoneal Natural Killer cells (NK cells) in endometriosis patients and, in a clinical review on the laparoscopic treatment of deep infiltrating endometriosis (DIE), which still remains a difficult confrontation for every surgeon, O. Triolo et al. compare the full thickness excision to pure shaving of such a lesion. While it is today accepted to surgically treat deep infiltrating endometriosis to the bowel and bladder by laparoscopy, the controversy whether to use full thickness excision or shaving remains and depends on the situation, the surgeon's decision, and the patent's wish.

Two research articles address the epidemiology of endometriosis in France by J. Cottenet et al. and certain demographic clinical features of endometrial polyps treated by hysteroscopy by Y. Zhang et al.

Concerning clinical and research aspects the other 2 papers focus on delivery after surgery of deeply infiltrating endometriosis by S. H. Enzelsberger et al. of Peter Oppelt's group of Linz, Austria, and on the negative finding of serum levels of the soluble factors sCD40L and CXCL1 for the diagnosis of endometriosis by the Viennese group of K. Walch et al. of Austria.

To conclude, we know that an early recognition of endometriosis in young girls can save years of suffering. Considering the current special issue we think the selected articles offer an ideal opportunity to update our knowledge on some new achievements to diagnose and treat this disease and its following steps as possible infertility and problems even at deliveries.

Liselotte Mettler
Dietmar Schmidt
Peter Maher

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Review Article

Full-Thickness Excision versus Shaving by Laparoscopy for Intestinal Deep Infiltrating Endometriosis: Rationale and Potential Treatment Options

Antonio Simone Laganà,[1] Salvatore Giovanni Vitale,[1] Maria Antonietta Trovato,[2] Vittorio Italo Palmara,[1] Agnese Maria Chiara Rapisarda,[2] Roberta Granese,[1] Emanuele Sturlese,[1] Rosanna De Dominici,[1] Stefano Alecci,[1] Francesco Padula,[3] Benito Chiofalo,[1] Roberta Grasso,[1] Pietro Cignini,[3] Paolo D'Amico,[1] and Onofrio Triolo[1]

[1]*Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, 98125 Messina, Italy*
[2]*Department of General Surgery and Medical Surgical Specialties, University of Catania, 95125 Catania, Italy*
[3]*Department of Gynecologic Ultrasound Imaging, Altamedica Fetal Maternal Medical Centre, 00198 Rome, Italy*

Correspondence should be addressed to Antonio Simone Laganà; antlagana@unime.it

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Endometriosis is defined as the presence of endometrial mucosa (glands and stroma) abnormally implanted in locations other than the uterine cavity. Deep infiltrating endometriosis (DIE) is considered the most aggressive presentation of the disease, penetrating more than 5 mm in affected tissues, and it is reported in approximately 20% of all women with endometriosis. DIE can cause a complete distortion of the pelvic anatomy and it mainly involves uterosacral ligaments, bladder, rectovaginal septum, rectum, and rectosigmoid colon. This review describes the state of the art in laparoscopic approach for DIE with a special interest in intestinal involvement, according to recent literature findings. Our attention has been focused particularly on full-thickness excision versus shaving technique in deep endometriosis intestinal involvement. Particularly, the aim of this paper is clarifying from the clinical and methodological points of view the best surgical treatment of deep intestinal endometriosis, since there is no standard of care in the literature and in different surgical settings. Indeed, this review tries to suggest when it is advisable to manage the full-thickness excision or the shaving technique, also analyzing perioperative management, main complications, and surgical outcomes.

1. Introduction

Endometriosis is a common benign and proliferative chronic disorder, characterized by the presence of endometrial glands and stroma outside the uterus. Ectopic endometrial tissue shows the same cyclic changes of the eutopic endometrium, according to the various phases of the menstrual cycle. The incidence in the female population is about 6–10%, with an average age at diagnosis ranging from 25 to 30 years [1, 2]. Endometriosis most frequently occurs in the pelvis. Therefore, its most distinctive presenting clinical features are menstrual irregularities, chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. The natural history of the disease has never been well defined because a consistent part of affected women are asymptomatic. Endometriosis is often diagnosed during laparoscopic investigation due to infertility [3, 4]. Three main clinical presentations have been described: peritoneal endometriosis, endometriotic ovarian cysts (i.e., endometriomas), and deeply infiltrating endometriosis (DIE) [5]. The latter is considered the most aggressive presentation of endometriosis, penetrating more than 5 mm in affected tissues [6] and affecting approximately 20% of all women with the disease [7, 8]. Endometriosis affects the bowel in 3%–37% of all cases, and histopathological diagnosis is usually straightforward [9]. More than 80% of digestive localizations concern the rectum and the distal sigmoid colon, and those lesions appear as fibrotic nodules also infiltrating the vagina, the uterine isthmus, the uterosacral

ligaments, or the adnexa. Intestinal DIE is often associated with ovaries and ureters coinvolvement, showing the most aggressive presentation [10]. DIE can cause a complete distortion of the pelvic anatomy, and it mainly involves uterosacral ligaments, bladder, rectovaginal septum, rectum, and rectosigmoid colon [11–13]. These infiltrating lesions respond as other implants to various hormonal therapies, but it is not a definitive management for symptomatic patients, for which a surgical treatment may be required [14]. Multiple minimally invasive surgical approaches and techniques are available for treatment of intestinal endometriosis and often require the expertise of both gynecologist and general or colorectal surgeons. The purpose of endometriosis surgery is to obtain good long-term outcomes regarding pain relief, recurrence rates, and fertility and to not compromise the function of involved organs. The laparoscopic shave excision consists in dissection, maintained as superficial as possible, to avoid compromising bowel integrity. Depending on the depth of lesion, to diminish the risk of postoperative bowel perforation, laparoscopically placed sutures are required if a portion of the intestinal muscularis propria is dissected. Intraoperative visual inspection with proctoscopy and an air leak test can ensure that no inadvertent proctotomy exists [15]. For DIE nodules of the rectum, the rectal shaving can be performed using traditional shaving technique, releasing first the nodule from the rectal wall, or with reverse technique, starting the resection from the posterior vaginal fornix [16]. Mucosal skinning consists of removing the DIE nodule from the bowel deep in the layers of the intestinal wall, keeping just the mucosa intact. The defect in the rectal wall is sutured at the end of the procedure [17]. Full thickness or disc excision is performed using electrocautery or carbon dioxide (CO_2) laser to perform the complete excision of nodules, after adequate laparoscopic mobilization of the intestine. The bowel is then repaired by laparoscopic suturing in the transverse axial plane to avoid potential stricture of the bowel lumen; alternatively an endolinear stapling device can be used [18]. In the anterior rectal wall, endometriosis nodules that are less than 3 centimetres in diameter and occupy less than one-third of the circumference can be treated with an alternative "closed" approach using a circular stapler, introduced transanally, that removes a full-thickness patch of the anterior rectal wall. The main advantage of this technique is a reduction of postoperative infectious complications [19, 20]. Laparoscopic resection of any gastrointestinal tract segment can be performed using more than one potentially successful strategy.

This review describes the state of the art in laparoscopic approach for intestinal DIE with a special interest in intestinal involvement, according to recent literature findings. Our attention has been focused particularly on full-thickness excision versus shaving technique in DIE with intestinal involvement. Particularly, the aim of this paper is clarifying from the clinical and methodological points of view the best surgical treatment of deep intestinal endometriosis, since no standard of care exists in the literature and in different surgical settings. Indeed, this review tries to suggest when it is advisable to manage the full-thickness excision or the shaving technique, analyzing also the perioperative management, the main complications, and the surgical outcomes.

2. Materials and Methods

This paper is a narrative overview synthesizing the findings of literature retrieved from searches of computerized databases. The database PubMed (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA) was used. Key research words were "endometriosis," "deep endometriosis lesions," "intestinal deep endometriosis involvement," "rectovaginal endometriosis," "laparoscopy in endometriosis," and "surgical technique of endometriosis." We focus our discussion on two different surgical laparoscopic techniques: full-thickness excision versus shaving. We looked for all original articles published in English through the end of 2014 and decided to extract every notable item of information concerning definition, symptoms, clinical features, differential diagnosis, preoperative evaluation (e.g., ultrasonography, MRI, rectal sigmoidoscopy, or colonoscopy), type of medical and surgical approach, type of complications, and postoperative approach in intestinal DIE.

3. Results and Discussion

3.1. Histology. Bowel endometriosis typically involves the serosa and muscularis propria, rarely involving the submucosa or mucosa, and usually is situated in the antimesenteric edge of the bowel [10, 21] and differs from peritoneal and ovarian implants, since they consist of smooth muscle with active glandular epithelium and scanty stroma. Mural thickening and intestinal stenosis are produced by fibrosis when larger endometriotic nodules invade the muscularis [22, 23]. There are two important basic characteristics of bowel endometriosis: multifocality and multicentricity. The former is defined as the presence of other lesions within a 2 cm area from the main lesion, and the latter is defined as the presence of other lesions beyond 2 cm from the main lesion. They seem to occur in 62% and 38% of surgical specimens, respectively [24, 25].

3.2. Clinical Presentation. The complexity of endometriosis results from its multiple clinical presentations, the multifocal pattern of distribution of the lesions, and the difficulty in the preoperative diagnosis [17]. The natural history of the disease has never been well defined due to its asymptomatic nature in a quite large number of the cases. In the mid-1990s, only 50% of deep endometriotic nodules >3 cm in diameter were diagnosed by physical examination [26]. With experience and awareness on the part of practitioners, the clinical diagnosis has improved. Nevertheless the use of only a physical examination continues to misdiagnose the vast majority of DIE. In women with moderate-to-severe presentation of the disease, some degree of intestinal symptoms may be present. Endometriosis-related intestinal symptoms may vary depending on the site of endometriotic implants and menstrual cycle [27]. It should be suspected in all women with invalidating hypogastric pain, especially dysmenorrhea, deep

dyspareunia, severe chronic pain, mictalgia, and dyschezia. Most pathognomonic signs are severe dyschezia, menstrual blood on stools, menstrual diarrhea, severe menstrual mictalgia, and radiation of pain to the perineum [11]. Symptoms can be nonspecific with considerable overlap with other clinical conditions, delaying diagnosis and treatment. Moreover, physical examination (especially vaginal examination) may be completely normal, which hampers the diagnosis in young females. Chronic pelvic pain, often more severe during menstruation or ovulation, is the most common symptom associated with endometriosis. Rectal involvement may result in alterations in bowel habits such as constipation, diarrhea, dyschezia, tenesmus, and, rarely, rectal bleeding [28–30]. Intestinal perforation due to endometriosis may occur in the colon [31] and also in an appendix with transmural endometriosis. Typical endometriosis symptoms, however, also occur in patients with other conditions such as irritable bowel syndrome (IBS) and pelvic inflammatory disease (PID). These overlapping symptoms create potential diagnostic difficulties because there are no simple noninvasive diagnostic tests that can be carried out. Differential diagnosis includes irritable bowel syndrome, solitary rectal ulcer syndrome, and rectal tumor [28]. Colonic endometriosis must be differentiated from Crohn's disease, diverticular disease, adhesions, or neoplasm. Also, for small bowel implants secondary to endometriosis, difficulty exists in differentiating this condition from Crohn's disease because a similar endoscopic and histologic image can be seen. Fauconnier and Chapron [32] have described a relationship between specific types of pelvic pain symptoms, characteristics of the lesions, and semiology of the painful symptoms. Painful symptoms connected with DIE may present particular characteristics which distinguish them from painful symptoms of other origins. The painful semiology was found to be specific for anatomical location and for the organ affected: dyspareunia was associated with involvement of the uterosacral ligaments, painful defecation during menses with involvement of the posterior area, noncyclic pelvic pain and functional bowel signs with bowel involvement, and functional urinary tract signs with involvement of the bladder. Painful defecation during menses and severe dyspareunia were specifically connected to DIE infiltration of the pelvic nerves. In most cases the pain is provoked or aggravated by mobilization of the organs affected by the DIE lesions. The relationship between the severity of dysmenorrhea in women with posterior DIE and the indicators of the extent of the disease was evaluated by Chapron et al. [33]. The presence of a rectal or vaginal infiltration and extensiveness of adnexal adhesion has been shown to correlate with the severity of dysmenorrhea. The combination of endometrioma and pain is significantly related to the simultaneous presence of DIE [34]. Furthermore, another study by Chapron et al. [35] found that the mean number of DIE lesions was significantly higher and more severe in patients presenting an associated ovarian endometrioma. Thus, in a clinical context suggestive of DIE, when there is an ovarian endometrioma, the practitioner should investigate the extent of the disease to check for severe and multifocal DIE lesions. The history of patients at the time of adolescence has revealed that some events or symptoms in early menstruation are statistically more frequently associated with a later surgical diagnosis of DIE. Patients with DIE have significantly more positive family history of endometriosis and more absenteeism from school during menstruation. The oral contraceptive pill use and duration of treatment are more frequent and longer in patients with DIE. There is a higher incidence of pill use for severe primary dysmenorrhea before 18 years of age in patients with DIE [36]. Patients with a history of surgery for endometriosis show an increased prevalence of deeply infiltrating endometriosis. Furthermore, surgical history for endometriosis correlates significantly with number and severity of deeply infiltrating endometriosis lesions especially in the case of intestinal lesions [37]. Although solid data linking symptoms to size and localization of deep endometriosis are lacking, clinical symptoms remain crucial to suspect DIE, to use other diagnostic tools, and to decide on medical and/or surgical therapy [11]. Lafay Pillet et al. [38] developed a clinical model using the reproductive history and clinical symptoms of women with endometriomas to predict DIE based on clinical symptoms. Four variables were found to be independently associated with DIE: visual analogue scale of gastrointestinal symptoms ≥5 or of deep dyspareunia >5, duration of pain greater than 24 months, and severe dysmenorrhoea. A score <13 defined a low-risk group while a score ≥35 defined a high-risk group. In cases suggestive of DIE lesions, additional radiologic studies may help the skilled surgical team to identify and localize the deep lesions.

3.3. Diagnosis and Preoperative Work-Up of Intestinal Deep Infiltrating Endometriosis. Many exams can be used for the evaluation of bowel endometriosis; physical examination is helpful to detect the 50% of rectovaginal nodules >3 cm in diameter [26]. The aim of clinical and instrumental investigation is to (1) document the extent of the disease (2), plan a multidisciplinary treatment, and (3) counsel patients regarding the type of intervention and the possibility of intra- and postoperative complications.

Transvaginal ultrasonography is a routinary and noninvasive gynecologic exam that, according to a recent meta-analysis, can detect bowel endometriosis with pooled estimates of sensitivity and specificity of 91% and 98%, respectively [39]. By ultrasound evaluation, nodules appear as heterogeneous, hypoechoic, and more rarely speculated masses [40].

Barium enema examination and magnetic resonance imaging (MRI) are, with transvaginal ultrasonography, the gold standard for the noninvasive evaluation of bowel endometriosis, with or without involvement of the rectovaginal septum.

Barium enema is useful for assessing the extent of the disease; the radiological image of deep invasion of the bowel wall consists in an extrinsic mass compressing the lumen in association with the fine crenulation of the mucosa. Also bowel strictures, especially at the rectosigmoid junction, are characteristic of this disease. The limit of this diagnostic procedure is the impossibility of the exact evaluation of the distance to the anal sphincter [41]. MRI is useful for the diagnosis of multifocal endometriotic nodules and

to define anatomical relationships, with a sensitivity and a specificity around 90%. MRI shows contrast enhanced mass or hyperintense foci on T1-weighted or fat-suppression T1-weighted images that are specific for hemorrhagic foci or hyperintense cavities secondary to endometriosis. On T2-weighted images nodules can be seen as hypointense masses with the signal of the tissue close to that of pelvic muscles [42, 43]. Rectosigmoidoscopy or colonoscopy are rarely used in clinical practice because endometriosis is an extrinsic and typically nontransmural disease [39, 41].

3.4. Medical and Surgical Treatment of Intestinal Deep Infiltrating Endometriosis. Treatment of intestinal DIE is difficult and challenging. Medical management of DIE with colorectal extension (with nonsteroidal anti-inflammatory drugs, oral contraceptives, gestagens, antigestagens, or GnRH agonists) is based on suppression of the symptoms, is not curative, and is often associated with significant side effects [14]. Nevertheless it is not clear if the medical management approach prevents disease progression, especially in more severe cases of endometriosis with colorectal extension. In addition, discontinuation of this therapy commonly results in recurrence [44]. Therefore, it is widely agreed that surgical management is the primary treatment for more severe forms of endometriosis, such as symptomatic DIE with colorectal extension [45, 46]. There is no consistent evidence in the literature to determine whether medical preoperative treatment is associated with a significant benefit; nevertheless costs and side effects of these therapies should be considered [47]. Some authors suggest that preoperative danazol treatment could be useful to increase the pregnancy rate [48].

To diagnose and uniformly classify bowel endometriosis, exploratory laparoscopy is necessary. The above-mentioned imaging techniques are noninvasive and helpful to confirm the clinical suspicion and to assess the extent of the disease. Usually a gynecologist expert in endoscopic surgery perform the exploratory laparoscopy; in our opinion the cooperation with a colorectal surgeon is recommended. The surgeon has to look for the presence of suspicious lesions in the uterus, uterosacral ligaments, pelvic peritoneum, ovaries and ureters, sigmoid colon, and the upper rectum. An extraperitoneal surgical approach is sometimes necessary to explore the pouch of Douglas because it is often obliterated by perilesional adhesions [9, 49]. The aim of the surgery is to obtain pain relief, prevent recurrence rates, and improve fertility; it is also important to prevent the formation of postoperative adhesions. To achieve these results a total removal of endometrial implants without compromising ovarian function is mandatory.

The therapeutic strategy should not be influenced by the association of different types of endometriotic lesions, such as endometriomas, peritoneal endometriosis, or DIE; the complete excision of all implants, saving normal tissue, is of paramount importance [50, 51].

Nevertheless, more than 70% of women with DIE still underwent segmental bowel resection [52].

Several surgical procedures for endometriosis with bowel involvement have been described using a laparoscopic, a laparotomic, a transvaginal, or a combined approach.

Laparoscopy is preferred to open surgery since it is usually associated with a better and shorter postoperative recovery and a better cosmetic result [53]; both procedures are equally safe and effective in the treatment of endometriosis. As it is usually hoped for an oncologic disease, also for the treatment of deep endometriosis, it is recommended to refer the patient to an expert center that offers a minimally invasive treatment in a multidisciplinary context [54].

Laparoscopic surgical procedures for rectosigmoid DIE lesions can have a conservative or a radical purpose. Nodulectomy is used for a conservative approach and can be performed using several techniques: traditional or reversal rectal shaving (defined as superficial peeling of bowel serosal and subserosal endometriosis with diathermy loop or laser), mucosal skinning, full-thickness anterior rectal wall excision (defined as selective excision of the bowel endometriotic lesion without opening of the bowel wall), and full-thickness disc excision (defined as selective excision of the bowel endometriotic lesion, followed by closure of the bowel wall). The aim of these approaches is strictly intended to remove localized endometriosis nodules. Radical surgery consists in segmental bowel resection of the affect tract, followed by primary colorectal anastomosis with or without protective ileostomy (depending on the distance between DIE localization and anal sphincter).

The preoperative imaging examinations of intestinal DIE lesions should contain information of fundamental importance for the planning of procedure, such as size of the lesion, depth of infiltration, distance from anal verge, and multicentricity and multifocality of the lesions. The size of the nodule and the percentage of bowel circumference involved by the DIE lesion can be similarly evaluated by MRI and TVUS. In general, only patients with intestinal DIE lesions measuring up to 25–30 mm may be candidates for conservative surgery, either shaving rectal/mucosal skinning or disk resection [17]. The depth of infiltration of endometriotic lesions into the bowel wall is another important variable to consider in the surgical treatment of choice. In this context, a distinction can be drawn between the presence of endometriotic lesions on the bowel serosa and endometriotic lesions infiltrating the muscularis. Lesions of the serosa without infiltration do not justify any specific bowel procedure from a surgical point of view. This superficial form of serosal bowel endometriosis may be treated by surgical shaving or eventually by full-thickness discoid excision if shaving resulted in significant bowel trauma [52].

In general, classical shaving should be indicated for superficially DIE lesions affecting the intestinal wall no deeper than the muscular layer, preserving the mucosa layer. Full-thickness anterior rectal wall excision or discoidal resection are appropriate options when there is evidence of singular endometriotic nodule, smaller than 30 mm, infiltrating intestinal wall deeper than the muscular layer and affecting less than 1/3 of the intestinal circumference. Segmental bowel resection is appropriate when DIE lesion is bigger than 30 mm [52].

The distance of the DIE lesion from the anal verge is important for surgical planning. This distance can be determined by TVUS or pelvic/abdominal MRI with greater

accuracy. An independent risk factor for the occurrence of anastomotic leaks after intestinal segmental resection is the colorectal anastomosis being less than 10 cm away from the anal verge; therefore, it is advisable to consider a temporary protective ileostomy in these cases [17]. Finally an important characteristic that should be taken into account before deciding on the surgical strategy for DIE is multifocality and multicentric involvement. In almost 70% of the cases, intestinal endometriosis lesions are associated with DIE in other locations, justifying specific associated surgical procedures for the uterosacral ligaments, vagina, bladder, and/or ureter. In the presence of multifocal or multicentric lesions, the option of surgery is usually restricted to intestinal resection in order to obtain the complete treatment of the disease [52]. Owing to the paucity of comparative studies [29, 55], it should be emphasized that the present available data are provided by retrospective series reported by surgeons who generally perform only one technique. Consequently, it is unclear from the literature when to use which procedure, and there are no available objective criteria to indicate the use of one procedure rather than the other, so surgical management is often based on little evidence and tends to reflect the personal convictions and experience of surgeons [29, 55, 56].

To summarize, when the intestinal tract is involved, a multidisciplinary approach has been proposed as mandatory [57, 58], since best results in terms of improvement of symptoms and quality of life can be guaranteed by a complete surgical excision of all endometriotic implants [29, 52–59]. Deep infiltrating endometriosis is a global pathology that may involve different structures. A multidisciplinary approach should be recommended to achieve appropriate disease management. Collaboration between gynaecologists, urologists, and colorectal surgeons enabled a successful management of the case in one surgical intervention providing minor risk of complications, shorter hospital stay, and faster functional recovery [60, 61].

3.5. Postoperative Care of Intestinal DIE. Antibiotics should be administered as one shot when the intestinal wall has not been opened, whereas full-thickness resection requires 7 days of antibiotic treatment. Following a muscularis defect and single-layer suture, or full-thickness resection and double-layer suture, the patient remains nil by mouth for 4 and 7 days, respectively. Postoperative care after surgery requires strict follow-up with early repeat laparoscopy to immediately treat any complications, including bleeding, infection, late ureteral or bowel perforation, or fistulae. When a complication occurs more than two weeks after surgery, the risks and advantages of immediate intervention should be discussed considering the patient's clinical condition [11, 62].

3.6. Complications and Recurrence of the Disease after DIE Surgery. Conservative procedure demonstrates low rate in morbidity and urinary/intestinal postoperative complications compared to a radical approach. Nevertheless, on the one hand, sometimes complete resectability is not totally achieved by conservative approach due to the presence of microscopic residual endometriosis close to margin of resection, which increases the recurrence risk [63]. On the other hand, colorectal resections have good results in long-term pain relief and fertility. The more common complication of the radical treatment of intestinal DIE is anastomotic leakage followed by rectovaginal fistula. Anastomotic leakage occurs more frequently when anastomosis is performed close to the anal sphincter. Protective ileostomy can help to reduce this complication [64, 65]. Postoperative rectovaginal fistula occurs more frequently when both rectum and vagina are opened during the procedure. In this case, a two-stage approach with vaginal surgery followed by colorectal resection can reduce the risk of fistula [62]. Recurrence is a possible complication after laparoscopic segmental bowel resection and occurs in about 20% of cases [66]. Some authors describe a higher recurrence rate for conservative management compared to a radical approach (17.6% and 5.8%, resp.), while other authors did not show any significant difference [67, 68]. Several factors may play role in recurrence rate: accumulating evidence suggests that positive bowel resection margins, obesity, and age are significantly associated with endometriosis recurrence. Wide margin of excision, independently from the type of surgical approach, seems to be the greatest factor capable of decreasing the recurrence rate [22]. Lesion's characteristics should guide surgeons regarding the surgical choice technique: discoid bowel resection should be preferred when maximum diameter does not exceed 3 cm with a maximum bowel circumference involvement of 50% [55]. Histological features can also provide information concerning possible rate recurrence: multicentric bowel involvement, characterized by deep nodules with surrounding fibrosis, reduces the probability of radical excision and consequently increases the recurrence rate [24, 25]. As it widely accepted, the extension and localization of the disease can play a pivotal role in the arising and exacerbating of chronic pelvic pain [4, 69] and related decrease in quality of life [70]. In addition, accumulating evidence suggests that the interaction between immune system and endometriotic cells may cause a breakdown of the peritoneal immune surveillance [71, 72], resulting in a diminished apoptosis of endometriotic cells [73, 74] and disturbance of epigenetic expression of several genes of paramount importance for the progression of the disease [75, 76].

4. Conclusions

The debate on what is the standard of care in surgical treatment of intestinal deep infiltrating endometriosis is not completely clarified. According to our data analysis, universally accepted points are a standardized preoperative assessment for bowel endometriosis' diagnosis, an adequate patient counseling, and a multidisciplinary minimally invasive surgical approach in an expert center. A patient-tailored approach is required and the less invasive radical option should be chosen.

Laparoscopy is preferable to laparotomy, as it decreases postoperative discomfort, operative morbidity, length and costs of hospitalization, improve cosmetic healing, and facilitate return to normal function. A colorectal surgeon expert on intestinal endometriosis should make a correct decision

regarding whether to perform a full-thickness excision, a shaving, or a bowel resection.

Taking advantage of the ongoing evolution of minimally invasive approaches, future investigations should be focused on ensuring the radical excision of endometriotic lesions saving the function of all the organs involved by the disease, using minimal surgical access possible. Future efforts should improve long-term outcomes with regard to symptoms, quality of life, cosmetic outcome, recurrence rate and fertility.

Disclosure

The authors alone are responsible for the content and writing of the paper.

Competing Interests

All authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

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Research Article

Delivery after Operation for Deeply Infiltrating Endometriosis

Christina Allerstorfer,[1] Peter Oppelt,[1] Simon H. Enzelsberger,[1] Andreas Shamiyeh,[2] Wolfgang Schimetta,[3] Omar Josef Shebl,[1] and Richard Bernhard Mayer[1]

[1]*Department of Obstetrics and Gynecology, Kepler University Clinic, Campus IV, Krankenhausstrasse 26-30, 4020 Linz, Austria*
[2]*Second Surgical Department, Ludwig Boltzmann Institute for Surgical Laparoscopy, Kepler University Clinic, Campus III, Krankenhausstrasse 9, 4020 Linz, Austria*
[3]*Department of Applied Systems Research and Statistics, Johannes Kepler University, 4040 Linz, Austria*

Correspondence should be addressed to Peter Oppelt; peter.oppelt@gespag.at

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Background. It has been suggested that, during pregnancy, endometriosis can cause a variety of disease-related complications. *Objectives.* The purpose of the study was to find out if women with histologically confirmed endometriosis do have a higher risk of adverse pregnancy outcome and if they suffer from a higher rate of complications during labor. *Study Design.* 51 women who underwent surgery because of deeply infiltrating endometriosis in the General Hospital Linz and the Women's General Hospital Linz and who gave birth in the Women's General Hospital Linz after the surgery were included in our survey. *Results.* 31 women (60.8%) had a spontaneous delivery and in 20 women (39.2%) a caesarean section was performed. There were no cases of third- and fourth-degree perineal lacerations. Collectively there were 4 cases (7.8%) of preterm delivery and one case (2.0%) of premature rupture of membranes. In two women (6.5%) a retained placenta was diagnosed. *Conclusions.* Our study is the first description on delivery modes after surgery for deeply infiltrating endometriosis. We did not find an elevated risk for perineal or vaginal laceration in women with a history of surgery for deeply infiltrating endometriosis, even when a resection of the rectum or of the posterior vaginal wall had been performed.

1. Introduction

Endometriosis is defined as the presence of endometrium-like tissue outside of the uterine cavity [1]. Deeply infiltrating endometriosis (DIE) is defined as endometriotic lesions in the rectovaginal septum, the vaginal fornix, and the peritoneum or if the bowel, the ureter, or the bladder is infiltrated by the disease [2].

Due to the lack of large cohort studies, the prevalence of endometriosis is still unknown [3], but it is estimated that 10 to 15 percent of women in the reproductive age are affected by the disease [4]. As endometriosis is regarded to be a condition of the premenopausal woman, its peak of prevalence coincides with a woman's reproductive period [5].

The question if endometriosis has an influence on fertility, pregnancy, and obstetrical outcome has been subject to different studies in the last years.

It has been suggested that, during pregnancy, endometriosis can cause a variety of disease-related complications, such as miscarriage, bleeding from ectopic implants, preterm birth, fetal growth restriction, preeclampsia, or obstetrical bleeding [6].

Endometriosis is regarded as the major risk factor for SHiP (sudden hemoperitoneum in pregnancy), which is a rare but potentially hazardous complication that can be caused by the decidualization of ectopic lesions during pregnancy and in the postpartum period [3, 7]. But not only can decidualization cause massive intraperitoneal hemorrhage, it can also lead to weakening of the intestinal wall and therefore cause spontaneous rectal perforation during pregnancy [8, 9]. So far 12 cases of bowel perforation during pregnancy have been reported, but endometriosis has been diagnosed in 3 cases only [6].

The influence of endometriosis on the development of preeclampsia is debatable. Brosens et al. showed a significantly reduced risk of preeclampsia in women with endometriosis, while Falconer reported that women with endometriosis seem to be at a higher risk for the development of preeclampsia [10, 11].

The risk of preterm birth seems to be elevated in women with endometriosis, and Conti et al. also found an increased risk for SGA fetuses and preterm premature rupture of membranes [12–14].

Women with endometriosis seem to be at higher risk for placenta previa, especially when there are rectovaginal endometriotic lesions present [15]. According to a study from Vercellini et al. the rate of placenta previa in women with endometriosis is more than tenfold higher than in the general population (3.7 percent versus 0.3 percent) [15].

While possible influences of endometriosis on pregnancy have been described, little is known about the influence the disease can have on the obstetrical outcome. While two studies described a higher risk for delivery through caesarean section in women with endometriosis, a study performed by Conti et al. did not find a positive correlation [3, 13, 14].

There are no guidelines concerning the mode of delivery in pregnant women after surgery for deeply infiltrating endometriosis. Even the "Guideline on the Management of Women with Endometriosis" does not address this issue [16]. The "Guideline for Diagnosis and Therapy of Endometriosis" only suggests that the mode of delivery should be discussed with each patient individually [17].

Hypothesis. Do women with histologically confirmed endometriosis have a higher risk of adverse pregnancy outcome or complications during delivery and does the diagnosis of deeply infiltrating endometriosis (DIE) have influence on the choice of the delivery mode?

2. Materials and Methods

We included all women on whom surgery because of deeply infiltrating endometriosis was performed in the General Hospital Linz between 01.01.2009 and 31.12.2013 and in the Women's General Hospital Linz between 01.01.2013 and 31.12.2013 and who gave birth in the Women's General Hospital Linz after the surgery until 31.03.2015 (the General Hospital Linz and the Women's General Hospital Linz are now part of the Kepler University Clinic). Only women with histologically verified endometriotic lesions were included in the survey.

We looked through the patient records to gain information about the surgery as well as details about the delivery.

Concerning the performed surgery we collected the following information:

(i) Date of surgery.

(ii) Performed surgery.

(iii) ENZIAN classification.

(iv) rAFS classification.

(v) Affected structures (adenomyosis, endometriosis of the ovary, endometriosis of the fallopian tube, endometriosis of the peritoneum, endometriosis of the vagina, endometriosis of the rectovaginal septum, endometriosis of the uterovesical fold, endometriosis of the colon, and endometriosis of the ureter).

(vi) Duration of surgery.

We used the ENZIAN classification to classify all patients because it is a common and validated classification system for deeply infiltrating endometriosis (Figure 1) [18].

Concerning the delivery we extracted the following information from the patient records:

(i) Number of previous pregnancies.

(ii) Number of previous births.

(iii) Period of time between the surgery and the pregnancy.

(iv) Artificial reproduction techniques.

(v) Duration of pregnancy.

(vi) Complications during pregnancy (gestational diabetes, partus praematurus, premature rupture of membranes, placenta previa, preeclampsia, placental abruption, and placental retention).

(vii) Mode of delivery.

(viii) Duration of expulsion stage.

(ix) Birth injuries.

(x) Length of stay in the hospital.

(xi) Data of the newborn (birth weight, body length, head circumference, APGAR score, and umbilical blood gases).

Two-sided 95% confidence intervals (95% CI) were calculated for the incidences of several kinds of birth procedures and complications as well as for the duration of the expulsion stage.

For subgroup comparisons (spontaneous delivery versus caesarean) all data sets of metric variables were checked for normal distribution (test of normality: Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%).

Normally distributed data sets were compared by the t-test (test for variance homogeneity: Levene test, type I error = 5%) for independent samples, metric variables without normally distributed data sets and variables measured on ordinal scales by the exact Mann-Whitney U test, and dichotomous variables by Fisher's exact test.

Logistic regression analysis (forward stepwise method with Wald statistics) and multiple regression analysis (stepwise) were carried out to detect independent prognostic factors for caesarean and for the duration of the expulsion stage.

Independent variables were as follows:

(i) ENZIAN A.

(ii) ENZIAN B.

(iii) ENZIAN C.

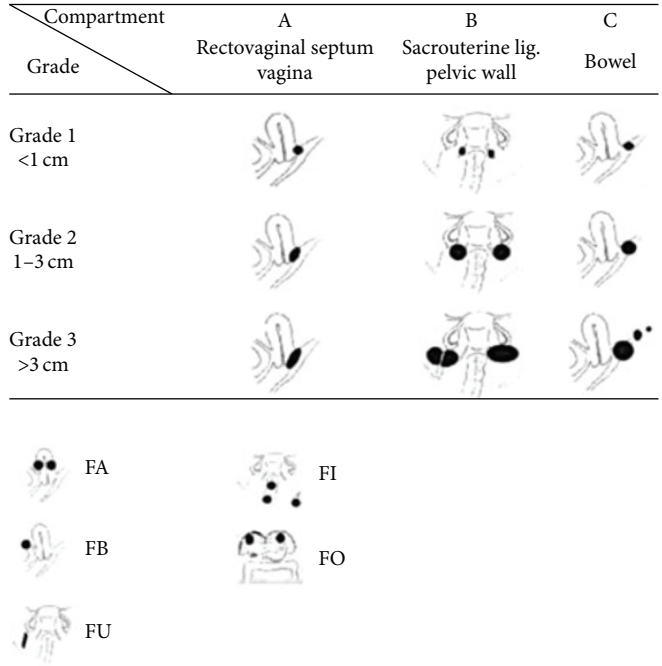

Figure 1: The revised ENZIAN classification of endometriosis.

(iv) Age at the time of surgery (years).

(v) Period of time between surgery and delivery (months).

(vi) Duration of surgery (minutes).

(vii) Number of parturition processes (before the surgery).

(viii) Birth weight (gram).

(ix) Head circumference (centimeter).

Type I error was not adjusted for multiple testing. Therefore the results of inferential statistics are descriptive only. Statistical analysis was performed using the open-source *R* statistical software package, version 3.0.2.

Approval for the survey was obtained by the local institutional ethics committee on 20 July 2015 (reference number K-71-15).

Figure 2: Patients described by the ENZIAN classification.

3. Results

A total of 51 women met all inclusion criteria and were included in our survey.

The average age at the time of surgery was 29.2 years ± 4.27 (mean ± SD).

In 12 cases the left rectouterine ligament was removed, in 7 cases the right rectouterine ligament was removed, and in 8 patients the rectouterine ligament had to be removed on both sides. In three patients, the vagina was surgically opened because endometriotic lesions in this area were removed. A resection of the sigmoid colon was performed in one case, and in three patients a resection of the rectum was carried out.

In 14 patients, the vagina or the rectovaginal septum was affected by endometriosis (ENZIAN A), in 30 cases the rectouterine ligaments, the parametria, the pelvic wall, or the ureter (extrinsically) was affected (ENZIAN B), and in 8 patients infiltration of the rectum (ENZIAN C) was diagnosed (Figure 2).

Concerning the mode of delivery, 31 women (60.8%) had a spontaneous delivery and in 20 women (39.2%) a caesarean section was performed: in 11 of these 20 cases a primary caesarean section was performed, and in 4 cases the indication for the primary caesarean section was the endometriosis itself. In 9 cases a secondary caesarean section had to be performed.

The mean period of time between the surgery and the delivery was 19.7 months in the group of women that had a caesarean section and 22.7 months in the group of women that gave birth spontaneously.

In the group of spontaneous births there were 7 cases (22.6%) of first-degree perineal tears and 6 cases (19.4%) of second-degree perineal tears. Collectively there were no cases of third- or fourth-degree perineal tears. An episiotomy was

Table 1: Arterial umbilical blood pH.

	Min	Median	Max	*N*
Caesarean section	7.19	7.30	7.38	20
Spontaneous delivery	7.13	7.27	7.45	31
Total	*7.15*	*7.28*	*7.42*	*51*

performed in 10 cases (32.3%). In three women (9.7%) a vaginal tear was diagnosed.

There were 4 cases (7.8%) of preterm delivery and one case (2.0%) of premature rupture of membranes. In two women (6.5%) a manual removal of the placenta because of a retained placenta had to be performed.

Collectively there were no cases of placenta previa or preeclampsia.

When looking at the umbilical cord gas the mean arterial pH was 7.30 when a caesarean section had been performed and 7.27 in women who gave birth spontaneously, which means that, concerning the umbilical cord cases, there was no statistically significant difference between these two groups ($p = 0.054$) (Table 1).

Table 2 shows the obstetrical outcome for women in which surgery in compartment ENZIAN A had been performed. Five of these 14 women gave birth spontaneously and there was no case of vaginal laceration. In 9 cases a caesarean section was performed (5 cases of primary caesarean section and 4 cases of secondary caesarean section). In 4 of the 5 cases of primary caesarean section, the indication for the caesarean operation was provided because of the endometriosis.

Table 3 shows information about the delivery mode in women with surgery in the compartment ENZIAN C. Of the affected 8 women, only two gave birth spontaneously. In 5 cases a primary caesarean section and in one case a secondary caesarean section were performed. In 4 of the 5 cases of primary caesarean operation, the caesarean section was performed because of the endometriosis.

One of the two women that had a spontaneous delivery had a history of rectum resection due to endometriosis and there was no fourth-degree perineal laceration in this woman.

Our results show that operation for deeply infiltrating endometriosis does have a statistically significant influence on the choice of the delivery mode when the compartments ENZIAN A and C are affected or a rectum resection has been performed (Table 4).

There was no higher risk for pregnancy complications or adverse pregnancy outcome collectively.

4. Comments

Previous studies have shown that deeply infiltrating endometriosis can be associated with a various number of complications during pregnancy and delivery [6].

However, our results did not show an association between previous surgery due to deeply infiltrating endometriosis and adverse pregnancy outcome.

Our results do show that the risk for abdominal delivery seems to be elevated in women with endometriosis. The caesarean rate collectively was 39.2%, while according to Statistik Austria in 2014 the rate of abdominal delivery in the overall population in Austria was 29.8% [19]. This finding is conclusive with the results of a survey conducted by Stephansson et al., who also found a highly elevated rate of caesarean sections in women with endometriosis compared to women without the disease [12].

Collectively, women with endometriosis of the compartment ENZIAN A or ENZIAN C had a statistically higher risk for delivery through caesarean section than women without endometriosis in these compartments ($p = 0.020$ and $p = 0.031$). There was also a statistically significant elevated caesarean rate when a rectal resection had been performed ($p = 0.029$).

The mean period of time between the surgery and the delivery was longer in the group of women that gave birth spontaneously than in the group of women where a caesarean section was performed (22.7 months versus 19.7 months), although this finding was not statistically significant ($p = 0.329$).

The influence of endometriosis on the development of preeclampsia during pregnancy is still unclear. Brosens et al. found that the risk for preeclampsia in women with endometriosis can be increased, decreased, or unchanged [3]. Collectively, we did not have a case of preeclampsia.

Although Lin et al. showed an increased risk of placenta previa in pregnant women with endometriosis [14], we cannot confirm this observation as there was no case of placenta previa collectively. We also found no case of placental abruption.

There are case reports of massive gastrointestinal or intraperitoneal bleedings due to decidualization of endometriotic lesions during pregnancy or in the postpartum period [3, 7]. However, collectively we did not have a complication like these.

Menzlova et al. reported a case about a fourth-degree perineal laceration after spontaneous birth in a woman with previously diagnosed endometriosis of the rectovaginal septum [20]. Collectively, endometriosis of the compartment ENZIAN A was diagnosed in 14 women, of whom 5 women gave birth spontaneously. One of these five women even had a history of surgical opening of the vagina because endometriotic lesions in the vaginal wall had to be removed. However, we had no case of third- or fourth-degree perineal laceration and there was especially no case of vaginal laceration in this group.

Collectively a resection of the rectum had been performed in 6 cases. One of these six women gave birth spontaneously, while in the remaining five cases a caesarean section was performed (Table 3). The woman who gave birth spontaneously suffered from a second-degree perineal laceration, but there was no injury of the rectum or the vaginal wall.

Literature describes that rectum resection due to endometriosis may lead to several complications, including rectovaginal fistula or anastomotic insufficiency [21]. A survey conducted by Remzi et al. described a significantly higher risk of sphincter injury in women who underwent an ileal pouch-anal anastomosis and afterwards delivered spontaneously

Table 2: Patients with operation in compartment ENZIAN A.

	ENZIAN A	ENZIAN B	ENZIAN C	Open vagina	Delivery mode	Vaginal laceration
1	3	3	3	Yes	Secondary CS	
2	3	3	3		Primary CS	
3	2	0	2		Primary CS	
4	2	2	1	Yes	Primary CS	
5	2	2	0		Spontaneous delivery	No
6	2	2	0		Secondary CS	
7	2	0	0		Spontaneous delivery	No
8	1	2	2		Spontaneous delivery	No
9	1	1	1		Primary CS	
10	1	1	1		Primary CS	
11	1	0	0		Secondary CS	
12	1	0	0		Spontaneous delivery	No
13	1	2	0		Secondary CS	
14	1	1	0	Yes	Spontaneous delivery	No

Table 3: Patients with operation in compartment ENZIAN C.

	ENZIAN A	ENZIAN B	ENZIAN C	Open vagina	Rectum resection	Bladder resection	Delivery mode
1	3	3	3	Yes	Yes		Secondary CS
2	3	3	3		Yes		Primary CS
3	2	0	2		Yes		Primary CS
4	1	2	2		Yes		Spontaneous delivery
5	2	2	1	Yes	Yes	Yes	Primary CS
6	0	2	1				Spontaneous delivery
7	1	1	1		Yes		Primary CS
8	1	1	1				Primary CS

Table 4: Influence of DIE on the mode of delivery.

Severity of infiltration of the vagina and rectovaginal septum (ENZIAN A)	$p = 0.020$
Severity of infiltration rectum (ENZIAN C)	$p = 0.031$
Resection of the rectum	$p = 0.029$

compared to women who delivered via caesarean section [22].

Ravid et al. reported decreased long-term function in some women after ileal pouch-anal anastomosis because of ulcerative colitis after pregnancy, independently of the mode of delivery [23].

Although we found no such complications collectively, it is debatable if spontaneous delivery after rectum resection increases the risk of such complications and if abdominal delivery should be recommended in these cases.

A survey by Bulletti et al. found that spontaneous delivery can have a positive influence on dysmenorrhea and the recurrence of endometriosis. In this study, women that gave birth spontaneously had a longer pain-free interval than women on whom a caesarean section was performed [24]. However, as we did not investigate the postpartum period collectively, we cannot confirm or refute this finding.

A limitation of the present survey is the relatively small number of patients included. In our mind, further studies should be conducted, especially focusing on the mode of delivery after rectum resection and the influence on the mode of delivery on endometriosis associated symptoms such as dysmenorrhea.

5. Conclusion

Our study is the first description on delivery modes after operation for deeply infiltrating endometriosis. In our patient collective of women with spontaneous delivery, we did not have relevant laceration regarding an operation for DIE in history, even when a resection of the posterior vaginal wall or the rectum had been performed.

Concerning the small number of patients with resection of the rectum because of endometriosis and spontaneous delivery ($n = 1$), there is no conscientiousness for a recommendation.

Collectively, there was no higher risk of adverse pregnancy outcome after operation for DIE in history in women with spontaneous birth as well as in women with caesarean section, although women with lesions in compartments ENZIAN A and ENZIAN C as well as after rectum resection were more likely to have abdominal delivery.

Additional Points

Women with histologically verified endometriosis do not have a higher risk of adverse pregnancy outcome but are more likely to have a caesarean section.

Disclosure

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Competing Interests

The authors report no competing interests.

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Review Article

Decreased Cytotoxicity of Peripheral and Peritoneal Natural Killer Cell in Endometriosis

InCheul Jeung,[1] Keunyoung Cheon,[2] and Mee-Ran Kim[3]

[1]*Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, 64 Daeheung-ro, Jung-gu, Daejeon 34943, Republic of Korea*
[2]*Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, 59 Dongsu-ro, Bupyeong-gu, Incheon 21431, Republic of Korea*
[3]*Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, 222 Banpodae-ro, Seocho-gu, Seoul 06591, Republic of Korea*

Correspondence should be addressed to Keunyoung Cheon; violia@catholic.ac.kr and Mee-Ran Kim; mrkim@catholic.ac.kr

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Endometriosis causes significant chronic pelvic pain, dysmenorrhea, and infertility and affects 10% of all women. In endometriosis, ectopic endometrium surviving after retrograde menstruation exhibits an abnormal immune response characterized by increased levels of activated macrophages and inflammatory cytokines. Particularly, dysfunctional natural killer (NK) cells play an important role in the pathogenesis of the disease by either facilitating or inhibiting the survival, implantation, and proliferation of endometrial cells. NK cells in the peritoneum and peritoneal fluid exhibit reduced levels of cytotoxicity in women with endometriosis. Several cytokines and inhibitory factors in the serum and peritoneal fluid also dysregulate NK cell cytotoxicity. Additionally, increased numbers of immature peripheral NK cells and induction of NK cell apoptosis are evident in the peritoneal fluid of women with endometriosis. The high rate of endometriosis recurrence after pharmaceutical or surgical treatment, which is associated with dysfunctional NK cells, indicates that new immunomodulatory management strategies are required. A good understanding of immune dysfunction would enable improvement of current treatments for endometriosis.

1. Introduction

In endometriosis, ectopic endometrium survives, causing a disease characterized by implantation of endometrial tissue outside the uterus; this, in turn, triggers pain and infertility. Ectopic endometrium, which is thought to originate via retrograde menstruation, causes significant chronic pelvic pain, dysmenorrhea, and infertility, accompanied by inflammatory changes [1, 2]. This widespread estrogen-dependent disease is estimated to affect 10–15% of all women and up to 50% of women with chronic pelvic pain and infertility [3–5]. Almost 50% of adolescents with intractable dysmenorrhea or pelvic pain are diagnosed with endometriosis, but it is not yet clear why only certain women develop the condition [3].

The most widely accepted theory, which was developed by Sampson, holds that that endometrial tissue refluxed to the Fallopian tubes fails to be cleared and attaches to the peritoneum. Some 70% of women who menstruate regularly exhibit bleeding reflux, but only 10% develop endometriosis [6–8]. Several factors are likely to influence susceptibility to the condition. The high rate of recurrence of endometriosis after pharmaceutical or surgical treatment indicates that researchers need to further define the pathophysiology of the condition, which, in turn, would facilitate work toward an effective treatment.

Recently, it has been suggested that abnormal immune function and dysregulation of immune mediators are responsible for the poor response to treatment, and poor clearance, of ectopic endometrium. Immune status is now considered to play an important role in the initiation and progression of endometriosis. Several studies have shown that the levels of activated macrophages, T cells, B cells, and inflammatory

cytokines are increased in women with endometriosis [9, 10]. Specifically, natural killer (NK) cells have been suggested to play an important role in the pathogenesis of the disease by either allowing or inhibiting the survival, implantation, and proliferation of endometrial cells [11, 12]. Reductions in NK cell cytotoxic function have been observed in the peritoneal fluid (PF) of patients with endometriosis [13, 14], implying that a defect in NK cell cytotoxic function, preventing elimination of endometrial cells from ectopic sites, may cause endometriosis.

In this review we define the immunological changes evident in women with endometriosis, with a specific focus on NK cells and the contributions of immunological factors to reductions in the functions of such cells.

2. Role of the Immune System in Endometriosis

Immune cells play key roles in the detection and clearance of abnormal cells [15]. It has been proposed that impairment of the immune response, resulting in inadequate removal of refluxed menstrual debris, is an important contributor to endometriosis [16, 17]. Recent studies on the immunological changes associated with endometriosis have focused on the significance of NK cells.

3. Cellular Immunological Changes in the Peritoneal Cavity of Women with Endometriosis

Endometrial fragments refluxed during menstruation induce inflammation within the peritoneal cavity [18]. Normally, neutrophils and macrophages are among the first immune cells to be recruited to this area. Macrophage numbers are increased in the PF of patients with endometriosis [19]; however, these cells fail to act as scavengers of endometrial tissue and are primary contributors to the elevations in proinflammatory and chemotactic cytokine levels found in the PF [20]. In addition to encouraging the growth of peritoneal implants, macrophages are a major source of angiogenic mediators, including TNF-α and IL-8 [21]. Macrophages seem to be involved in the growth and development of endometriotic tissue, but macrophage depletion does not prevent endometrial cell implantation in the peritoneum, suggesting that the mechanisms of implantation and pathogenesis differ [22, 23].

The neutrophils of women with endometriosis exhibited a slower rate of apoptosis than did those of control women [24]. Dendritic cells (DCs), a type of antigen-presenting cells (APC), activate naive T cells to become cytotoxic or T helper cells. One study found that depletion of DCs caused growth of an endometriotic lesion [25], but another reported that DC depletion attenuated the development of endometriosis [26]. The role played by DCs thus needs further study.

4. Natural Killer Cells

NK cells, which comprise 15% of all circulating lymphocytes, particularly those of the innate immune system, protect against tumor development and viral infections. The cells have both cytolytic and immunomodulatory capabilities [27, 28]. NK cells destroy other cells by secreting lytic granules containing granzymes, perforin (at immune synapses), and cytotoxins or cytokines, such as IFN-γ [29, 30]. Significant populations of NK cells are found in lymphoid tissues, such as the bone marrow and blood, as well as in nonlymphoid tissues, such as the liver and gut [31–33].

The level of CD56 expressed by NK cells appears to correlate with NK cell function: CD56dim NK cells are more cytotoxic and express higher levels of immunoglobulin-like NK cell receptors and FC-γ receptor III (CD16) than do CD56bright NK cells. In contrast, CD56bright NK cells are potent producers of cytokines, particularly IFN-γ and TNF-α, following activation by monocytes, but they exhibit low-level natural cytotoxicity and low levels (or an absence) of the FC-γ receptor CD16.

5. NK Cell Dysfunction and Endometriosis

Following translocation of refluxed endometrial tissue into the peritoneal cavity, the endometrial fragments must survive the immune response and attach and invade the peritoneal membrane to establish a lesion. In endometriosis, dysfunctional NK cell cytotoxicity may allow endometrial fragments to survive in the peritoneum [34].

Most studies have found that the numbers of cytotoxic NK cells are reduced in the PF and peripheral blood of endometriosis patients and that this is accompanied by an overall decrease in NK cell activity [14, 35–37]. In such patients, the populations of NK cells (CD32CD56+) are significantly decreased, whereas the proportions of immature NK cells (CD272CD11b2) among CD32CD56+ NK cells are increased in the PF. Functional impairment and diminished cytotoxicity of NK cells within the peritoneal cavity have also been well documented in such patients [34]. The NK cell levels of granzyme B, perforin, TRAIL, and CD107a are reduced in the PF of patients with endometriosis, indicating that the NK cells are functionally defective.

The levels of the inflammatory cytokines IL-6, IL-8, IL-1b, IFN-γ, and TNF-α increase in the PF of patients with endometriosis, which is consistent with the elevated levels noted in the serum [38–41]. Certain chemokines, especially CXCL8 (IL-8), CCL-2 (MCP-1), and CCL5 (RANTES), can serve as biomarkers identifying patients with endometriosis, but the accuracy of such tests can be improved by including other noninflammatory markers in the biomarker panel.

6. An Altered NK Cell Phenotype in the Peritoneal Cavity

Markers of NK cell cytotoxicity include the natural receptors NKp46, NKp44, and NKG2D, CD16 (a cell surface marker), and CD107a [42] and CD69 (markers of activation). The levels of all of these markers are significantly reduced in the peritoneal NK cells of endometriosis patients. One study found that NK cell cytotoxicity was reduced in the PF of endometriosis patients but recovered upon immunomodulatory treatment; the expression levels of the activation marker CD107a were compared before and after treatment.

Table 1: Change of the immunoregulatory factors in the NK cell cytotoxicity.

Decreased cytotoxic activity	Increased inhibitory activity
Cytotoxic function	Inflammatory cytokines
Granzyme B, perforin, TRAIL, CD107a	IL-6, IL-8, IL-1b, IFN-γ, TNF-α
Cell-activating receptors	Noninflammatory cytokines
NKp46, NKp44, NKG2D, CD16 (cell surface marker)	CXCL8, CCL-2 (MCP-1), CCL5 (RANTES)
CD69 (markers of activation)	Antigen
	HLA-G, HLA-E, HLA-I
	Inhibitory receptors
	ITIM-KIRs, KIR2DL1, NKB1, EB6, I-CAM
	Apoptosis
	FasL (CD95)

The levels of most cell-activating receptors are decreased when NK cells are downregulated, whereas the levels of most inhibitory receptors are increased upon upregulation. Such up- or downregulation may be mediated by cytokines, but the detailed mechanisms remain unknown.

One study found that expression of the human leukocyte antigen-G (HLA-G; the ligand of KIR2DL4) in ectopic endometrial cells prevented detection of such cells by patrolling NK cells, allowing survival of the endometrial cells and implantation of the peritoneum [43]. The level of the inhibitory cytotoxic receptor for HLA-E, CD94/NKG2A, was also significantly increased on the peritoneal NK cells of endometriosis patients; the receptors may inhibit the release of cytolytic granules by such cells, allowing endometriotic lesions to grow [44, 45].

Killer cell inhibitory receptors (KIRs) are representative receptors recognizing major histocompatibility complex class I molecules on target cells; the receptors regulate NK cell cytotoxicity to target cells. Such inhibitory NK cell receptors contain Ig domains (KIR2DL1, KIR2DL2, KIR3DL1, and KIR3DL2) in their extracellular regions [46] and immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic portions [47, 48]. Ligand binding facilitates the recruitment of SHP-1 and SHP-2 and the suppression of immune responses, including NK cell cytotoxicity [49, 50]. Many studies have reported upregulated levels of ITIM-KIRs, KIR2DL1 [51–53], NKB1, EB6 [54], the soluble intracellular adhesion molecule-1 (I-CAM), and HLA-I in the PF of endometriosis patients; the levels of cytokines correlated directly with the extent of inhibition of NK cytotoxicity [55, 56].

Recently, IL-6 in the PF of endometriosis patients has been identified as a possible immunosuppressant of NK cell cytotoxicity, and it may play a crucial role in impairing NK cell function by regulating SHP-2 expression [47].

Women with endometriosis have higher numbers of immature peripheral NK cells than do those without the disease [36]. The proportion of mature NK cells increases after surgical removal of endometrial lesions, suggesting that certain cytokines produced by the lesions influence the differentiation of peripheral NK cells.

7. Cytokines in the PF of Endometriosis Patients

The TNF-α level is increased in the PF of women with endometriosis [57–59], but clinical trials of anti-TNF-α therapies did not alleviate pain symptoms [60].

The level of FasL, which induces NK cell apoptosis by binding to the ligand receptor CD95, was increased in the PF of women with endometriosis [61, 62], and endometriosis peritoneal NK cells expressed significantly elevated levels of CD95 [63]. Thus, NK cells in the PF may undergo FasL-induced apoptosis, allowing the endometrial cells to survive.

The level of IL-6, another inhibitory cytokine, is dramatically increased in the PF of patients with endometriosis. The levels of mRNAs encoding IL-6-upregulated TFs, c-Myc, and SOCS-3 are also increased in PF cells, and IL-6 signaling has been shown to regulate cell growth, differentiation, and survival. Furthermore, IL-6 directly affects the differentiation of cytotoxic NK cells from CD34+ cells. IL-6 also affects the functional activities of such cells by increasing the levels of mRNAs encoding SHP-1 and SHP-2. IL-6 also increases KIR expression on NK cells (CD56+ cells) [64]. Some study shows that NF-κB may be one of major culprits in the pathogenesis of endometriosis, and its constitutive and inducible activation may be responsible for antiapoptosis, angiogenesis, invasiveness, and increased production of proinflammatory cytokines and chemokines [65].

8. Conclusions

The immunoregulatory factors involved in the NK cell cytotoxicity in PF and peripheral blood of women with endometriosis are shown on Table 1. The pathogenesis of endometriosis is associated with abnormal differentiation and function of cytotoxic NK cells. The phenotypes of peripheral blood and PF NK cells in women with endometriosis indicate that the NK cells are dysfunctional. Specifically, NK cells of the peritoneum and PF are less cytotoxic in women with endometriosis than in control women. Several cytokines and inhibitory factors in the serum and PS also negatively affect NK cell cytotoxicity. It remains possible, however, that the NK

cell abnormalities evident in women with endometriosis are, in fact, consequences of the pathology. Future research should seek to explain how the observed immunological changes in, and dysfunctionality of, NK cells are initiated. Novel strategies to manage endometriosis should be based on an understanding of the associated immunological problems and should prioritize improvements in NK cell functionality.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

Demographic and Clinical Features of Endometrial Polyps in Patients with Endometriosis

Ningning Wang,[1] Yufeng Zhang,[2] and Bin Liu[1]

[1]*Department of Obstetrics and Gynecology, The First Affiliated Hospital, Sun Yat-sen University, No. 58th Zhongshan 2nd Road, Guangzhou 510080, China*
[2]*Department of Gynecology, The Third Hospital of Nanhai, No. 45 Zhenxing Road, Lishui Town, Nanhai District, Foshan 528244, China*

Correspondence should be addressed to Ningning Wang; wangningning21cn@21cn.com

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Aims. To compare the clinical features of endometrial polyps (EPs) between patients with endometriosis (EM) (EM group) and without EM (non-EM group). *Methods and Results*. Seventy-six cases in the EM group and 133 cases in the non-EM group underwent laparotomy or hysteroscopy and laparoscopy; later, it was confirmed that the results by pathology from July 2002 to April 2008 in the Department of Gynecology and Obstetrics at the First Affiliated Hospital of Sun Yat-sen University. The recurrence of EPs was followed up after the surgery until 2013. The following parameters were assessed: age, gravidity, parity, infertility, and menstrual cycle changes, as well as polyps diameters, locations, number, association with the revised American Fertility Society (r-AFS) classification, and their recurrence. On review, 76 EPs cases of EM group histologically resembled EPs but the majority of EPs with EM occurred in primary infertility cases and in fewer pregnancy rate women who had stable and smaller EPs without association with the AFS stage. The recurrence rate of EPs in EM group was higher than that in non-EM group. *Conclusion*. It is important to identify whether infertile patients with EM are also having EPs. Removing any coexisting EPs via hysteroscopy would be clinically helpful in treating endometriosis-related infertility in these patients.

1. Introduction

Endometriosis (EM) is defined as functional endometrial glands and stroma tissue that are located outside the uterine cavity. It affects approximately 2–17% of women in their reproductive years, and it typically manifests as chronic pelvic pain, congestive dysmenorrhoea, heavy menstrual bleeding, and deep dyspareunia. It is suggested that 47% of infertile women have EM [1, 2]. Although its pathogenesis is not clear, endometriosis associated with infertility is gradually accepted to be partially related to endometrial polyps (EPs) [3–6].

EPs, the local hyperplastic growth of endometrial glands and stroma covered by epithelium, can affect between 7.8% and 34.9% of women, especially infertile women [7, 8]. EPs can occur as a single polyp or multiple polyps, can be sessile or pedunculated, and can range in size from millimeters to centimeters [9, 10]. Occasionally, EPs can contain smooth muscle fibers called adenomyomatous polyps [11]. They are frequently encountered with abnormal uterine bleeding (AUB). Similar to endometriosis, EPs can also be associated with intracavitary bleeding and can present an abnormal environment for embryo implantation [12, 13]. Hysteroscopy is superior to other treatment methods because hysteroscopic polypectomy appears to improve fertility and increase pregnancy rates by using direct visualization to completely remove the polyps while leaving the adjacent endometrium intact [14–19].

In cases of infertility, EM and EPs can be closely associated with each other in some respects. For example, some studies reported a higher frequency of EPs in EM patients [3, 4, 20]. However, the characteristics of polyps in the EM patients and the manner in which they differ from those in patients without EM have not yet been elucidated. The objective of the present study was not only to evaluate the association of EM with EPs but also to investigate the characteristics of EPs in EM patients.

2. Patients and Methods

2.1. Patient Groups. A retrospective comparison was conducted of the data from 76 patients (EM group) who had been diagnosed with EM with EPs and 133 patients (non-EM group) who had been diagnosed with EPs without EM based on pathology, all of whom had undergone laparotomy or hysteroscopy and laparoscopy between July 2002 and April 2008 in the Department of Gynecology and Obstetrics at the First Affiliated Hospital of Sun Yat-sen University. The recurrence of EPs was followed up after the surgery until 2013. The two groups of patients had no internal medicine complications and had not taken any steroid hormone medications within 3 months before the surgery. There was no significant difference between the two groups with respect to the presence of uterine fibroids and adenomyosis ($P = 0.90$ and $P = 0.67$, resp.). The eutopic endometrial pathological types in the two groups were not different with respect to the menstrual cycle stage ($P = 0.12$). This study was approved by our hospital ethics committee.

2.2. Data Collection and Criteria. A retrospective analysis and comparison of demographic and clinical characteristics between the two groups as clinical data [age and symptoms (e.g., menstrual changes, gravida, parity, and abortion, including medical abortion and spontaneous abortion times)], operative data (EPs: size, number, location, and type; EM:r-AFS stages I–IV), and pathological data were conducted. The EPs size was measured via preoperative vaginal ultrasound and confirmed during diagnostic hysteroscopy prior to resection or by gross appearance. The sizes were estimated using the largest polyp as a reference. The cases with prolonged operative times due to multiple operations for other indications or complications were excluded from the final analysis.

The diagnosis of EPs was made by histopathological examination. Specifically, the diagnosis was made according to the presence of irregularly dilated endometrial glands and thick-walled vessels scattered within fibrotic stroma. The type of EPs was determined based on the angle between the polyp and the adjacent uterine wall. (1) Pedunculated-type polyps were defined when the angle of the polyp surface to the endometrium was <90 degrees. (2) Sessile-type polyps were those with an angle ≥90 degrees [21]. The presence and diagnostic criteria of uterine hemorrhage were divided into the following four categories [22]: (1) menorrhagia, (2) hypermenorrhea, (3) metrorrhagia, and (4) polymenorrhea. In our study, we considered hypermenorrhea together with menorrhagia as menorrhagia and metrorrhagia together with polymenorrhea as polymenorrhea because patients were often confused regarding the distinction between the different types. Histological and pathological information was also collected, including the presence and degree of the accompanying endometrium in the proliferative or secretory stage, adenomyosis, and leiomyoma, as well as the presence of EPs and EM.

2.3. Statistical Analysis. Statistical analysis was performed using SPSS 13 Statistical Software (SPSS Inc., Chicago, IL, USA). Multivariate logistic regression analysis was performed, in which the occurrence of EPs was used as the dependent variable, while the age, gravidity, and parity were used as independent variables. Quantitative data, such as age, polyp diameter, and number of polyps, are expressed as the means and 95% confidence intervals (95% CIs). Differences between the groups were assessed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The patients' polyps, along with infertility type, menstrual cycle changes, polyp location, and EM r-AFS stage, were compared with the Pearson chi-square test and Fisher's exact test for qualitative variables. A P value < 0.05 was considered to be statistically significant.

Table 1: Age, gravida, and parity related to endometrial polyps associated with endometriosis.

Independent variable	B	χ^2	P	OR
Constant	0.32	0.17	0.68	1.38
Age	−0.01	0.20	0.66	0.99
Gravida	−0.01	0.00	0.93	0.99
Parity	−0.90	9.14	0.00	0.41

3. Results

The average age of the EPs patients in the EM group was 38.37 ± 0.74 years, while that of the EPs in non-EM group was 40.0 ± 10.55 years ($P > 0.05$). After a follow-up period to 2013, 76 patients of EM and 133 patients of non-EM group were contacted for a phone interview. Two persons could not be reached by the phone.

3.1. Endometrial Polyps in Patients with Endometriosis Related to Decrease in Number of Pregnancies. The incidence of EPs in EM group was not related to the age and gravidity. However, it was negatively related to parity ($P = 0$, OR = 0.41); specifically, the less the parity, the higher the incidence of EPs in EM group (Table 1). The incidence of infertility in EPs patients of the EM group was significantly higher than that in EPs patients of non-EM group ($P = 0.00$), and the incidence of EPs in EM patients was significantly increased in primary infertility patients (Table 2).

3.2. Clinical and Pathological Features of Endometriosis Patients with Endometrial Polyps. EPs with EM tended to be a stationary state; that is, the original menstrual cycle and menstrual volume were maintained. However, EPs in non-EM group occurred with menorrhagia ($P = 0.00$) (Table 3). Further the EPs size and the menstrual changes in the two groups are not related; that is, the size of the EM patients with EPs has no effect on menstruation change comparing between menstrual cycles ($F = 2.02$, $P = 0.14$) and between the two groups in the same menstrual cycle ($F = 2.08$, $P = 0.15$) (Table 4). There was no difference when we compared the relationship between the types of menstruation and the locations of the EPs in the two groups. But the polyps in the corpus in the two groups were closely related to the menorrhagia status (Table 5). The EPs in patients with EM

Table 2: Endometrial polyps associated with endometriosis and infertility.

Group	n	Primary infertility (%)	Secondary infertility (%)	Pregnancy (%)	χ^2	P
EM	76	27 (35.5)	7 (9.2)	42 (55.3)	32.06	0.00
Non-EM	133	8 (6.0)	9 (6.8)	116 (87.2)		

Table 3: Comparison of the menstrual cycles between the two groups.

	EMs (%)	Non-EMs (%)	χ^2	P
Menorrhagia	23 (30.3)	78 (58.6)		
Polymenorrhea	12 (15.8)	16 (12.1)	16.23	0.00
Unchanged	41 (53.9)	39 (29.3)		

Table 4: Relationship between the menstrual cycle and the size of the endometrial polyps in the two groups (mm, mean ± SD).

Groups	Menstrual cycle	n	EP diameter (mm) ($\overline{x} \pm s$)
EM	Menorrhagia	23	11.22 ± 8.10
	Polymenorrhea	12	9.91 ± 10.10
	Unchanged	41	8.29 ± 7.28
Non-EM	Menorrhagia	78	13.62 ± 12.38
	Polymenorrhea	16	10.50 ± 9.14
	Unchanged	39	10.72 ± 7.57

were smaller (Table 6), concentrated in the corpus and uterus, and had a sessile trend. There was no significant difference with respect to the number, distribution, and type of polyps between the two groups (Table 7). The size and number of EPs in patients in EM group were not correlated with the r-AFS stage ($P = 0.19$, $F = 1.64$ and $P = 0.88$, $F = 0.22$, resp.) (Table 8).

3.3. The Recurrence of Endometrial Polyps in Two Groups. The recurrence rate of EPs in EM patients in our study was higher in EM patients with EPs, and there was a positive association between the recurrence rate and follow-up period; specifically, the 2-year recurrence rate was 23.08% postoperatively, whereas the 5-year recurrence rate was as high as 56.41% (Table 9).

4. Discussion

The precise pathogenesis of endometriosis in patients with EPs is not clear. However, the most widely accepted characteristic mechanism for endometriosis is retrograde menstruation with the transport of endometrial cells, metaplasia of coelomic epithelium, and hematogenous or lymphatic spread of endometrial cells. Other factors, such as genetic, immunological, and inflammatory factors, are involved in this process, in which eutopic endometrial fragments become implanted in the pelvis or other organs. A combination of these theories is likely to characterize the features of endometriosis. Furthermore, because blood reflux is common when women are of reproductive age, the eutopic endometrial status in endometriosis patients is mainly considered to be abnormal at the same time [23–25].

Previous studies [17, 18, 20], together with our research, revealed a significantly increased risk of EPs in women with endometriosis compared with those without endometriosis. Moreover, Zheng et al. [20] indicated that endometriosis patients have a significantly higher risk of EPs, especially patients with endometriosis greater than stage I. Our research further reported that EPs associated with endometriosis exhibited the same structure as other polyps and often occurred in infertile women, especially in those with primary infertility, or there were fewer pregnancies in women with endometriosis. Based on our present study, EMs with EPs are not closely related to the clinical symptoms and r-AFS stage.

Furthermore, our results showed that the EPs associated with EM were in a relatively quiescent state; that is, there is little risk of the severity of menstrual disorders increasing, and the original menstruation pattern is often maintained. It is recommended for EM patients with infertility to have routine vaginal ultrasound and hysteroscopy examinations to assess EPs. At the same time, this examination should be conducted more carefully because polyps associated with EM are generally distributed in a similar manner with other polyps but have a smaller size. The recurrence rate of EPs in EM patients in our study was higher in EM patients with EPs, and there was a positive association between the recurrence rate and follow-up period; specifically, the 2-year recurrence rate was 23.08% postoperatively, whereas the 5-year recurrence rate was as high as 56.41%.

There could be intrinsic factors that make EM more likely to occur in association with EPs, which should mainly be associated with infertility. Some authors found both EM and EPs that exhibited an overgrowth of the endometrium, a process that requires the support of estrogen. Additionally, previous research revealed that the expression patterns of estrogen receptor (ER) and aromatase are both altered in EM and EPs patients [26–28]. Additionally, increased proliferation and decreased apoptosis have been observed in the eutopic endometrium in patients with EM [24, 25]. An altered estrogen metabolism with increased proliferation and decreased apoptosis in the eutopic endometrium of women with EM could facilitate the formation of EPs.

EPs formed when the local hormone and its receptor were abnormal. At the same time, it is possible that the vessel axis of the functional polyps could actually originate from the evolution of the vascular changes that are associated with endometritis. Inflammatory factors could play an important role in EPs formation in association with EM-related infertility. In the eutopic endometrium of EM patients, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP) 1, 2, and 9, and angiogenesis factors 1 and 2 levels were higher than those in normal endometrium [29–31]. Thus, the

Table 5: The association of the endometrial polyp locations with menstruation in the two groups.

Menstruation	Group	n	EPs location				χ^2	P
			Corpus	Horn	Cervix	Fundus		
Menorrhagia	EM	23	15	3	2	3	2.06	0.73
	Non-EM	78	56	12	6	4		
Polymenorrhea	EM	12	12	0	0	0	2.52	0.28
	Non-EM	16	13	0	1	2		
Unchanged	EM	41	34	4	1	2	1.31	0.86
	Non-EM	39	31	5	1	2		

Table 6: Comparison of the sizes of the polyps in two groups (mm, mean ± SD).

Group	N	Polyp diameter (mm) ($\overline{x} \pm s$)	t	P
EM	76	9.43 ± 8.01	−2.08	0.04
Non-EM	133	12.39 ± 10.84		

Table 7: Comparison of the characteristics of the polyps in two groups.

	EM	Non-EM	χ^2	P
Number				
1	58	95	1.44	0.70
≥2	18	38		
Location				
Corpus	61	100		
Horn	7	17	2.37	0.67
Cervix	3	8		
Fundus	5	8		
Type				
Sessile	4	2	2.45	0.19
Pedunculated	72	131		

Table 8: Endometrial polyps in endometriosis patients associated with different r-AFS stages.

r-AFS stage	n	Diameter of the polyps (mm) ($\overline{x} \pm s$)	Number of polyps
Stage I	31	9.10 ± 7.93	1.81 ± 2.40
Stage II	10	5.10 ± 4.43	1.90 ± 2.51
Stage III	23	10.26 ± 8.25	2.35 ± 2.71
Stage IV	12	12.33 ± 9.28	2.02 ± 2.31

vascular growth factor associated with VEGF-A expression may coexist differently than in non-EM patient. If there is a difference in the VEGF-A levels between EM patients with EPs with and without primary infertility, the EPs in patients with primary infertility must be studied. Additionally, it is worthwhile to determine whether local estrogen and its receptors that are associated with inflammatory factor regulation affect the formation of EPs in EM patients with infertility.

Table 9: The recurrence of endometrial polyps in the two groups.

Follow-up	EM (%) 39/76	Non-EM (%) 40/133	χ^2	P
≤2 yr	9 (23.08)	8 (20.00)		
2–5 yr	13 (33.33)	11 (27.50)	16.23	0.00
≥5 yr	17 (43.59)	21 (52.50)		

Based on the clinical analysis, patients with EM combined with EPs have smaller polyps size, exhibiting unchanged menstrual cycle and higher recurrence rate and having high rates of primary infertility or fewer pregnancies in patient complaints. It is important to identify whether infertile patients with EM are also having EPs. Hysteroscopic polypectomy together with the removal of endometriotic foci will significantly increase the likelihood of achieving a pregnancy.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

The Serum Levels of the Soluble Factors sCD40L and CXCL1 Are Not Indicative of Endometriosis

Petra Pateisky, Dietmar Pils, Lorenz Kuessel, Ladislaus Szabo, Katharina Walch, Reinhard Obwegeser, René Wenzl, and Iveta Yotova

Department of Obstetrics and Gynecology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria

Correspondence should be addressed to Iveta Yotova; iveta.yotova@meduniwien.ac.at

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Endometriosis is a benign but troublesome gynecological condition, characterized by endometrial-like tissue outside the uterine cavity. Lately, the discovery and validation of noninvasive diagnostic biomarkers for endometriosis is one of the main priorities in the field. As the disease elicits a chronic inflammatory reaction, we focused our interest on two factors well known to be involved in inflammation and neoplastic processes, namely, soluble CD40 Ligand and CXCL1, and asked whether differences in the serum levels of sCD40L and CXCL1 in endometriosis patients versus controls can serve as noninvasive disease markers. A total of $n = 60$ women were included in the study, 31 endometriosis patients and 29 controls, and the serum levels of sCD40L and CXCL1 were measured by enzyme-linked immunosorbent assay. Overall, there were no statistically significant differences in the levels of expression of both sCD40L and CXCL1 between patients and controls. This study adds useful clinical data showing that the serum levels of the soluble factors sCD40L and CXCL1 are not associated with endometriosis and are not suitable as biomarkers for disease diagnosis. However, we found a trend toward lower levels of sCD40L in the deep infiltrating endometriosis subgroup making it a potentially interesting target worth further investigation.

1. Introduction

Endometriosis is a common gynecologic disorder that affects between 6 and 10% of women in their reproductive years [1]. It is already known that immunologic changes play a pivotal role in the development and progression of endometriosis [2]. An analysis of the peritoneal fluid of patients with endometriosis [3] showed differences in the expression pattern of chemokines, cytokines, and other proteins, compared to controls [4, 5], suggesting an altered microenvironment in the peritoneal cavity of endometriosis patients [6] that encouraged the development and persistence of endometriotic lesions [7, 8]. Based on this proinflammatory state of the ectopic lesion environment, endometriosis is often considered a condition that demonstrates patterns similar to that of a chronic systemic inflammatory disease [9]. Due to an increased cell proliferation rate, survival, and neovascularization in ectopic sites, the disease is often considered as a benign neoplastic condition. Moreover, some reports have shown that endometriosis is a risk factor for certain types of ovarian cancer [10, 11]. Changes in the tissue or the peritoneal cavity might be reflected by altered blood levels of several circulating proteins as well [12]. Yet, no single factor has been determined to serve as a reliable marker for the detection of the disease, not even the quite imprecise, partly advocated marker CA 125 [4, 13]. The combination of several differentially expressed factors appears to be the most promising approach in the search for a signature that would indicate a more precise suspicion and/or diagnosis of endometriosis [12, 14].

CD40 Ligand and CXCL1 (chemokine CXC motif ligand 1, synonym: GRO-α: growth-related protein-alpha) are proteins that play important roles in endothelial cell activation, the release of inflammatory cytokines, the regulation of apoptosis, and the regulation of angiogenesis and lymphocyte recruitment [15, 16]. Soluble CD40 Ligand is the soluble form of the CD40 Ligand, which is a type II transmembrane-bound protein. An increase of sCD40 Ligand in the blood is found in various autoimmune disorders, as well as in chronic inflammatory diseases [17, 18]. Recently, it has been

shown that sCD40 Ligand levels are altered in the plasma of patients with PCOS [19, 20]. In a previous study of endometriosis patients, levels of CD40L and CD40 did not differ between patients and controls, but the sCD40 Ligand levels were not evaluated [21]. CXCL1 belongs to the α-subgroup of chemokines. It binds to the CXCR2 receptor and induces chemotaxis of neutrophils, lymphocyte migration, and angiogenesis via endothelial cell migration and proliferation [22, 23]. It has been shown that the expression pattern of certain CXC chemokines and their receptors is upregulated in endometriosis patients and in ovarian carcinomas [24]. Furthermore, data exists on higher concentrations of CXCL1 (GRO-α) in the peritoneal fluid of patients with endometriosis compared to patients without endometriosis [5], suggesting the involvement of this factor in the pathogenesis of endometriosis, possibly by influencing the microenvironment of the peritoneal cavity. However, the circulating levels of this chemokine in endometriosis have not yet been investigated.

In this study, we investigated the levels of sCD40 Ligand and CXCL1 in endometriosis patients and controls in order to search for possible differences in secretion levels. Furthermore, the potential of these proteins to serve as biomarkers either for detecting the disease or for identifying certain subgroups was evaluated.

2. Materials and Methods

2.1. Patient Population and Surgery. The present prospective cohort study was conducted at the tertiary referral certified Endometriosis Center of the Medical University of Vienna and was approved by the institutional ethics committee of the Medical University of Vienna (EK 545/2010). Between December 2010 and April 2012, sixty premenopausal women who were scheduled to undergo laparoscopic surgery were included in the study after their verbal and written informed consent prior to study inclusion.

Included were premenopausal women between 18 and 50 years of age who were scheduled to undergo surgery due to suspected endometriosis, pelvic pain of unknown reason, adnexal cysts, an infertility workup, or leiomyoma uteri. Women who had received hormonal treatment orally for at least one month prior to surgery and/or intramuscularly for at least three months, as well as patients with any malignant disease, acute inflammation or infection, and systemic autoimmune disorders, such as systematic lupus erythematosus or rheumatoid arthritis, were excluded from the study. Patient characteristics are shown in Table 1. Serum samples were obtained preoperatively from the patients directly, in a fasting state, on the day of surgery. In addition, all patients were asked to fill in a questionnaire in order to evaluate their pain symptoms (visual analogue scale (VAS): 0 = no pain; 10 = excessive pain), which, together with patients' detailed anamnesis sheet, resulted in a very well-characterized patient cohort.

The presence or absence of endometriosis was confirmed visually by laparoscopy and additional histopathological analysis. All surgeries were performed by the same group of experienced surgeons, who are part of the endometriosis core working group in our department. Endometriosis was classified according to the revised American Fertility Society Score (rAFS) [25] and in case of deep infiltrating endometriosis by the ENZIAN score [26]. Patients without evidence of endometriosis were classified as controls. The menstrual cycle phase was evaluated by histological analysis of endometrial biopsy obtained from every patient via diagnostic dilatation and curettage (D&C). In unclear situations, the specification was based on hormonal analysis.

2.2. Sample Preparation. The collected blood was centrifuged according to our standard protocol at 3000 rpm for 10 minutes at 4 degrees Celsius, 30 min to one hour after sampling. The serum was stored at −80 degrees for further processing. The serum sCD40 Ligand and CXCL1 (GROα) concentrations were measured by enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' protocols. All experiments were performed in duplicate. The sCD40L-serum levels were measured using the commercially available human sCD40L Instant ELISA (Cat. number BMS239INST human sCD40L, eBioscience). Concentrations were measured in ng/mL. The CXCL1 serum levels were measured using the commercially available human CXCL1/GRO alpha Quantikine ELISA Kit in concentrations as pg/mL (Cat. number DGR00 Quantikine ELISA Human CXCL1/GROα Immunoassay, R&D Systems).

2.3. Statistical Analysis. The statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS, Version PASW 18.0, Chicago) and R-package software (Version 3.0.2). The distribution of the concentrations of the two measured variables differed from a normal distribution; thus, data was transformed to a logarithmic scale (log 10) for statistical analysis and graphical visualisation (in tables raw values are used). Data with a normal distribution is shown as mean ± standard deviation and was evaluated with the Student t-test. Categorical data is expressed as numbers (percentages) and was compared using the χ^2-test. A p value of <0.05 was considered statistically significant. The confidence intervals for the p value of <0.05 for multiple statistical analysis were set at the 95% level. For comparison between the two groups (endometriosis patients and controls), the median of the log 10 values with the interquartile ranges is shown in boxplots. The Mann-Whitney-Hugh test was used for the comparison between the two groups and the Kruskal-Wallis test for the comparison of more groups for categorical data.

3. Results

3.1. Patients with Endometriosis Have Lower BMI Compared to Controls. Before evaluation of the ELISA data, we looked at the clinical characteristics (Table 1) of our patient population and asked whether there is an association of clinical parameters with the disease. Interestingly, BMI differed significantly between endometriosis patients and controls ($p = 0.002$) in our study cohort of 60 Caucasian-origin patients (Table 1). The distribution of the individual endometriosis stages

Table 1: Patient characteristics.

Baseline characteristics of the endometriosis patients and controls			
Characteristic	Endometriosis, $n = 31$	Controls, $n = 29$	p value
Age	34.8 ± 6.9[a]	37.5 ± 6.9[a]	NS
BMI	21.8 ± 4.0[a]	25.6 ± 5.0[a]	.002
Dysmenorrhea	27 (87.1)	17 (58.6)	
Mild dysmenorrhea[b]	9 (29)	5 (17.2)	.013
Moderate-to-severe[b] dysmenorrhea	18 (58.1)	12 (41.4)	
Dyspareunia	18 (58.1)	12 (41.4)	
Mild dyspareunia[b]	9 (29)	2 (6.9)	NS
Moderate-to-severe[b] dyspareunia	9 (29)	10 (34.5)	
Cycle phase			
Proliferative	17 (54.8)	21 (72.4)	NS
Secretory	14 (45.2)	8 (27.6)	

Note. Values in parentheses represent percentages. NS: not significant.
[a]Values are given in mean ± standard deviation.
[b]Minimal/mild dysmenorrhea/dyspareunia covers VAS from 1 to 5 points, and moderate-to-severe dysmenorrhea/dyspareunia covers VAS from 6 to 10 points.

Table 2: Endometriosis patient characteristics. For lesion count, multiple citations are possible.

Endometriosis patient characteristics	
Number of patients (n)	$n = 31$
Peritoneal lesions	19 (61.3)
Ovarian lesions	4 (12.9)
Both types	8 (25.8)
Deep infiltrating endometriosis	13 (41.9) of total
rAFS stage	n
I	8 (25.8)
II	5 (16.1)
III	12 (38.7)
IV	6 (19.4)

Note. Values in parentheses represent percentages.

according to the rAFS system is shown in Table 2. Table 3 shows the mean and median values for sCD40L and CXCL1, as well as pain scores in the endometriosis and control groups. In accordance with previous findings, pain scores in the endometriosis group measured with the VAS were, by trend, higher than in the control group, although they did not reach statistical significance. Therefore, lower BMI and higher pain scores seem to be associated with endometriosis.

3.2. The sCD40L and CXCL1 Secretion Is Neither Disease Nor Menstrual Cycle Phase-Dependent. The Mann-Whitney-Hugh test revealed no statistically significant differences in log 10 sCD40L levels and log 10 CXCL1 levels between endometriosis patients and controls ($p = 0.223$ and $p = 0.78$, resp.) (Figure 1). Nevertheless, there was a slight trend toward a decrease in sCD40L levels in endometriosis patients. The levels of sCD40L and CXCL1 were further compared between controls, minimal-to-mild endometriosis patients (rAFS stage I + II), and moderate-to-severe endometriosis patients (rAFS stage III + IV), which, again, revealed no statistically significant differences between the groups ($p = 0.405$ and $p = 0.921$, resp.) (Figure 2).

To exclude the effect of the different patterns of expression due to differences in cycle phase-dependent regulation of both proteins in controls and endometriosis patients, we analyzed the data after dividing it into subgroups (proliferative versus secretory phase) and searched for cycle phase-specific differences in sCD40L and CXCL1 in controls and endometriosis. Although there seemed to be a trend toward slightly higher levels of both proteins in the proliferative phase compared to the secretory phase of the menstrual cycle in endometriosis patients and in controls (Figure 3), we did not see statistically significant differences associated with the cycle phase (sCD40L, $p = 0.340$ and CXCL1, $p = 0.626$, resp.). This suggests that there is no cycle phase-dependent regulation of sCD40L and CXCL1 secretion.

3.3. Patients with Deep Infiltrating Endometriosis Have Lower Serum sCD40L Levels Compared to Controls. As different types of lesion locations might influence the intensity of the inflammatory reaction, we tested whether the levels of sCD40L secretion correlate with the type of the lesion. For this purpose, we divided the endometriosis patients into different groups according to lesion location/type of lesion. A tendency toward a decrease in sCD40L levels in the endometriosis group was seen in accordance with the results of our analysis of all endometriosis patients. In the comparison between controls and endometriosis patients with deep infiltrating endometriosis ($n = 13$), there was a more pronounced difference in the decrease in sCD40L levels between the groups ($p = 0.059$) (Figure 4).

4. Discussion

Endometriosis is a disease characterized by the presence of permanent lesions and a continuous inflammatory reaction. Retrograde menstruation is seen as one of the main pathogenetic mechanisms, but as almost 90% of women show

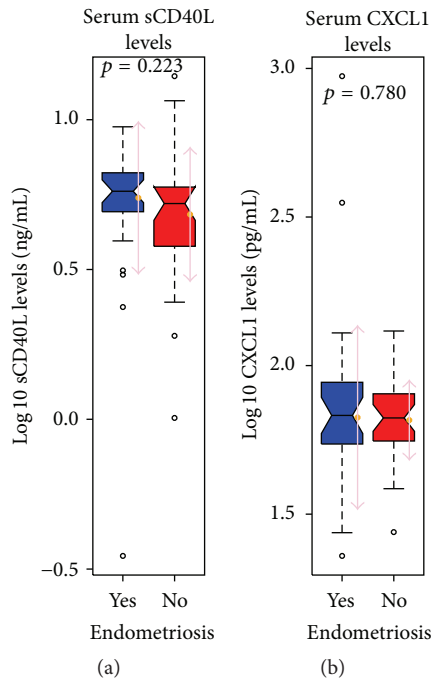

Figure 1: Patients with endometriosis did not show a statistically significant change in the serum levels of both sCD40L and CXCL1. Boxplots showing the comparison between the levels of expression of sCD40L (a) and CXCL1 (b) in serum of patients with endometriosis versus controls. The levels are presented as log 10 and the p values are indicated above each plot. Arrows next to the boxplots indicate mean ± standard deviation.

Table 3: Distribution of pain scores measured with the visual analogue scale (VAS), with values from 0 to 10 in endometriosis patients and controls plus serum levels of sCD40L and CXCL1 (numbers represent raw values).

	Serum values of sCD40L and CXCL1 and pain scores within groups		
Parameter	Endometriosis	Controls	p value
sCD40L[c]	5.38 ± 2.73[a] 5.25 (3.46–5.99)[b]	5.56 ± 1.83[a] 5.77 (4.93–6.69)[b]	NS
CXCL1[c]	68.57 ± 21.74[a] 66.65 (53.82–80.70)[b]	107.96 ± 170.85[a] 67.96 (49.96–90.03)[b]	NS
Dysmenorrhea	5.68 ± 3.45[a] 7.00 (3.00–8.00)[b]	4.07 ± 4.11[a] 3.00 (0.00–8.00)[b]	NS
Dyspareunia	3.13 ± 3.29[a] 3.00 (0.00–7.00)[b]	2.93 ± 3.75[a] 0.00 (0.00–6.00)[b]	NS

Note. NS: not significant.
[a]Numbers represent mean ± standard deviation.
[b]Numbers represent median and interquartile range.
[c]Concentration of sCD40L is given in ng/mL, and concentration of CXCL1 is given in pg/mL.

patterns of this phenomenon, a proinflammatory microenvironment must be in place in order to promote permanent lesion establishment [6, 27]. In previous studies, it was shown that several inflammatory mediators and proteins involved in angiogenesis are differently expressed between endometriosis patients and controls in the peritoneal fluid and in the tissue itself. Some publications reported differences in the serum values of certain interleukins, cytokines, and some angiogenic factors [28], all supporting the theory of a proinflammatory state that fosters the development and growth of endometriotic lesions [6].

In this study, we could not show statistically significant differences between the controls and endometriosis patients in the levels of the two investigated circulating proteins. Neither did we find significant differences in sCD40L and CXCL1 when looking at patient subgroups with different stages of the disease. Nevertheless, we could confirm the data from the work by Panoulis et al. [21], who could not show differences in the levels of CD40L-protein family in the serum of endometriosis patients compared to controls, using our well-characterized patient cohort. Furthermore, we showed that taking into account the stage of the disease

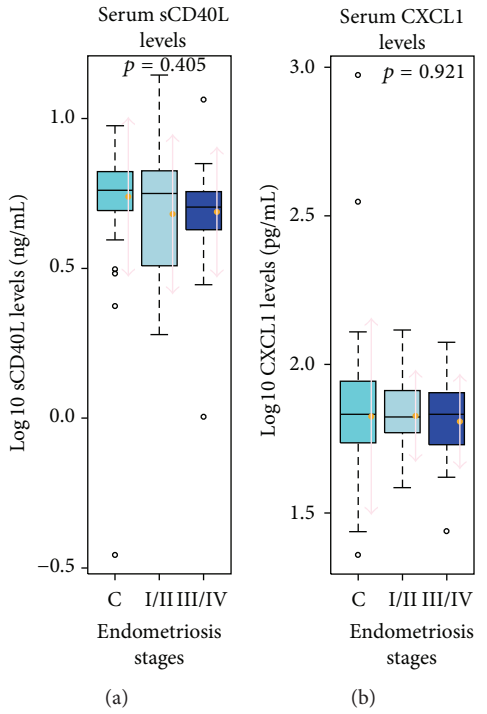

FIGURE 2: The sCD40L and CXCL1 secretion is disease stage independent. Levels of sCD40L (a) and CXCL1 (b) in the control group and based on the different stages of endometriosis classified by rAFS stage in the endometriosis patients, with no statistically significant differences. C: control group, I/II: endometriosis rAFS minimal-to-mild disease, and III/IV: endometriosis rAFS moderate-to-severe disease.

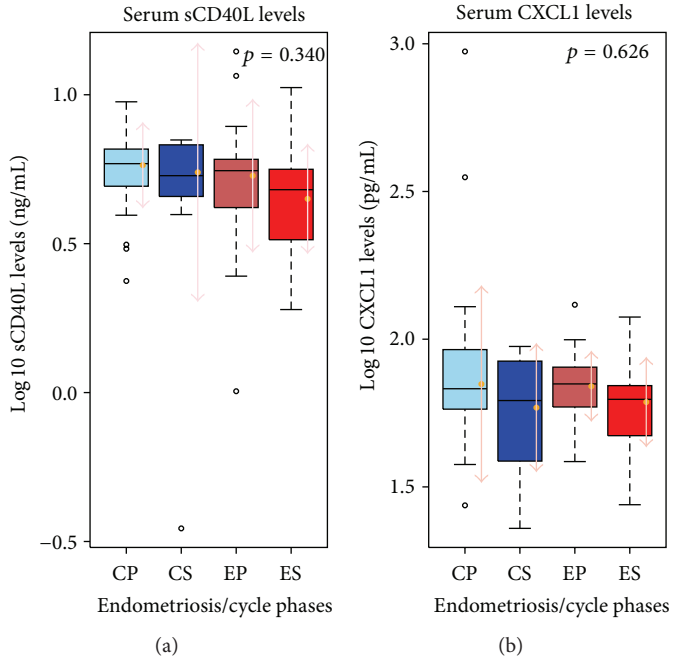

FIGURE 3: The serum levels of sCD40L and CXCL1 are not differentially regulated during the menstrual cycle in patients with endometriosis versus controls. Boxplots showing levels of sCD40L (a) and CXCL1 (b) among endometriosis patients and controls by menstrual cycle phases, with no statistically significant differences. CP: control proliferative phase, CS: control secretory phase, EP: endometriosis proliferative phase, and ES: endometriosis secretory phase.

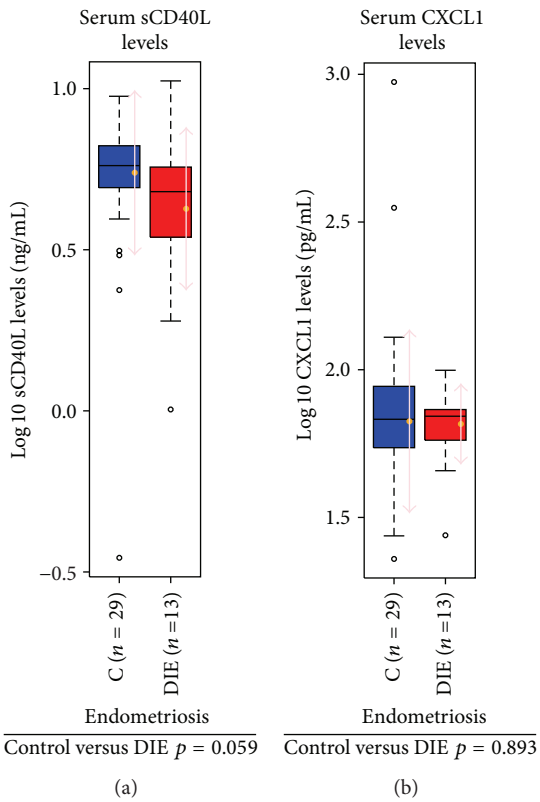

Figure 4: Patients with deep infiltrating endometriosis (DIE) show a tendency of reduced sCD40L levels and no changes in the levels of CXCL1 in serum when compared to controls. Boxplots showing levels of sCD40L (a) and CXCL1 (b) among controls and endometriosis patients with DIE. The number of samples for each group is given in brackets on the x-axis and the p values of the comparison between the groups are shown below each graph. C: control, DIE: deep infiltrating endometriosis.

is an important factor in endometriosis studies, which is sometimes neglected. Comparing the two groups of patients, control versus endometriosis patients, we found a trend toward a decrease in sCD40L levels in the endometriosis group, which almost reached the criteria of significance ($p = 0.059$) in the subgroup of patients who suffered from deep infiltrating endometriosis. This suggests a role for sCD40L in more severe cases of endometriosis where the local tissue damage, infiltration, and the initiated inflammatory reaction are more pronounced. As previously shown, CXCL1 is a useful marker in ovarian and cervical cancer and plays a role as a regulator of tumor homeostasis and vascularization and is a good marker for tumor-mediated systemic inflammation [29, 30]. However, our findings argue against the notion that CXCL1 has a function as a circulating regulator of systemic inflammation in endometriosis [5, 24].

It should be noted that, as with all relatively small cohort studies, our findings need to be interpreted carefully, as, in our patient cohort, the significantly different BMI between endometriosis patients and controls could have introduced a bias regarding the levels of circulating cytokine. To date, there is no information in the literature that discusses this possibility. Patients in the endometriosis group showed, overall, a lower BMI, which is in accordance with the data described by others linking endometriosis to a leaner body habitus [31]. In addition, the influence of BMI on the presence of endometriosis, especially in infertile patients [32], might also influence the severity of the inflammatory reaction (locally or systemically) and, consequently, possibly alter the symptoms of the patients. In the PCOS-study from Oktem et al. [20], this factor might have had an important impact on the observed changes in sCD40L levels, as all patients had high BMI values (both controls and endometriosis patients). In our study, the control group had higher BMI values and showed a tendency toward higher levels of sCD40L in the serum. Therefore, a future expanded analysis that includes a larger patient cohort will answer an interesting scientific question about whether the changes in serum sCD40L levels can be linked to advanced stages of endometriosis and whether and how the levels of this particular chemokine correlate with different BMI categories.

5. Conclusions

In conclusion, although we could not detect a statistically significant difference in sCD40L and CXCL1 levels between endometriosis patients and controls, this study adds useful clinical data showing the putative relationship between the levels of inflammatory related sCD40L protein and deep infiltrating endometriosis making it a potentially interesting target worth further investigation.

Competing Interests

The authors declare that they have no competing interests regarding the publication of this paper.

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Research Article

Epidemiology of Endometriosis in France: A Large, Nation-Wide Study Based on Hospital Discharge Data

Peter von Theobald,[1,2] Jonathan Cottenet,[3] Silvia Iacobelli,[1,4] and Catherine Quantin[3,5,6]

[1]*Centre d'Etudes Périnatales de l'Océan Indien (EA 7388), CHU de la Réunion, Site Sud, 97448 Saint-Pierre, France*
[2]*Department of Gynecology and Obstetrics, Hospital Felix Guyon, CHU de la Reunion, Site Nord, 9740 Saint Denis, France*
[3]*CHRU Dijon, Service de Biostatistique et d'Informatique Médicale (DIM) and Université de Bourgogne Franche-Comté, 21000 Dijon, France*
[4]*Néonatologie, Réanimation Néonatale et Pédiatrique, CHU de la Réunion, Site Sud, 97448 Saint-Pierre, France*
[5]*INSERM, CIC 1432 and Dijon University Hospital, Clinical Investigation Center, Clinical Epidemiology/Clinical Trials Unit, 21000 Dijon, France*
[6]*INSERM UMR 1181 "Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases" (B2PHI), University Bourgogne Franche-Comté, 21000 Dijon, France*

Correspondence should be addressed to Peter von Theobald; peter.vontheobald@chu-reunion.fr

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We aimed to assess the prevalence of hospitalization for endometriosis in the general population in France and in each French region and to describe temporal trends, rehospitalization rates, and prevalence of the different types of endometriosis. The analyses were carried out on French hospital discharge data and covered the period 2008–2012 and a population of 14,239,197 women of childbearing age. In this population, the prevalence of hospitalization for endometriosis was 0.9%, ranging from 0.4% to 1.6% between regions. Endometriosis affected 1.5% of hospitalized women of childbearing age, ranging from 1.0% to 2.4% between regions. The number of patients hospitalized for endometriosis significantly increased over the study period ($p < 0.01$). Of these, 4.2% were rehospitalized at least once at one year: ranging from 2.7% to 6.3% between regions. The cumulative rehospitalization rate at 3 years was 6.9%. The types of endometriosis according to the procedures performed were as follows: ovarian (40–50%), peritoneal (20–30%), intestinal (10–20%), and ureteral or bladder (<10%), with significant differences between regions. This is the first detailed epidemiological study of endometriosis in France. Further studies are needed to assess the reasons for the increasing prevalence of endometriosis and for the significant differences in regional prevalence of this disease.

1. Introduction

Endometriosis is a frequent illness in young women between 15 and 49 years of age. Its prevalence is estimated at 10 to 50% in the literature [1–3] but no well-conducted nationwide epidemiological studies are available. Its etiology is unknown. Focal ectopic endometrial cells are located mainly in the pelvis, causing intra-abdominal bleeding, inflammation, adhesions, and retractions due to fibrosis. The main symptoms are pelvic pain (dysmenorrhea, dyspareunia, painful defecation or micturation, and painful ovulation) and infertility (due to fallopian tube lesions, adhesions, or direct toxicity of cytokines released by the ectopic cells). Complications such as bowel occlusion, hydroureteronephrosis, ovarian abscess, rectorrhagia, and hematuria may occur. The symptoms are of variable intensity and not always proportional to the extent of the illness. The disease is frequently asymptomatic [3]. The main types of endometriosis are ovarian endometriosis (endometriomas), peritoneal endometriosis, bowel endometriosis, and ureteral and vesical endometriosis.

They are frequently found in association depending on the extent of the disease. Less frequently, endometriosis may involve the diaphragm, the pleura, the mediastinum, or the meninges. Diagnosis is difficult and is mainly based on the symptoms, vaginal ultrasound, and MRI imaging, with a delay of 4 to 11 years between the first symptom and diagnosis [4–6]. Diagnosis can only be confirmed by surgery, in most cases by laparoscopy followed by a pathology assessment. Endometriosis is a chronic disease with a recurrence rate of 25 to 50% after conservative treatment [7–9].

As hospitalization as well as surgical investigation is mandatory for the diagnosis, which frequently initiates treatment and involves the most symptomatic patients, we looked at the French hospital discharge database and the Programme of Medicalisation of Information System (PMSI) to assess the prevalence of hospitalization for endometriosis in the population of France. Our main objective was to assess the prevalence of hospitalization for endometriosis in France and in every region of France. Our other objectives were (i) to assess temporal trends in the number of patients, (ii) to assess rehospitalization rates, and (iii) to describe the prevalence of the different types of endometriosis in every French region.

2. Materials and Methods

2.1. Programme of Medicalisation of Information System. PMSI was established in France in 1991 and extended in 1997 to all French healthcare facilities [10]. It has compiled discharge abstracts for every admission since 2008 and is an instrument for the financial management and each hospital's budget, which depends on the medical activity described in the PMSI. Diagnoses identified during the admission are coded according to the 10th edition of the international classification of diseases (ICD-10).

All procedures performed during the hospitalization are coded according to the French Common Classification of Medical Procedures (CCAM). Each hospital produces its own anonymous standardized data, which are then compiled at the national level. PMSI provides a huge amount of epidemiological information concerning hospitalized French patients [11–19].

2.2. Study Design. PMSI abstracts for all patients discharged between 1 January 2008 and 31 December 2012 with a main or associated diagnosis ICD code for endometriosis (N800 to N809) were extracted from the national database. Patients were then separated according to the French region they lived in so as to map the prevalence of endometriosis. Only the first hospitalization was considered and rehospitalizations were analyzed separately. Patients were localized according to their postal code of residence (to assess the prevalence among 15–49-year-old females of each region and the prevalence among 15–49-year-old female patients admitted to hospital).

In all patients with a main diagnosis of endometriosis alone (N800 to N809), we identified the rate of procedures performed during hospitalization or in the following year with the codes of the CCAM. We defined "specific procedures" related to the most frequently involved organs like the peritoneum, bowel, ureter, bladder, and ovaries and quoted the proportion of each specific procedure among all procedures (Table 1).

Table 1: List of codes for the "organ specific procedures."

Procedures addressing	CCAM codes		
Peritoneal endometriosis	HPNA001		
	HPNC001		
Bowel endometriosis	JFFA012	HHFA009	HJCA001
	JFFA014	HHFA010	HJCC001
	JFFC001	HHFA011	HJFA002
	HHFA002	HHFA014	HJFA004
	HHFA006	HHFA016	HJFA011
	HHFA008	HHFA017	HJFA017
Ureteral endometriosis	JCCA003		
	JCCC003		
	JCEA001		
	JCEA002		
	JCEA003		
	JCEA005		
Vesical endometriosis	JDFA011		
	JDFA017		
	JDFC023		
	JDCA003		
	JDCC016		
Tubo-ovarian endometriosis	JJFA002	JJFC003	
	JJFA003	JJFC004	
	JJFA004	JJFC006	
	JJFA005	JJFC008	
	JJFA007	JJFC009	
	JJFA008	JJFC010	
	JJFA010		

2.3. Statistical Analysis. The Chi square test was used to compare the prevalence of hospitalization among regions and to compare the specific procedure rates with the total procedure rates.

To evaluate trends in the number of women with endometriosis from 2008 to 2012, we used a Poisson regression.

2.4. Ethics. This study was approved by the National Committee for Data Protection (registration number 1576793). Written consent was not needed for this study. The data from the PMSI database were transmitted by the national agency for the management of hospitalization data (ATIH number 2015-111111-47-33).

3. Results

Hospitalization for a diagnosis (main or associated) of endometriosis occurred in 0.9% of women of childbearing age (between 15 and 49 years of age) in France during the study period. In fact, in a total population of 14,239,197

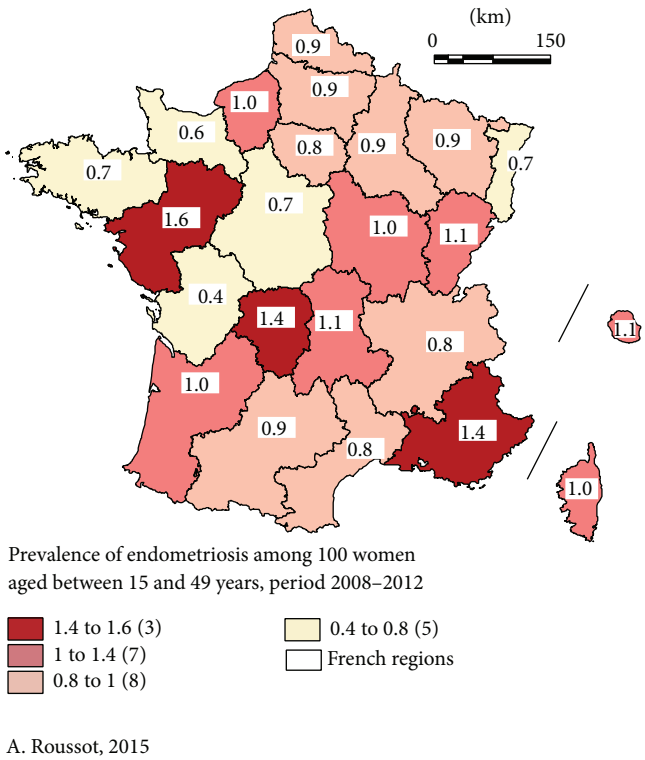

Figure 1: Prevalence of patients hospitalized for main or associated diagnosis of endometriosis in the general population.

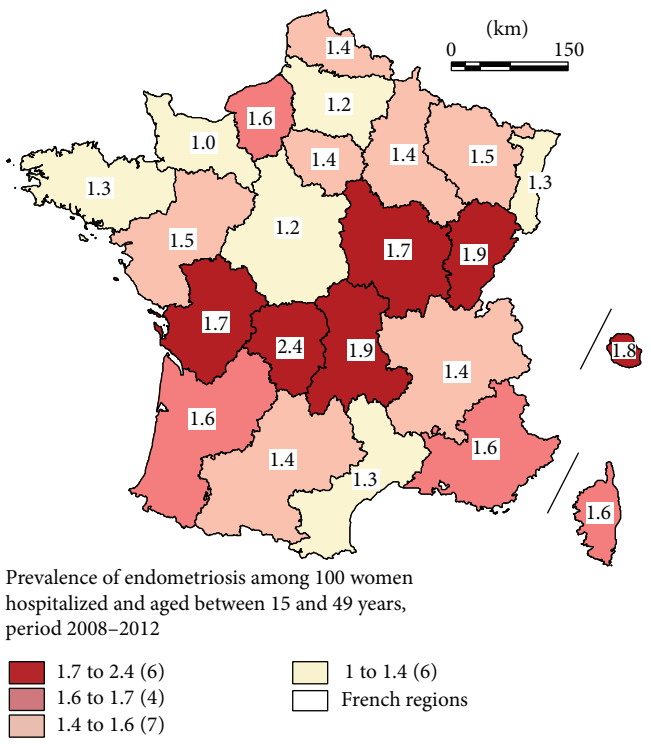

Figure 2: Prevalence of patients hospitalized with a main or associated diagnosis of endometriosis in hospital.

women of childbearing age in France, 125,178 patients were hospitalized at least once for endometriosis between 2008 and 2012.

The prevalence of hospitalization for endometriosis in the general population according to region ranged from 0.4% (Poitou-Charentes) to 1.6% (Pays de la Loire) (Figure 1).

The prevalence in hospital varied in the same way (Figure 2).

Endometriosis was diagnosed in 1.5% of hospitalized female patients between 15 and 49 years of age, ranging from 1.0% (Basse-Normandie) to 2.4% (Limousin). Comparing Figure 1 (prevalence in the general population) and Figure 2 (prevalence in hospital), evident differences appear. For instance, the regions Pays de la Loire and PACA had the highest prevalence in the general population but a lower prevalence in hospital, and the region Poitou-Charentes had the lowest prevalence in the general population but an above-average prevalence in hospital ($p < 0.01$).

The mean age of the 125,178 patients was 37.9 ± 8.0 years.

Concerning trends, the number of patients hospitalized for endometriosis increased significantly ($p < 0.01$) from year to year: from 26,492 in 2008 to 28,322 in 2012 (+6.9%), while the population of women between 15 and 49 years of age decreased from 14,455,332 in 2008 to 14,239,197 in 2012. Every year, in France, about 458 more patients were hospitalized for endometriosis although the population of women between 15 and 49 years of age fell by an average of 54,034 per year. Of these patients, 4.2% were rehospitalized at least once at one year during the study period, ranging from 2.7% (region Bretagne) to 6.3% (region Ile-de-France). The cumulative rehospitalization rate in France was 4.1%, 5.6%, and 6.9% after 1, 2, and 3 years, respectively, taking into account the fact that all of the patients during the period 2008–2010 had the necessary follow-up of 3 years. The types of endometriosis according to the procedures performed are shown in Figure 3. There were 40 to 50% of ovarian procedures, mainly removal of endometriomas, 20 to 30% were procedures for peritoneal lesions, 10 to 20% concerned extension of the endometriosis to the bowel, and less than 10% were procedures to cure ureteral or bladder endometriosis. Here again, the rates varied between the regions.

4. Discussion

This paper presents the results of the first French study on the epidemiology of endometriosis in a national population-based setting. Few well-conducted studies have reported data on the prevalence of endometriosis and no data are available on its incidence in women without a previous diagnosis [20–22]. Available data consist of prevalence estimates of diagnosed disease among selected hospital or clinical populations (infertile patients, patients with pelvic pain, etc.) and differences in the reported prevalence of the disease vary by as much as 30–40 times [21–23]. For instance, studies

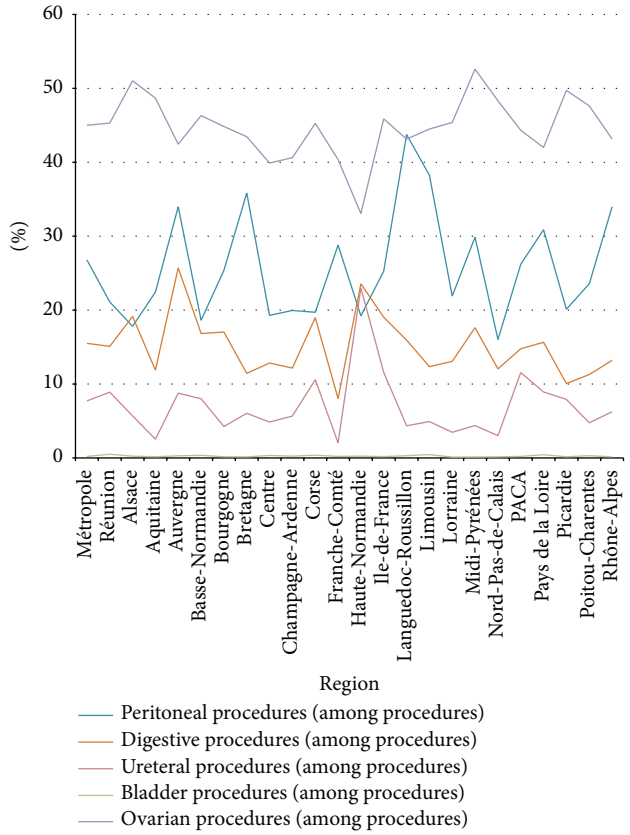

Figure 3: Type of endometriosis according to the procedures performed (% among procedures).

that analyzed the frequency of endometriosis in women who underwent surgery for fibroids suggested a prevalence of endometriosis of about 10% [24], but women with fibroids might share the same risk factors as those for endometriosis [25]. Other explanations for these large variations include differences in the indications for surgery, the differing degrees of attention paid by surgeons to the accurate identification of endometriotic lesions, and selective mechanisms that draw patients with suspected endometriosis towards specialized centers [2, 3, 20].

Formal estimates of the prevalence of pelvic endometriosis in the general female population are lacking [21]. In the literature, there is only one rather old study, somewhat similar to our current work. It is based on diagnoses for patients discharged from short-stay nonfederal hospitals in the United States [26]. This study reported that in 1980 endometriosis was a first-listed diagnosis for 97,000 hospital discharges in females between 15 and 44 years of age.

This figure represented 0.9% of all first-listed diagnoses, 1.3% of all first-listed diagnoses minus deliveries, and 6.3% of all first-listed diagnoses of diseases of the genitourinary system (International Classification of Diseases- (ICD-) 9-CM codes 580–629) for females between 15 and 44 years of age. In 1980, women between 15 and 44 years of age in the United States spent an estimated 582,000 days in short-stay nonfederal hospital for health problems for which endometriosis was the first-listed discharge diagnosis. In another study, the annual cost of endometriosis in the United States in 2002 was estimated at $18.8 to $22 billion [23]. In a recent meta-analysis, the overall direct inpatient costs for patients diagnosed with endometriosis were estimated at $12,644 per patient based on the 2002 HCUP database [27]. Our team intends to conduct a further study to estimate the cost of endometriosis in France.

Beyond medicoeconomic studies, it may be interesting to compare the characteristics of regions with very high or very low prevalence in order to identify etiological factors or, at least, risk factors, like the population, pollutants, food habits, or other extrinsic factors. Many of these, mainly pesticide components [28] or other chemicals even in sun lotions [29], have been suspected and assessed in the literature. Of course, genetic factors may also be involved. According to the literature, 30% of endometriosis patients have a family history of endometriosis [30]. Comparison with other countries using the same discharge data system would be interesting as the prevalence in this study already ranges from 0.4% to 1.6% within a single country and as these differences were stable over 5 years.

Our study revealed some marked differences in several regions with regard to prevalence in the general population compared with prevalence in hospital.

These differences were due to other diseases responsible for hospital admissions in the same group of female patients aged 15–49 years, diseases that vary from one region to another. They may also have been caused by the selection of patients: surgery for endometriosis has to be performed in reference centers with a specially trained multidisciplinary team and every region does not have such a surgical department. This means that the two figures give different but complementary information about the prevalence of endometriosis. Our in-hospital prevalence can be compared to the prevalence calculated in the previously cited North American National Center for Health Statistics in 1982 [26]: endometriosis represented 0.9% of all first-listed diagnoses and in our study, 30 years later on another continent, it was 1.5%. Unfortunately, we do not have the numbers in our population in 1982, but we can suppose that the difference could be explained by the increasing trend found in our series and, possibly, by the improvement in healthcare facilities (imaging techniques, laparoscopy, etc.). It may be surprising that, every year from 2008 to 2012, about 458 more patients were hospitalized for endometriosis even though the population of women between 15 and 49 years of age fell by 54,034 per year over the same period in France. As hospitalization concerns only the most symptomatic patients (pain, infertility, and complications), it seems likely that the improvement in imaging techniques is not the main explanation for this significant trend, because asymptomatic or paucisymptomatic patients do not undergo surgery. Either tolerance to symptoms like pain or infertility is decreasing in a society where quality of life is improving (and quality of life is severely impaired by endometriosis [5]) or this illness is really becoming more and more frequent. Our study cannot answer this question but it underlines the notion that if there are more patients in hospital, the cost

of endometriosis will rise. Our study shows the relative frequency of the different types of endometriosis resulting in hospitalization in a nonselected population, or more exactly the entire population of a whole country: the most frequent were ovarian and peritoneal endometriosis. No other reports in the literature based on nationwide data collection describe the proportion of operations related to each pelvic organ involved. It might be interesting to compare our findings with those in other countries to see if the relative proportions are the same or if endometriosis has different patterns. There may be different types of endometriosis, possibly related to different etiologic factors in different geographic areas. The rehospitalization rate increased with time: after 3 years, 6 to 7% of women had been back in hospital. Our study cannot say whether this was due to a complication, a recurrence, or another reason like in vitro fertilization, for instance. In the literature, recurrence rates vary between 10 and 56% after 5 years [31, 32] and our rehospitalization rate may appear very low compared with published recurrence rates. However, many recurrent patients do not undergo repeat surgery but are treated medically at home.

There may be some limitations to our study. Given the reliance on ICD-10 codes for the selection of patients and the ascertainment of outcomes, there was a potential for underdetection-related biases for endometriosis even though this disease, when diagnosed, is considered debilitating by gynecologists and thus coded. Coding practices may vary among institutions. Nevertheless, coding quality is checked by medical information professionals in each hospital to correct diagnoses and to increase the recorded comorbidity level. Moreover, as many patients are not admitted to hospital, this study did not assess the prevalence of endometriosis in the whole population but only the prevalence of hospitalization for endometriosis. In fact, the diagnosis of endometriosis is very difficult and frequently delayed [4–6, 23]. This may explain the age of the patients at the time of their hospitalization (almost 38 years). Studies have shown the existence of asymptomatic forms of endometriosis [3, 33–35]. On the other hand, many endometriotic patients suffer from comorbidities, such as adenomyosis, irritable bowel syndrome, and interstitial cystitis, which can all contribute to the symptomatology. The diagnosis of endometriosis can only be confirmed at surgery (usually laparoscopy) as there are no noninvasive diagnostic methods to effectively screen for endometriosis. Pelvic ultrasound and MRI may lead to a suspicion of the disease and sometimes quantify its invasiveness, but these are limited to moderate or severe forms of the disease and are not suitable for the detection of minimal or mild endometriosis. No biomarker has been identified to date [23]. This means that assessing the prevalence of endometriosis in the general population is very difficult because of the complexity of the diagnosis; it may thus be underestimated. The prevalence obtained from the discharge data is interesting because it concerns only the most symptomatic patients, who require hospitalization and thus have surgical proof of endometriosis. These data are robust and are not based on selected categories of patients; they reveal trends in disease prevalence and make it possible to calculate hospital inpatient costs. Another limitation concerns the difficulty of analyzing all of the factors that may explain differences between the French regions. Further research may be needed, including local investigations to collect information that is not available in our data.

5. Conclusion

This nationwide study is the first French study to estimate the prevalence of hospitalization for a main or associated diagnosis of endometriosis in each region of the country (0.4% to 1.6%). It revealed a significant trend towards an increase in hospitalizations for endometriosis in France with time. This study also provides information about the relative proportion of procedures for the different types of endometriosis and addresses the question of rehospitalization. This work may be considered the first of many more-detailed epidemiological studies of endometriosis in France in order to study risk factors and to assess the cost of endometriosis in France.

Competing Interests

The authors declare that they have no competing interests.

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