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DISSERTATION

***Surgical outcome in patients with complex deep infiltrating
Endometriosis***

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von

Elene Abesadze
aus Tiflis, Georgien

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1 Abstract

1.1 In englischer Sprache

Background:

Endometriosis (EN) is the most common gynaecological disease, presented by the presence of endometrial-like tissue outside the uterine cavity. It is still poorly understood and not so widely investigated, although endometriosis was first described in 19th century. Till nowadays the etiology and the pathophysiology of EN is unclear and so far, there is no clear statement about the treatment of EN. One of the reasons is complex anatomical dissemination of the lesions. Endometriosis is categorized in three different phenotypes: ovarian endometrioma, superficial peritoneal endometriosis and deep infiltrating endometriosis (DIE). DIE is the most severe form of this disease with an estimated prevalence in 8–12% of women with EN and in 1% of all women in reproductive age.

Methodology:

This study encloses seven-year data of the patients with DIE in their reproductive age, who underwent organ sparing surgery. These patients were divided in 3 different groups according to the anatomical manifestation of DIE. The first group of n=148 comprised patients with central (CPE) and lateral pelvic endometriosis (LPE) including n=41 cases of deep lateral pelvic endometriosis (dLPE) affecting sacral plexus. The second group enclosed n=34 patients with rectovaginal (RVE) and retrocervical endometriosis (RCE). N=54 patients were enrolled in the third group with complex DIE involving posterior compartment peritoneum (PCPE). The database was made based on clinical history, surgical technique, intra-operative findings, pre- and postoperative questionnaire and postoperative follow-up, enclosing EN-related symptoms, complications, fertility rate and recurrence rate. Final results were evaluated by visual analog scale (VAS), numerical rating scale (NRS) and statistical analysis Graph pad Prism 5.

Results:

In general, all three study groups demonstrated postoperatively improvement of EN-complaints, fertility rate and low rate of complications. The intensity of the symptoms was analysed by VAS score (pain scale system from 0-10). First group of patients with dLPE demonstrated median VAS score drop for EN-related symptoms from 5-8 to zero and only n=3 recurrences postoperatively. Second group with RVE and RCE endometriosis reported

completely symptom free status in n=18 patients (53%), zero recurrence and n=12 postoperative pregnancies (from n=17 patients with primary or secondary infertility preoperatively). Third group, with complex DIE accompanied by posterior compartment peritoneum EN showed also complete absence of EN-related symptoms postoperatively in n=36(67%) patients. N=28 women seeking fertility had a high rate of postoperative fertility, reporting n=12(43%) successful pregnancies.

Conclusion:

Proper clinical diagnosis could limit disease development and prevent the delay in time of diagnosis. But for patients with already existing DIE, choosing an appropriate treatment strategy including surgical technique is crucial to avoid further EN progression and improve their quality of life.

1.2 In deutscher Sprache

Einführung:

Endometriose (EN) ist die am häufigsten auftretende gynäkologische Erkrankung, welche sich durch die Präsenz von Endometrium-artigen Geweben außerhalb der Gebärmutterhöhle manifestiert. Die Erkrankung wird bis heute noch schwer erkannt und wenig erforscht, obwohl die erste Beschreibung der Endometriose bereits im neunzehnten Jahrhundert erfolgte. Die Etiologie und Pathophysiologie der EN sind bis heute unklar, und bisher ist die Behandlung der EN nicht klar definiert. Einer der Gründe dafür ist die komplexe Verteilung der Läsionen. Die EN wird in drei Phänotypen kategorisiert: die EN des Ovars, die oberflächliche EN des Beckenperitoneums und die tiefinfiltrierende EN(TIE). Letztere stellt die schwerste Form der EN mit einer geschätzten Prävalenz von 8 bis 12% der von EN betroffenen Frauen dar und 1% von allen Frauen im reproduktiven Alter.

Methodik:

Diese Studie umfasst 7 Jahren Daten von Frauen im reproduktiven Alter, die organerhaltende Eingriffe erhielten. Die Patientinnen wurden entsprechend der anatomischen Manifestationen der EN in drei Gruppen eingeteilt. Die erste Gruppe mit n=148 bestand aus Patientinnen mit zentraler(CPE) und lateraler Becken-EN(LPE), einschließlich n=41 Fälle von tiefer lateraler EN(dLPE), welche auch den Plexus sacralis betrafen. Die zweite Gruppe umfasste n=34 Patientinnen mit rektovaginaler(RVE) und rektozervikaler EN(RCE). In die dritte Gruppe wurden n=54 Patientinnen mit TIE aufgenommen, welche auch das posterior Peritoneumkompartiment(PCPE) beinhalten. Die Datenbank wurde basierend auf der Anamnese, der operativen Technik, den intraoperativen Befunde, den prä- und postoperativen Patientenfragebogen und dem postoperativen Follow-up angefertigt und enthält EN-bezogene Symptome, Komplikationen, Fertilitätsrate und Rezidivrate. Die Resultate wurden mittels der visuellen Analogskala(VAS), der Numerische Rating-Skala(NRS) und einer statischen Analyse mit GraphPad PRISM 5 präsentiert.

Resultate:

Im Allgemeinen wiesen alle drei Gruppen postoperativ eine Verbesserung der EN-bezogenen Beschwerden, der Fertilitätsrate und eine niedrige Rate an Komplikationen auf. Die Intensität der Symptome wurde mit der VAS auf einer Schmerzskala von Null bis zehn dargestellt, dabei fiel dieser Wert in der ersten Gruppe mit dLPE postoperativ von fünf bis acht auf Null, außerdem lag die Rezidivrate hier bei n=3. In der zweiten Gruppe mit RVE und RCE waren n=18(53%) Patientinnen komplett symptomfrei, die Rezidivrate lag bei Null und es zeigten sich n=12 postoperative Schwangerschaften (von n=17 Patientinnen, welche preoperativ

primär oder sekundär unfruchtbar waren). In der dritten Gruppe mit PCPE berichteten n=36 (67%) Patientinnen postoperativ keine EN-bezogenen Symptome. N=28 Frauen mit Kinderwunsch hatten eine hohe postoperative Fertilitätsrate mit n=12(43%) erfolgreichen Schwangerschaften.

Fazit:

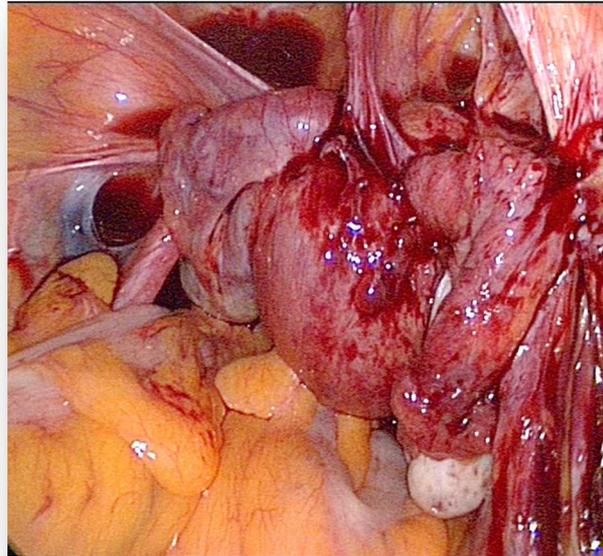
Eine angemessene klinische Diagnostik hat das Potential, den Krankheitsverlauf zu begrenzen und Verzögerungen im Diagnoseverlauf zu verhindern. Allerdings ist bei Patientinnen mit bereits bestehender TIE die passende Behandlungswahl einschließlich chirurgischer Eingriffe entscheidend um weitere EN-Progression zu vermeiden sowie ihre Lebensqualität zu verbessern.

2 Introduction

Endometriosis (EN) affects 10-20 % of women within their reproductive age (Giudice, 2010), impacting their physical, mental, and social well-being. Endometriosis is still not fully understood, affecting women, therefore underestimated, and not so widely investigated. Another issue is a delay of the diagnosis (Hudelist et al., 2012, Arruda et al., 2003). The median time between onset of first symptoms and exact diagnosis/treatment is approximately 7 years (Husby et al., 2003). The absolute number of diagnosed and unknown endometriosis cases of German women lay in between 1.77- 3.54 million (Ulrich et al., 2014) and worldwide 176 million (G. David Adamson, 2010). Endometriosis is a challenging and frequently frustrating clinical problem for the gynecologist. The population of women being studied has a significant effect on the prevalence estimates of endometriosis. Another main problem is recurrence, which for example in Germany appears in 50-80% of Endometriosis patients after surgical treatment (Schweppe and Ring, 2002). Since the first characterization of endometriosis by John Sampson in 1921, various groups of researchers tried to reach a consensus regarding the pathogenesis, mechanism of morbidity, and management of this condition. The complexity of this disease and the short comings in our knowledge base conspire to make our approach to the patient more difficult. Endometriosis is an estrogen dependent chronic inflammatory disease, generally located in, but also outside, the pelvis where it can interfere anatomic, hormonal, immunologic environment, and neurogenic environment (Kim and Adamson, 1999, Mechsner et al., 2010, Mechsner et al., 2009) (Chiantera et al., 2018). Endometriosis is very current clinical issue since it often causes pain, dysmenorrhea, dyspareunia, non-cyclical pelvic pain, infertility, and bleeding disorders. As a chronic disease, it importantly affects quality of life, sexual and psychological health (Moradi et al., 2014). In 70% of women affected by Endometriosis, the diagnosis starts with the clinical history and is often confirmed by a pelvic examination, transvaginal ultrasound, and sometimes by Magnetic resonance imaging (MRI). Within society most women think that during the menstruation phase the appearance of pain shortly before and during the secretory phase is a rather normal thing. However, the use of painkillers and 2-3 days per month spent in bed is already a hint towards a malfunction, which is rarely identified by most of the gynecologists. Typically, EN is diagnosed in patients at age between 25 and 35 years (Buck Louis et al., 2011), but endometriosis occurring in premenarchal girls (Dessole et al., 2012) and postmenopausal women (de Almeida Asencio et al., 2019) has been reported as well.

Nowadays, from the three different types of endometriosis (superficial peritoneal, ovarian and deep infiltrating EN) the most severe form is deep infiltrated endometriosis (DIE), described as > 5mm infiltration of the peritoneum (Koninckx and Martin, 1992). Interestingly, at the

beginning DIE was defined as a adenomyosis externa (Cornillie et al., 1990). 10% of women diagnosed with this Endometriosis have the deep infiltrating form (Seracchioli et al., 2007). This type of endometriosis is very complex and therefore requires thorough anatomical knowledge of the pelvic floor and specific technical experience. This process could involve several anatomical structures at the same time (Fig.1): the uterus (Endometriosis lesions inside of uterus muscular tissue, this condition is the main reason of sterility), pelvic wall, bladder, cervix, rectum and sigma with infiltration of muscular tissue, lumbo-sacral nerves, and diaphragm (Vercellini et al., 2004), is usually associated with severe symptoms and constitutes a complex treatment (Carmona et al., 2012). As of today, surgery is acknowledged worldwide as the gold standard treatment for DIE (Arcoverde et al., 2019). However, the main question is which surgical technique is more appropriate? This study focused on the application of new, minimally invasive surgical techniques combined with hormonal therapy and postoperative outcome of the patients with DIE, as the data regarding this topic remains poorly investigated.



3 Materials and Methods

The main aim of this research was to observe and analyse preoperative findings, surgical technique, and postoperative outcome in three different groups of patients with various expressions of deep infiltrated endometriosis. The mean age for these patients was 34 years (± 5.4), the women with DIE in their reproductive age, undergoing mainly organ-sparing surgery in our department between 2010 and 2018. , three study groups were formed according to disease localization: a) n=148 patients with central pelvic endometriosis (CPE) and lateral pelvic endometriosis (LPE), in this group mainly focusing on n=41 women with deep LPE (dLPE), b) n=34 patients with rectovaginal/rectocervical (RVE/RCE) and c) n=54 patients with complex DIE affecting posterior compartment peritoneum (PCP) as well (Fig.2). The surgical technique was divergent for each manifestation of EN. The criteria for the study group selection were clearly defined and it will be explained later. But the methods of

evaluation of clinical data including preoperative findings, intraoperative and postoperative findings were same for each groups, including:

- a) clinical history of patients collected in the outpatient clinic of the Endometriosis Centre Charité including preoperative EN-related complaints, fertility, EN-recurrence, previous treatments (conservative or operative).
- b) preoperative questionnaire based on the VAS score, defining the intensity of EN-related symptoms like dysmenorrhea (pain in the pelvis, before or during the menstrual period.), dysuria (painful urination), dyschezia (painful defecation), dyspareunia (painful sexual intercourse), chronic pelvic pain, cyclical pelvic pain, sciatica (pain affecting the back, hip, and outer side of the leg, caused by compression of a spinal nerve root in the lower back), and paraesthesia (an abnormal sensation, typically tingling or pricking 'pins and needles', caused chiefly by pressure on or damage to peripheral nerves).
- c) Preoperative diagnostic methods like common gynecological examination, ultrasound, MRI and endosonography.
- d) Intraoperatively the anatomical localization and severity of EN was categorized with the revised American society of reproductive medicine score (rASRM) and the classification of Deep Infiltrating Endometriosis score (ENZIAN) (Tuttlies, F.,2015, Haas, D.,201ö3, Johnson, N.P.,2017).
- e) Surgical treatment was always individual to every group of the patients. DIE is complex, involving many organs at the same time and the aim of each and every surgical tactic was to remove as much of the endometriosis tissue as possible whilst preserving the functionality of affected organs.
- f) postoperative outcome including intraoperative complications, early postoperative complications, and recurrence rate.
- g) postoperative EN-related symptoms were evaluated by the interviewing study patients in our outpatient clinic or by the phone-interview. The questionnaire was composed of questions regarding symptoms related to dysmenorrhea, dyspareunia, dyschezia, chronic pelvic pain and cyclic pelvic pain, and was later evaluated using the VAS and Numerical rating scale (NRS).
- h) postoperative pregnancies were recorded based on the medical history, as all the study patients visited our outpatient clinic within 6 months for the control examination.
- i) Moreover, the methods of fertilization were also captured: spontaneous pregnancy or assisted fertilization and postoperative miscarriage as well.
- j) The evaluation of the preoperative database, intraoperative status, postoperative outcome, and efficacy of surgical procedures were summarized by the statistical

analysis. Here we used Graph pad Prism 5 with p value test and t nonparametric test. As first research was a collaborative work, here was used SPSS Software 18 including the Pearson Chi-square exact test and Kruskal-Wallis test. Overall, data analysis included age, pre-operative and postoperative complaints, operative procedures, recurrence rate, complications, fertility rate. This analysed the divergence between pre- and postoperative findings.

3.1 Study criteria and surgical technique

Table. 1	CPE/LPE/ n=148	dLPE n=41
Mean time of the follow-up, y (±SD)	3 years (±1,3)	3 years (±1,3)
Mean age of the patients, yr (±SD)	35 (±3)	35 (±3)
Preoperative hormonal treatment, n (%)	40 (27.3%)	*
Pre-operative Infertility rate n (%)	*	*
Adenomyosis n (%)	30 (44%)	*
Previous surgery for endometriosis, n (%)	*	*
Procedures		
The mean time of the operation	4-3hours	4-3hours
Retrocervical EN excision n (%)		
Rectovaginal EN excision n (%)	29 (70.7%)	*
Vaginal dissection of EN n (%)	28 (68.3%)	*
Cyst-excision n(%)	15 (10%)	15 (37%)
Partial bowel resection n(%)	82(55%)	29 (70.7%)
Protective ileostomy	11 (7%)	11 (27%)
Partial bladder resection n(%)	9 (6%)	9 (22.0%)
Neurolysis n(%)	73 (48%)	41 (100%)
Ureterolysis n(%)	92(62.2%)	37 (90.2%)
Peritonectomy	116 (78%)	36 (87.8%)
Adnexectomy	88 (59%)	13 (32%)
Appendectomy	*	*
Diaphragm resection	*	*
Lymphadenectomy	*	*
Umbilicus partial resection	0	0
Follow-up		
Symptom free status postoperatively n (%)	129(87%)	31(76%)
Postoperative Pregnancy n=	*	*
Recurrence, n	13 (8,8%)	10 (24%)
Complication (%)	17(11%)	10(17%)
° SD - standard deviation		
* Not investigated		

The first group of patients n=148 with CPE and LPE enclosed n=41 women with dLPE/Tab.1). dLPE affected the area of parametrium, urether, hypogastric and sacral plexus, with or without plexus infiltration. This type of EN manifestation is quite common, but still not widely investigated. Nerve infiltration with EN can be overly complex, therefore not frequently operated on, as it needs experienced surgical team trained in neuropelveology. The idea of this investigation was to analyze the efficiency of Laparoscopic Neuro-Navigation (LANN) technique in patients with LPE and mostly with deep infiltration. The intention of this chosen treatment was to excise

as much EN-lesions as possible, even on the terms of nerve infiltration not damaging the functionality of the organs innervated from this exact nerve fibers (like bladder, rectum, musculoskeletal system and etc.). This study was a part of collaborative research and we worked here together with the Italian group from University of Palermo. From n=148 patients

with both central and lateral EN focus was on the patients with dLPE. LANN technique is based on the laparoscopic exposure and nerve-sparing method (neurolysis). As dLPE was presented by the infiltration of lateral pelvic structures, the dissection started in pararectal space passing medially to the ureter and laterally to the internal iliac artery downwards to the level of the coccygeal bone following the sacral bone. This way it was easier to identify the pelvic nerves (hypogastric, sacral, splanchnic nerves), uncover the infiltration of the nerve roots with EN and spare them during radical excision of EN.

Table. 2	RVE (n=19)	RCE (n=15)
Mean time of the follow-up, y (±SD)	3 years (±1,3)	2years (±1,2)
Mean age of the patients, yr (±SD)	34(±5,4)	31(±4,8)
Preoperative hormonal treatment, n (%)	12	9
Pre-operative Infertility rate n (%)	8(23, 5%)	9(26, 4%)
Adenomyosis n (%)	14(41%)	12(35%)
Previous surgery for endometriosis, n (%)	10(53%)	9(60%)
Procedures		
The mean time of the operation	4-3hours	3,2 hours
Retrocervical EN excision n (%)	0	15(100%)
Rectovaginal EN excision n (%)	19(100%)	0
Vaginal dissection of EN n (%)	10(29%)	0
Cyst-excision n(%)	6 (31%)	8 (53%)
Partial bowel resection n(%)	10 (57%)	10(66%)
Protective ileostomy	2 (11%)	4 (27%)
Partial bladder resection n(%)	4 (21%)	2 (13%)
Neurolysis n(%)	14 (74%)	15(100%)
Ureterolysis n(%)	13 (68%)	13 (86%)
Peritonectomy	9 (47%)	12 (80%)
Adnexectomy	3 (16%)	0
Appendectomy	1 (5%)	1 (6%)
Diaphragm resection	0	2 (13%)
Lymphadenectomy	1 (5%)	0
Umbilicus partial resection	1 (5%)	0
Follow-up		
Symptom free status postoperatively n (%)	12(63%)	9(60%)
Postoperative Pregnancy n=	7(87.5%)	5(56%)
Recurrence, n	0	0
Complication (%)	1(2.9%)	1(2.9%)
° SD - standard deviation		

In the second group of patients were enrolled n=19 patients with RVE and n=15 with RCE (Tab.2), together n=34 with. Till nowadays, there is no clear definition of RVE and RCE, as mostly both manifestations are considered and defined as RVE. Extremely near anatomical exposer could be the reason for that. The objectives of this study were to a) demonstrate the difference between RVE and RCE, placing the exact anatomical borders between them; b) choosing the appropriate surgical method for each manifestation and lastly c) investigating the efficiency of chosen surgical techniques. As anatomical manifestation of RVE is considered as the infiltration of rectum, vagina, rectovaginal pouch and RV septum, consequently, here was performed vaginal-combined

assisted laparoscopy in this group of patients. It started with the vaginal excision of the infiltrated area. The prepared area was then shifted on the rectum and the dissected part of vagina closed by suture. This was later followed by laparoscopical preparation of the EN-nodules and excision of all lesions as the whole conglomerate. RCE is considered to be the infiltration of the retroperitoneal space and posterior vaginal fornix behind or beneath the cervix usually without rectal involvement. Therefore, on these anatomical terms we used

single laparoscopy, as the excision of EN-lesions was completely possible from the abdominal area.

The third group with DIE involved n=54 patients with PCPE (Tab.3.). As this was a pilot retrospective study, the PCPE was mostly a part of very complex endometriosis (majority rASRM Stage IV) and there was no control group involved. Surgical technique was based on

Table. 3	DIE with PCPE (n=54)
Mean time of the follow-up, y (±SD)	2,5 years (±1,2)
Mean age of the patients, yr (±SD)	35 ± 7
Preoperative hormonal treatment, n (%)	30 (56%)
Pre-operative Infertility rate n (%)	28(%)
Adenomyosis n (%)	37(68,5%)
Previous surgery for endometriosis, n (%)	34 (63%)
Procedures	
The mean time of the operation	3 hours
Retrocervical EN excision n (%)	13(24%)
Rectovaginal EN excision n (%)	22(41%)
Vaginal dissection of EN n (%)	7(13%)
Cyst-excision n(%)	13 (24%)
Partial bowel resection n(%)	27(50%)
Protective ileostomy	14 (26%)
Partial bladder resection n(%)	7(12%)
Neurolysis n(%)	18 (33%)
Ureterolysis n(%)	32 (59%)
Peritonectomy	54 (100%)
Adnexectomy	5(9%)
Appendectomy	0
Diaphragm resection	0
Lymphadenectomy	0
Umbilicus partial resection	0
Follow-up	
Symptom free status postoperatively n (%)	36 (67%)
Postoperative Pregnancy n=	13(46%)
Recurrence, n	1(1.8%)
Complication (%)	1(1.8%)
° SD - standard deviation	

removing complete posterior peritoneum (same as cytoreduction) together with deep infiltrated EN-lesions. Most of the surgeries were complex and surgical procedures included cyst-excision, partial bowel resection, partial bladder resection, neurolysis and ureterolysis (Tab.3). The main purpose of the research was to understand the efficiency of total pelvic posterior compartment peritonectomy regarding fertility rate, recurrence and severity of EN-related complaints. This surgical approach was based on the idea of peritoneal EN being a widespread neurogenic inflammatory process, infiltrating surrounding tissues as well. As, mostly microscopically inflamed Peritoneum is presented macroscopically without typical endometriotic lesions, this way complete posterior compartment peritonectomy

enabled the entire removal of the EN process.

4 Results

At the time of surgery, the median age of study group was 35 years old (between 20-56y). 65% of the patients were nulliparous. The majority of the patients from all three groups took hormonal treatment (HT) preoperatively. The overall data of the study patients is presented in table 1. Primary indication of surgical treatment was ongoing EN-related symptoms mostly not responsive to HT or other treatments, recurrence, and infertility. EN-related complaints were severe in all groups (Tab.4,5,6) reporting an overall median VAS-score of 8 (scale from 0 to

10). 56% patients from the second group and 62% from the third group were operated one or several times prior to our surgery. The location of endometriosis, width and depth of the infiltration was classified by the ENZIAN score and rASRM staging as mentioned above.

4.1 Intraoperative evaluation:

Intraoperative imaging demonstrated high complexity of the EN in most of the cases. According to the rASRM classification stage IV was reported in 73% patients from the first group, in 51% from CPDIE group and in 54 % with DIE involving PCP. Presented Tables 4,5 and 6 demonstrate preoperative EN-related symptoms for each group, in order to get a better understanding of the direct proportion between preoperative complaints and intraoperative

findings (EN-localisation).

Table 4 Preoperative Symptoms for LPE	Percentage
Dysmenorrhoea	100 %
Cyclic pelvic pain	56%
Chronic pelvic pain	73%
Dyschezia	55%
Dysuria	13%
Dyspareunia	44%
Sciatica	6%
Paraesthesia	1,3%

In the first group endometriosis manifestation was exposed macroscopically in vagina/cervix n=67 (44%) cases, in rectum n=82 (55.4%), in bladder n=19 (12.8%), in uterosacral ligaments n=82 (55.4%), in uterus n=56 (38%), in ovaries n=88 (60%), in parametrium n=112 (76%), in ureters n=92 (62 %), in hypogastric plexus n=32 (22%) and in sacral plexus n=41 (28%).

Table 5 Preoperative Symptoms for CPDIE	Percentage
Dysmenorrhoea	85%
Cyclic pelvic pain	79%
Chronic pelvic pain	52%
Dyschezia	94%
Dysuria	17%
Dyspareunia	82%
Sciatica	18%
Paraesthesia	3%

In the second group with CPDIE endometriosis infiltration involved rectosigmoid junction in n=21 (62 %) cases, fallopian tubes in n=4(12%), bladder in n=4(12%), nerves in n=16 (44%), appendix in n=2 (6%), lymph nodes in n=1 (3%), umbilicus in n=1(3%), diaphragm in n=2 (6%).

In the third group of patients with PCPE endometriosis was demonstrated on posterior peritoneum n=54 (100%), in ovaries n=13(24%), uterus n=37(69%), rectum n=27(50%), bladder n=7(12%), nerves n=18(33%), ureter n=32(59%). Postoperatively, in all cases endometriosis was histologically confirmed. As mentioned above, surgical procedures were complex and requiring multistage surgical resections to remove completely the EN-lesions. The list of procedures is demonstrated in table 3. Compared to overly complex multivisceral surgeries we had a low percentage of complications.

Table 6 Preoperative Symptoms for PCPE	Percentage
Dysmenorrhoea	93%
Cyclic pelvic pain	81%
Chronic pelvic pain	59%
Dyschezia	56%
Dysuria	20%
Dyspareunia	72%
Sciatica	17%
Paraesthesia	4%

4.2 **Complication rate:**

First study reported one intraoperative complication enclosing common iliac vein injury and it was treated successfully during the same surgical procedure. Overall, early postoperative complications were demonstrated only in 12% (Tab.1.) of the patients from this group, including vesico-/ureterovaginal fistula, sepsis prolonged urinary catheterization, and postoperative ileum.

Second group reported not intraoperative, but two cases of early postoperative complication (Tab.2). In both cases revision surgery was immediately required. In the first case (patient with RVE) during the re-operation was not impossible to detect the problem area. Finally, on the third postoperative day the CT urography confirmed a urinary tract leakage, which was treated by the insertion of the urethral stent. In the second case (patient with RCE) revision surgery demonstrated the vaginal fistula, a complication following anastomotic insufficiency. Here was performed laparotomy including the closure of the vagina, ureter re-anastomoses and application of the colostomy (Hartmann situation) closed later after 1 year.

In the third group, only a single early-postoperative complication was recorded (Tab.3). It was urinary leakage on the left side, which required re-laparoscopy, intraoperative Double-J (DJ) ureteral stenting and inserting a pelvic drainage. Later, the patient was discharged from the clinic in the subjective wellbeing. The stent was removed 6 months later, but the patient was admitted in the hospital several times in between, due to the fever episodes,

pyelonephritis and pancreatitis. Finally, this patient underwent an antibiotic therapy before stent removal.

4.3 Postoperative Outcome:

Our strategy was conceptual, therefore postoperatively most of the patients received supportive adjuvant therapy with hormonal treatment (HT). Mainly the women seeking fertility underwent therapy with GnRH-analogs only for three months (during the wound healing process) before IVF. The rest of the women received HT including dienogest, combined hormonal contraceptives, gonadotropin-releasing hormone agonist and hormonal Intrauterine devices.

Overall, early and long-term follow-up in all three groups reported a significant decrease in both EN-related complaints and the intensity of the symptoms.

Postoperatively, the study reported noticeable pain relief in the first group. The median VAS-Score for dysmenorrhea fell from 8 to 0 and for dyspareunia from a median of 5 to 0. In the first study, chronic pelvic pain was considered as a main predictor of dLPE and postoperatively none of the patients reported the same symptom. The long-term follow-up recurrence was recorded in only 12% dLPE and altogether in 8.8% of the patients.

The second group of patients with RVE and RCE demonstrated overall 62% symptom free status postoperatively, including 57% RVEP and 43% RCEP. Postoperatively the pain intensity decreased moderately. In RVEP the mean VAS score for dysmenorrhea dropped from level 5 to 4 and in RCEP from 8 to 6. In general, EN-related symptom intensity for both groups dropped from level 7 to 4. Dyspareunia, one of the main symptoms of CPE, was reported postoperatively in only 2 RVEP patients, the rate of occurrence decreasing from 91% to 6%. The number of patients with dyschezia and dysuria dropped significantly postoperatively in both groups as well: in RVEP from 53% to 12% and in RCEP 29% to 11%. The final statistical analysis demonstrated no significant difference in postoperative outcome, between RCEPs and RVEPs.

Postoperatively, in the third group the study demonstrated 67% patients with symptom-free status and therefore rapid improvement in quality of life. Severity of EN-related complaints was decreased significantly from median VAS score level 7 to 1. Interestingly for complaints, such as cyclic pelvic pain and dyspareunia the postoperative VAS score dropped to zero. In this group 5-year follow-up data reported only one case of recurrence. Re-operative treatment confirmed re-manifestation of endometriosis histologically. Here the endometriosis infiltration progressed from rASRM stage I to stage II. Respectively, the surgery included hysterectomy, neurolysis and total parametrectomy.

4.4 Postoperative fertility outcome

was investigated in the second and third study. In both groups, there was a group of patients with a history of fertility problems. The second group with RVE and RVC reported preoperative n=8 RVEP and n=9 RCEP seeking fertility (Tab.2). Of these patients, 82% had a history of primary sterility (n=7 RVEP and n=7 RCE). In the mean follow-up time of 6 months postoperatively n=7 RVEP and n=5 RCEP achieved pregnancies, reporting 70.5% spontaneous pregnancies overall.

The third group with PCPE had a higher percentage 50%(n=28) of preoperative infertility, including 75% primary and 25% secondary infertility. The period of infertility varied from 1 to 10 years. Following-up after a mean time of 6 months demonstrated n=13 (46%) postoperative pregnancies. Moreover, most of the pregnancies 54% were achieved spontaneously.

All pregnancies from both study groups were followed by live birth and healthy infants.

5 Discussion

Endometriosis affects many essential areas of a woman's life beginning with her self-esteem as a woman and leading to an impact on her relationships, including family planning, with behavioural, sexual (Norinho et al., 2020), or emotional consequences. Moreover, 50 % of endometriosis patients receive long-term medical treatment, due to ongoing complaints (Hoo et al., 2017). As mentioned above, there are more than 3 million diagnosed and unknown endometriosis cases in Germany (Juhász-Boss et al., 2014, Ulrich et al., 2014), meaning almost 20% of women in Germany have problems having normal quality of life. Besides severe physical limitations caused by the pain, the major problem is a high recurrence rate of 50-80% (Meuleman et al., 2014, Seracchioli et al., 2007) even after surgical and hormonal treatment. The most severe form of endometriosis is DIE and occurs in approximately 10% of patients with EN (Seracchioli et al., 2007). The aim of our study was to investigate the efficacy of specific surgical approach for each type of DIE. DIE is characterized (Koninckx et al., 1991, Chapron et al., 2003) by a variable anatomic manifestation, presented as an isolated nodule on the pelvic peritoneum or as a complete and diffuse infiltration of pelvic organs (Martin et al., 1989, Vercellini et al., 2004). Therefore, surgical treatment of DIE is extraordinarily complex and challenging. But why surgical therapy?! Until today, surgery is considered the best way to treat DIE (Redwine, 1992) (Angioni et al., 2015b). Although some studies determine surgery to be too radical or similarly effective as HT for DIE (Vercellini et

al., 2006, Vercellini et al., 2009, Ferrero et al., 2015), single hormonal treatment is only suppressive and frequently ineffective in the management of severe endometriosis and cannot be an option for patients trying to conceive (Abrao et al., 2015) (Angioni et al., 2015a) (Thomassin et al., 2004). In our study, the majority of patients 63% from all three groups took hormonal (conservative) treatment for many years prior to surgery without a significant improvement in EN-related complaints. Therefore, the surgical treatment has to be discussed as one of the important component in the DIE treatment. However, which surgical method is more acceptable in order to have better results and outcomes in future? The main source of real data could be the evaluation of preoperative data, intraoperative findings, surgical technique, and postoperative follow-up in patients with DIE, considering postoperative outcome, recurrence, and fertility rate. This data could provide a better understanding of Endometriosis mechanism as a whole. Taking the patient's history can be time-consuming, but anamnesis plays a key role for understanding DIE. Moreover, it is a good basis for the right diagnosis. It focuses not only on the location of the pain, but also on the history of the pain, its transmission, causes and characteristics. Furthermore, a proper clinical examination is of utmost importance for patients with DIE, as standard gynaecological examination might not be sufficient to achieve the right diagnosis (Chiantera et al., 2018), due to its complexity. For instance, DIE with bowel involvement is hard to determine preoperatively, as a routine gynaecological examination does not involve rectovaginal palpation and bimanual examination alone may not be fully accurate (Hudelist et al., 2011). Preoperatively, all patients from our study were examined rectovaginally, then followed by transvaginal ultrasound (TVS) imaging (Piketty et al., 2009). Most of the bowel infiltration cases were already diagnosed in our outpatient clinic prior to surgery. Here was also used additional means of investigation like Endosonography and MRI, as they provide further possibility in detecting EN lesions (Bazot et al., 2004, Roseau et al., 2000). A thorough inspection of the infiltrated area is crucial, as it enables the formation of a potential diagnosis, which can be underestimated during the ordinary clinical examination. Additionally, roper clinical diagnosis helps in planning the appropriate surgical technique. However, full detection of EN-lesions is still very demanding, as DIE also includes nerve involvement and the pain intensity does not always correlate with the stage of the disease (Chiantera et al., 2017, dell'Endometriosi, 2001, Fedele et al., 1992). Especially during the sacral plexus involvement, EN-lesions are difficult to access and very less is known until nowadays. In the first group, we investigated patients with sacral plexus und hypogastric nerve involvement, and chronic pelvic pain was a main predictor for dLPE. On the other hand, these patients also had complaints characteristic of CPE or other pelvic neuropathic pain syndromes, such as pudendal pain, gluteal pain, lower abdominal pain, sciatic pain, vulvar or coccygeal pain. Usual radiological imaging or gynaecological examination are not capable of determinining the exact diagnosis in the terms

of dLPE and require further knowledge of pelvic neurofunctional anatomy. In 2014 Prof. Possover founded a discipline called neuropelveology, which investigates the connection between pelvic organ function and neuro-functional anatomy (Possover et al., 2017). The neuropelveological diagnostic approach to pelvic neuropathies includes common neurological principles during vaginal or rectal examination. In the first study sacral plexus involvement was discovered in n=41(100%) patients with dLPE at initial laparoscopy. Of those patients n=32 (78%) needed sacral nerve neurolysis. Moreover, hypogastric plexus infiltration was reported in n=29 (71%) of the dLPE patients, followed by hypogastric plexus resection in n=21 (72%) cases. Therefore, knowledge of the topographic anatomy and understanding of the landmarks seem to be the most important factors for surgeon in avoiding intraoperative nerve injuries, sparing the nerves and maintaining functionality whilst at the same time removing EN-nodules completely. For these neurosurgical procedures was used the Laparoscopic Neuro-Navigation - LANN-technique (Possover et al., 2004, Possover et al., 2005, Lemos et al., 2016). Exposing pelvic splanchnic nerves makes the borders between healthy and altered tissues accessible and the excision of the infiltrated area easier. In the case of DIE, the anatomy of the pelvic nerves can be changed due to diffuse manifestation of EN and intraoperative electrical neurostimulation tactic with bipolar forceps helps to identify nerve roots (Possover, 2004). Neurostimulation was used in every case where neurosurgery was performed to check further functionality of the nerve roots before and after performed neurolysis/dissection. This surgical approach may seem too radical and associated with some severe complications, but the follow-up was very promising, reporting only one intraoperative complication, overall, 12% postoperative complications, 8.8% postoperative recurrence, reduced intensity of EN-related symptoms and 87% of postoperative symptom free cases. This data demonstrated that the complete removal EN-lesions, even in terms of nerve involvement, was beneficial for these patients.

For the second group, the primary differentiation was made between RVE and RCE. Rectovaginal endometriosis is frequently used for both terms, although this subtype is considered as an infiltration of RV septum, with possible infiltration of vagina and rectum (Martin and Batt, 2001, Batt et al., 2014). Additionally, RCE is considered as an infiltration in the upper part of posterior vaginal wall behind the cervix (Batt et al., 2014), also presented with or without rectal involvement (Abesadze et al., 2020). As mentioned above, preoperative examination played a huge role in the determination of exact EN-lesions. Here, the preoperative examination involved inspection of the posterior vaginal fornix with a speculum, rectosigmoid palpation and TVS imaging. In terms of complex involvement and suspected rectal infiltration further diagnostic methods like MRI and Endosonography were used. Classification of the RVE and RCE was generally based on clinical examination, as EN-

related symptoms for both groups were particularly similar (Tab. 3.). In this sequence we investigated n=19 RVEP and n=15 RCEP. The knowledge of the exact location provided the basis for selecting the right operative procedure, since the aim of these surgeries was complete excision of the DIE lesions for both terms. As in majority of RVEP n=16 (except 3 cases) vaginal involvement was reaching the lower 1/3 of vagina, consequently a combined vaginal-laparoscopy made it possible to access EN-nodules in rectovaginal septum from both sides and allowed removal of the whole conglomerate as one en-bloc specimen without additional unnecessary resections. The area of vaginal resection was closed with suture from the side of vagina. In case of rectal resection (and in RVEP was performed n=10) this approach reduced the risk of typical complications like suture insufficiency, leakages or fistulas (Meuleman et al., 2014, Bouaziz and Soriano, 2017) as both sutures were presented from different sides (one from vagina and second from abdomen) and the possible friction between them was minimised. For RCEP was adopted a single laparoscopic approach. RCE is considered to involve the upper part of the posterior vaginal fornix (Batt et al., 2014, Abesadze et al., 2020), therefore EN-nodules are mostly fully accessible from the abdominal side. However, both terms were overly complex, involving other organs like bladder, rectum, nerve fibres and peritoneum. Preoperatively, 56% of the women underwent one or more surgical treatments due to ongoing EN complaints. As this study involved women in their reproductive age, organ sparing surgery was the first method of choice. Patients who underwent hysterectomy were not enrolled in this study. To understand the complexity of the process, intraoperative classification is always necessary, like rASRM staging and Enzian score (Tuttles et al., 2005, Haas et al., 2013). 42% of RVEP and 60% of RCEP were presented with rASRM stage IV. Enzian classification revealed 60% of cases with level C, from which 43% RVE and 52% RCE. The analysis of EN-nodules character, surgical technique and postoperative outcome has formatted our follow-up data. This data demonstrated how delicate the process of complete excision of EN lesions was whilst retaining the functionality of the organs. Still both surgeries may seem too radical but fighting with entire process lowered the probability of postoperative recurrence, giving young women the chance for improved fertility and the quality of life. Moreover, some studies reported on the negative impact of delaying the surgical treatment on the ovarian reserve, disease progression and EN-related symptoms (Weintraub AY, (2014) , Ballard et al., 2006). Overall postoperative follow-up revealed elevated fertility rate in both groups. 50% of women from both groups were primarily operated due to fertility problems and in both groups the median duration of infertility was from 2-3years. 87,5 % of RVEP and 56% of RCEP with preoperative impaired fertility got pregnant postoperatively. Follow-up data reported significant EN-related pain relief in most of the patients as well: completely symptom free status in 63% of RVEP and 60% in RCEP, and in the rest of the patients a decrease of

preoperative VAS score mean level from 8 to 4. Overall, this research proves that complete removal of EN lesions in terms of RVE and RCE can be beneficial for the patients suffering from severe EN for many years and gives hope to patients trying to conceive.

Nowadays, the most common theory for the aetiology of endometriosis is retrograde menstruation, meaning an outflow of menstrual blood/endometrial cells through the fallopian tubes and infiltration of the pelvic cavity during menstruation (Sampson, 1927). Most of the lesions are considered to disseminate on the pelvic peritoneum and largely on the posterior compartment (Mahmood and Templeton, 1991), initiating cell structure remodelling and infiltration of the peritoneal surface (Khan et al., 2004, Dunselman et al., 2001). The presence of immunological factors like macrophages, increased number of pro-inflammatory cytokines and growth factors (Young et al., 2014, Hogg et al., 2020, Young et al., 2017, Monsanto et al., 2016) in EN-lesions confirms the inflammatory process in infiltrated peritoneum (Young et al., 2013, Berbic et al., 2009). Moreover, demonstrating nerve fibres and nerve growth factors (NGF) in EN-lesions confirms its neurogenic character (Tokushige et al., 2006, Tran et al., 2009) (Mechsner et al., 2009) (Liang et al., 2018) and points on the neuroinflammatory response. Consequently, the peritoneum can be considered as a main source of pain development and generation in EN patients (Arnold et al., 2013, Chiantera et al., 2017, Liang et al., 2018). Furthermore, the evidence of EN, nerve fibres and NGF (Barcena de Arellano and Mechsner, 2014) in a macroscopically healthy peritoneum (Balasch et al., 1996) proves that alteration of the tissues extends the visually infiltrated area and involves the surrounding tissues as well. Until today, the best way for imaging the peritoneal endometriosis is a laparoscopy (Brosens et al., 2004, Duckelmann et al., 2021). There are no clear predictors regarding EN-related symptoms for patients with PE (peritoneal endometriosis). Ongoing cyclic and acyclic pelvic pain, high recurrence rate in patients, who had already undergone surgical treatment, could be considered as the main signs of PE. In the first study group of patients with DIE 63% of women were already operated on due to EN and 56% took suppressive HT, but these patients still had ongoing complaints. It was obvious that there was further reason for ongoing complaints. During the surgical procedures was clear that DIE was often accompanied by peritoneal infiltration with visible inflammation. This evidence guided us to form a concept for the treatment of patients with PCPE, starting to perform complete posterior compartment peritonectomy as part of the major surgery and then analysing its impact on the postoperative outcome. Nowadays surgeons remove DIE completely, however small EN lesions are frequently left behind. Usually, visible peritoneal EN infiltrations are excised or coagulated (Pundir et al., 2017, Comptour et al., 2020), as they are not considered as sources of recurrence or as generators of the pain. Of the patients operated prior to our surgery, 29% had undergone single diagnostic laparoscopy, 59%

excision of visible EN-lesions and the remaining 12% laparoscopic coagulation of EN lesions. It means the inflammatory process was still present and postoperative single HT was insufficient. As mentioned above, PE can be presented beyond macroscopically visible EN typical lesions (red, white or brown pigmented lesions)(Stegmann et al., 2009). The results of immunobiological examination of a macroscopically normal peritoneum is relevant for understanding the pathogenesis of endometriosis. In this study histological examination confirmed PE in all peritoneal specimens. Although some studies criticize the popularity of surgical treatment and believe in the efficacy of single HT in these patients (Vercellini et al., 2018), a total posterior compartment peritonectomy seems to be effective in eliminating the wide inflammatory process, avoiding further EN development or recurrence. Postoperatively, our study reported 67% of symptom free cases and one recurrence. As mentioned above, in this study peritoneal EN was a part of complex DIE process, so this surgical method was a part of multimethod surgical approach. Therefore, the single efficiency of the posterior compartment peritonectomy can be doubtful, but on another hand removing wide inflammatory process could be a reason of decreased postoperative recurrence rate for example, as removing the whole process in one conglomerate could lower the chances of new EN-lesions development. To understand the accuracy of this method, later was conducted another research involving the patients only with peritoneal EN presentation (This research will be later attached to the files) (Duckelmann et al., 2021). However, our treatment involved additional supportive HT postoperatively, likewise in the second group of patients with RVE and RCE. Postoperative supportive HT was mostly a bridge between initial surgery and attempted pregnancy, giving the operated area time to recover and minimise further EN manifestation. 75% of patients with primary or secondary sterility took postoperative supportive HT in the period between 3 to 6 months, including dienogest, combined HT and GnRHa. Overall, 46% of the patients seeking fertility achieved postoperative pregnancies in the meantime of 6 months. Every pregnancy ended with a healthy childbirth. Positive results were reported regarding postoperative EN-related complaints and accordingly in quality of life. From the remaining 33% with persisting symptoms, preoperative mean VAS score level 8 reduced postoperatively to level 1. Interestingly most of these women had severe adenomyosis (endometriosis of uterus). It could be a reason for persisting symptoms (Krentel 2017) and possibly difficult to treat without hysterectomy. Finally, complete peritoneal excision led to a reduction in recurrence rate and an improvement in fertility rate. Till nowadays there was not any existing research regarding this exact topic, with the exception of one presentation from Trehan. There remains room for debate as our study did not include a control group and as a cohort retrospective study can be subject to question. Therefore, this study was followed by the next research investigating the patients only with

peritoneal EN and confirmed good complaint relief, improved fertility rate (63%) and low recurrence risk (Duckelmann et al., 2021).

Still, future prospective randomized studies should contribute to the capability of this method. This study was designed to present not only divergent surgical methods, but also to understand the efficacy and advantages of these treatments, giving the patients with DIE a chance for better life, family planning and simply to finally beat this enigmatic disease. Statistical analysis was performed to understand the reliability of the collected data and the potential of given surgical methods. Very little is known about the impact of these surgical methods on fertility rate and recurrence rate, and this aspect was central to this study. Future investigations should improve the understanding of these topics and raise hope for patients with DIE.

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7 Eidesstattliche Versicherung

„Ich, Elene Abesadze versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

„Surgical outcome in patients with complex deep infiltrating Endometriosis“

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum **07.04.2021**

Unterschrift

8 Anteilserklärung an den erfolgten Publikationen

Elene Abesadze hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Elene Abesadze, Jalid Sehouli, Sylvia Mechsner and Vito Chiantera

Possible Role of the Posterior Compartment Peritonectomy, as a Part of the Complex Surgery, Regarding Recurrence Rate, Improvement of Symptoms and Fertility Rate in Patients with Endometriosis, Long-Term Follow-Up

Journal of Minimally Invasive Gynecology, 2019 August

Beitrag im Einzelnen:

- Mitarbeit in der Planung des Projektes
- Erarbeitung der Projektstrategie mit Prof. Dr.med. Sylvia Mechsner und Prof. Dr.med. Vito Chiantera
- Selbstständige retrospektive Datenerhebung: Analyse aller Patienten, welche wegen tief infiltrierender Endometriose mit Beteiligung des posterior Kompartments in der Charité, Endometriosezentrum operiert wurden
- Planung der Operationstechnik
- Teilnahme bei der operativen Behandlung
- Auswahl einer geeigneten Untergruppe von Patienten, die die Kriterien erfüllten (die Infiltration des posterior Kompartment Peritoneums)
- Erstellung einer umfassenden Datenbank von ausgewählten Patienten
- Erstellung einer Follow-up Datenbank
- Aufarbeitung und Analyse der Follow-up Datenbank
- Aufarbeitung und statistische Auswertung des postoperativen Ergebnisses in allen Patienten
- Erarbeitung grafischer Darstellungen der Ergebnisse: Erstellung aller Tabellen mit Patientencharakteristika, Erstellung jeden Bildmaterials, Erarbeitung der erfassten Ergebnisse in Fig.2 und Fig.3
- Schreiben des Manuskripts und Auswahl der Literatur
- Mitarbeit an der Redaktion des Manuskripts
- Erarbeitung des zur Publikation führenden Manuskripts und Einreichen zur Publikation.

Publikation 2:

Elene Abesadze, Vito Chiantera, Jalid Sehoul, Sylvia Mechsner

Post-operative management and follow-up of surgical treatment in the case of rectovaginal and retrocervical endometriosis

Archives of Gynecology and Obstetrics. 2020 July.

Beitrag im Einzelnen:

- Mitarbeit in der Planung des Projektes
- Erarbeitung der Projektstrategie mit Prof. Dr.med. Sylvia Mechsner und Prof. Dr.med. Vito Chiantera
- Selbstständige retrospektive Datenerhebung: Analyse aller Patienten, welche wegen Rektovaginaler und Rektozervikaler Endometriose in der Charité, Endometriosezentrum operiert wurden
- Planung der Operationstechnik
- Teilnahme bei der operativen Behandlung
- Auswahl einer geeigneten Untergruppe von Patienten, die die Kriterien erfüllten (Frauen im reproduktiven Alter, die keine Hysterektomie erhalten haben)
- Erstellung einer umfassenden Datenbank von ausgewählten Patienten
- Erstellung einer Follow-up Datenbank
- Aufarbeitung und Analyse der Follow-up Datenbank
- Aufarbeitung und statistische Auswertung der postoperativen Ergebnisse in allen Patienten
- Erarbeitung grafischer Darstellungen der Ergebnisse: Erstellung aller Tabellen mit Patientencharakteristika, Erstellung jedes Bildmaterials, Erarbeitung der erfassten Ergebnisse in Fig.2, Fig.3 und Fig.4.
- Schreiben des Manuskripts und Auswahl der Literatur
- Mitarbeit an der Redaktion des Manuskripts
- Erarbeitung des zur Publikation führenden Manuskripts und Einreichen zur Publikation

Publikation 3:

Vito Chiantera, Marco Petrillo, Elene Abesadze, Giulio Sozzi, Margherita Dessolet, Mariano Catello Di Donna, Giovanni Scambia, Jalid Sehouli and Sylvia Mechsner

Laparoscopic Neuronavigation for Deep Lateral Pelvic Endometriosis: Clinical and Surgical Implications.

Journal of Minimally Invasive Gynecology, 2018 February

Beitrag im Einzelnen:

- Mitarbeit in der Planung des Projektes
- Erarbeitung der Projektstrategie mit Prof. Dr.med. Sylvia Mechsner und Prof. Dr.med. Vito Chiantera
- Retrospektive Datenerhebung: Auswahl einer geeigneten Untergruppe von Patienten mit tief infiltrierender Endometriose mit Beteiligung der Nerven und Nervenwurzel
- Erstellung einer umfassenden Datenbank von ausgewählten Patienten
- Erstellung einer Follow-up Datenbank
- Aufarbeitung und Analyse der Follow-up Datenbank
- Wesentlicher Beitrag zur Diskussion der Resultate in den einzelnen Zwischenschritten
- Wesentlicher Beitrag zur Diskussion des Manuskripts
- Mitarbeit an der Redaktion des Manuskripts
- Wesentlicher Beitrag zur Erarbeitung des zur Publikation führenden Manuskripts

Publikation 4:

A. M. Dückelmann, E. Taube, E. Abesadze, V. Chiantera, J. Sehouli, S. Mechsner

When and how should peritoneal endometriosis be operated on in order to improve fertility rates and symptoms? The experience and outcomes of nearly 100 cases

Archives of Gynecology and Obstetrics, 2021 January

Beitrag im Einzelnen:

- Mitarbeit in der Planung des Projektes
- Erarbeitung der Projektstrategie mit Prof. Dr.med. Sylvia Mechsner und Dr.med. Anna-Maria Dückelmann
- Mitarbeit bei der retrospektiven Datenerhebung: Auswahl einer geeigneten Untergruppe von Patienten mit ausschließlich nur posterior Kompartiment Peritoneum Infiltration.
- Teilnehmen in der Erstellung einer umfassenden Datenbank von ausgewählten Patienten.
- Mitarbeit bei der Erarbeitung grafischer Darstellungen der Ergebnisse: Erstellung des Bildmaterials Fig.6
- Mitarbeit an der Redaktion des Manuskripts.
- Wesentlicher Beitrag zur Diskussion der Resultate in den einzelnen Zwischenschritten.
- Wesentlicher Beitrag zur Diskussion des Manuskripts.
- Wesentlicher Beitrag zur Erarbeitung des zur Publikation führenden Manuskripts.

Unterschrift, Datum und Stempel der erstbetreuenden Hochschullehrerin

Unterschrift des Doktoranden/der Doktorandin

9 Druckexemplare der ausgewählten Publikationen

Possible Role of the Posterior Compartment Peritonectomy, as a Part of the Complex Surgery, Regarding Recurrence Rate, Improvement of Symptoms and Fertility Rate in Patients with Endometriosis, Long-Term Follow-Up.

Abesadze E, Sehouli J, Mechsner S, Chiantera V.

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Post-operative management and follow-up of surgical treatment in the case of rectovaginal and retrocervical endometriosis

Elene Abesadze¹ · Vito Chiantera^{1,2} · Jalid Sehoul¹ · Sylvia Mechsner¹

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Abstract

Introduction Deep infiltrating endometriosis (DIE) affects between 3.8% and 37% of all endometriosis patients, mostly affecting rectovaginal septum or retrocervical space and characterized by the severe endometriosis-related complaints. Nowadays, generally managed with surgery. However, this is associated with a risk of postoperative complications. To better evaluate intra- and postoperative complications and outcomes for rectovaginal (RVE) and retrocervical endometriosis (RCE), the preoperative management should be accurately described and compared.

Methodology This is a cohort retrospective study performed at the Endometriosis Centre of Charité-University Clinic, Berlin. 34 patients were investigated in their reproductive age, $n = 19$ with RVE and $n = 15$ RCE, operated between 2011 and 2015. The surgical approach was divergent in both groups. Single laparoscopy was performed in RCE patients (RCEP) and vaginal assisted laparoscopy in RVE patients (RVEP). Long-term postoperative outcome included complications, fertility rate and recurrence rate.

Results The median follow-up time was three years (y). Symptom-free status was revealed in $n = 12$ RVEP and $n = 9$ RCEP. Postoperatively, endometriosis-related complaints were presented in $n = 7$ RVEP and $n = 6$ RCEP, but with significant pain relief. From $n = 8$ RVE patients seeking fertility, pregnancy occurred in $n = 7$ and from $n = 9$ RCEP pregnancy appeared in $n = 5$ patients in the meantime of 6 months. Postoperative complications were reported in $n = 1$ RVEP with early postoperative bleeding, after ureter leakage and $n = 1$ RCEP with postoperative anastomotic insufficiency. The postoperative recurrence rate was equivalent to zero.

Conclusion The appropriate surgical approach for each group, preserving anatomy and functionality of the organs, seems to be very essential and efficient.

Keywords Rectovaginal endometriosis · Retrocervical endometriosis · Pelvic pain · Surgical technique · Recurrence rate · Fertility rate

Abbreviations

ART	Artificial reproduction treatment
CT	Computerized tomography
CPP	Chronic pelvic pain
DIE	Deep infiltrating endometriosis
EN	Endometriosis
EL	Endometriosis lesions
ENZIAN	Classification of deep infiltrating endometriosis

GnRHa	Gonadotropin-releasing hormone agonists
HT	Hormonal treatment
IVF	In vitro fertilization
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drugs
PI	Protective ileostomy
rASRM	Revised classification of Endometriosis by American society of reproductive medicine
RCE	Retrocervical endometriosis
RCEP	Retrocervical endometriosis patients
RVE	Rectovaginal endometriosis
RVEP	Rectovaginal endometriosis patients
SD	Standard deviation
TVS	Transvaginal sonography

✉ Sylvia Mechsner
Sylvia.mechsner@charite.de

¹ Department of Gynaecology, Charité - University Clinic, Endometriosis Centre Charité, Campus Virchow Clinic, Berlin, Germany

² University of Palermo, Palermo, Italy

VAS Visual analog scale
Y Years

Introduction

Endometriosis (EN) is the most frequent disease of the pelvic cavity in women of reproductive age [1]. Three different clinical presentations of EN lesions (EL) could be considered: peritoneal endometriosis, endometriomas and deep infiltrating endometriosis (DIE) [2]. DIE is the most severe form of lesions, because of infiltration and damage of adjacent organs like the bowel, the bladder and/or the ureter and effects around 10% of all endometriosis patients [3]. The most frequent affected area is the pouch of Douglas. Here, two manifestation forms of DIE, the rectovaginal with infiltration of the rectovaginal septum with or without infiltration of the vagina and retrocervical endometriosis [3–5] (Fig. 1) could be distinguished.

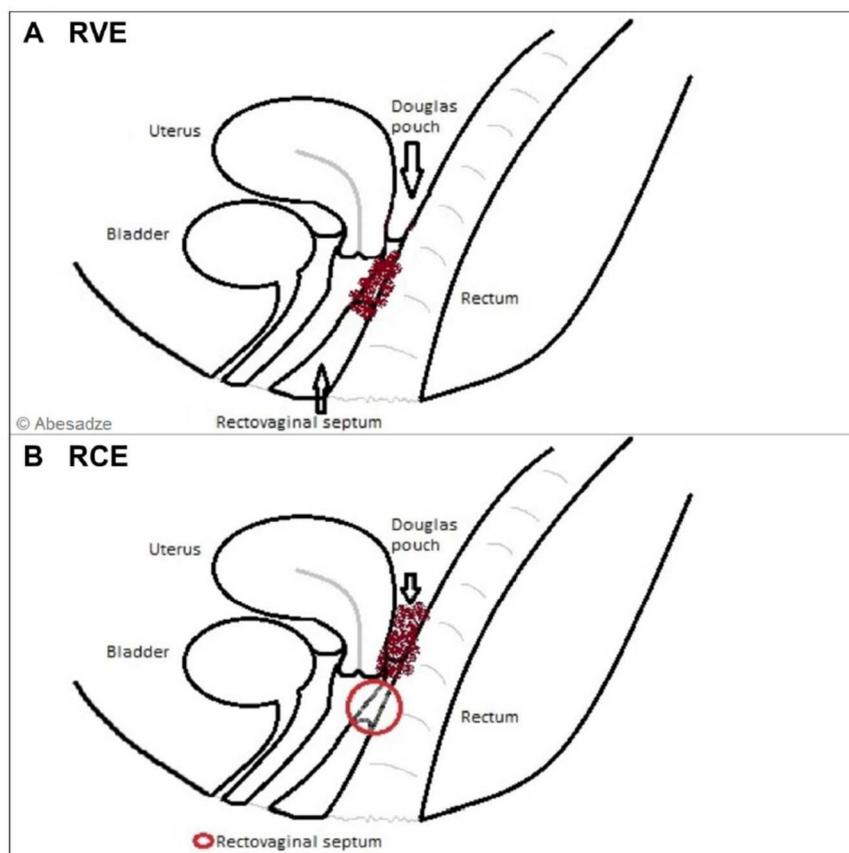
The exact definition of the topography of retrocervical and rectovaginal EN is mandatory for the understanding of the disease and for planning the surgical treatment. The term

rectovaginal EN (RVE) is often used for both retrocervical EN (RCE) and RVE [4], even though there are actually significant differences between these two terms and the surgical approach.

Moreover, Martin and Batt defined that an infiltration of the retroperitoneal space and posterior vaginal fornix behind or beneath the cervix is typically without rectal involvement, and is more typical for RCE [6] and the involvement of rectum, vagina, rectovaginal pouch and sometimes RV septum is more common RVE [6]. Clarified terminology is a basis for accomplishing the correct preoperative evaluation, informed consent, and intraoperative approach. In particular, the treatment of RCE is less complex than the treatment of RVE [6].

Another essential issue is a proper examination of the patient. Considering that, the complaints like, dysmenorrhea, pelvic pain, dyschezia, dyspareunia, sexual impairment and impaired fertility are similar for both RVE and RCE. Therefore, the right diagnosis is always a challenge. In both cases, it is essential to complete a bimanual examination with a rectovaginal examination to inspect the posterior vaginal fornix, uterosacral ligaments, paracervical tissue,

Fig. 1 Anatomical terms of location for rectovaginal (a) and retrocervical (b) endometriosis



softness of rectal and vaginal wall and finally the infiltration of the rectum. Nevertheless, in some cases, the rectal infiltrations are further away from the anus in the rectosigmoid colon and hard to palpate. Furthermore, vaginal ultrasound is mandatory to confirm involvement of the rectovaginal septum and bowel infiltration [7, 8]; it also a good way to differentiate rectovaginal from retrocervical endometriosis. To complete the preoperative planning, additional diagnostic methods like endosonography, sigmoidoscopy and magnetic resonance imaging (MRI) are necessary.

To date, surgical therapy is the first-rate treatment for symptomatic RCE and RVE as medical therapy is usually only temporarily effective and a complete excision of endometriotic tissues improves the chance to avoid recurrence and obtain a better follow-up [5, 9]. However, surgical treatment is complex and associated with complications. Our target was to evaluate the efficiency of laparoscopically assisted vaginal approach and single laparoscopy in two similar terms anatomically located on the different sites of the rectovaginal area, but also side-by-side. The purpose of this study was to analyze: the probability of minor and major complications pre- and postoperatively (like suture insufficiency), recurrence rate and postoperative outcomes. To our knowledge, there is no current study assuming the coordinated surgical approach for RVE and RCE.

Materials and methods

This is a single-center study comprising two groups of patients with symptomatic RVE and RCE (Table 1). This study was focused on a particular group of women of reproductive age with current or prospective family planning. The mean age for RVEP was 34 year (± 5.4) and 31 year (± 4.8) for RCEP ($n=17$ seeking fertility, of which $n=8$ RVE and $n=9$ RCE). We excluded patients who had undergone a hysterectomy because an organ sparing surgery was mandatory. All 34 patients were operated on between 2011 and 2015 at our department of gynecology Charité, Berlin Germany and postoperative follow-up was made from 2012 till 2018. Preoperative risk scores were assigned to patients. The study patients were divided into two groups. The first group comprised 19 women with RVE, $n=11$ (57%) with and $n=8$ (43%) without bowel infiltration and the second group presented $n=15$ patients with RCE, $n=10$ (66%) with and $n=5$ (34%) without bowel infiltration. The database was collected from the clinical history of patients. All 34 women were examined and diagnosed in our outpatient clinic. The clinical data were analyzed from the gynecological and digital examination. To evaluate suspected bowel infiltrations, additional diagnostic methods were performed such as endosonography, colonoscopy and MRI. On the day of the visit,

Table 1 General overview of the preoperative findings, surgical procedures and follow-up in 34 study patients

	RVE ($n=19$)	RCE ($n=15$)
Mean time of the follow-up, month (\pm SD)	3 years (± 1.3)	2 years (± 1.2)
Mean age of the patients, year (\pm SD)	34(± 5.4)	31(± 4.8)
Preoperative hormonal treatment, n (%)	12	9
Pre-operative infertility rate n (%)	8 (23, 5%)	9 (26, 4%)
Adenomyosis n (%)	14 (41%)	12 (35%)
Previous surgery for endometriosis, n (%)	10 (53%)	9 (60%)
Diagnostic laparoscopy with biopsy, n (%)	2 (11%)	3 (20%)
Incomplete excision, n (%)	4 (21%)	5 (33%)
Recurrence of EL, n (%)	4 (21%)	1(6%)
<i>Procedures</i>		
The mean time of the operation	4.3 h	3.2 h
Retrocervical EN excision n (%)	0	15 (100%)
Rectovaginal EN excision n (%)	19 (100%)	0
Vaginal dissection of EN n (%)	10 (29%)	0
Cyst excision n (%)	6 (31%)	8 (53%)
Hysterectomy n (%)	0	0
Partial bowel resection n (%)	10 (57%)	10 (66%)
Protective ileostomy	2 (11%)	4 (27%)
Partial bladder resection n (%)	4 (21%)	2 (13%)
Neurolysis n (%)	14 (74%)	15 (100%)
Ureterolysis n (%)	13 (68%)	13 (86%)
Peritonectomy	9 (47%)	12 (80%)
Adnexectomy	3 (16%)	0
Appendectomy	1 (5%)	1 (6%)
Diaphragm resection	0	2 (13%)
Lymphadenectomy	1 (5%)	0
Umbilicus partial resection	1 (5%)	0
<i>Follow-up</i>		
Symptom free status postoperatively n (%)	12 (63%)	9 (60%)
Postoperative pregnancy $n=$	7	5
Recurrence, n	0	0
Complication (%)	1 (2, 9%)	1 (2, 9%)

SD standard deviation

each patient took part in a verbal questionnaire based on visual analog scale (VAS) and numerical rating scale (NRS).

Surgery

The surgical tactics were divergent and performed by the same team: including vaginal-combined assisted laparoscopy in case of RVE [10] and single laparoscopy in patients with RCE [9]. The mean time of RVE operations

was 43 h and 32 h for RCE. In most of the cases, the disease was complex, involving other organs as well. Intraoperatively the severity and localization of the EN was assessed, using classification of the American society of reproductive medicine (rASRM) and a classification of Deep Infiltrating Endometriosis (ENZIAN score) (Tables 2, 3). The vaginal-combined laparoscopic technique started with the vaginal excision of the infiltrated area which was presented in Possover's work from 2000 [10]. It was followed by the preparation of the rectovaginal septum. The prepared part of the vagina was shifted on the rectum. The posterior fornix of the vagina was sutured to the posterior cervix. Later proceed with laparoscopic separation of the retroperitoneum along the coccygeal-sacral bone towards transvaginally exposed area, including nerve-sparing and laparoscopic neuro-navigation technique performed by the Possover's technique as well [11]. In the case of recto-sigmoidal infiltration, the whole conglomerate together with rectal EN was prepared and transected cranially by the laparoscopic stapling device, followed by the suprapubic laparotomy in order to prepare the bowel for anastomosis. In the final step, the transanal stapled anastomosis was completed. We had three cases of RVE, where the EL were not expanded too deep in the vagina, approximately 2 cm in diameter. Here, the lesions were resected with the single laparoscopy as one en bloc specimen, including entire posterior peritoneum of the pelvis, in two cases with and in one without vaginal resection. Here, the vaginal suture was applied laparoscopically as well. This procedure was only part of the complex surgical treatment, including partial bladder resection $n=4$ (21%, out of $n=19$ RVEP), ureterolysis $n=13$ (68%), neurolysis $n=14$ (74%, in particular thirteen hypogastric nerve

and one sacral plexus), partial nerve resection $n=1$ (5%) including hypogastric nerve, peritonectomy $n=9$ (47%), unilateral adnexectomy $n=3$ (16%), lymphadenectomy $n=1$ because of lymph node extension (not symptomatic) (5%) and partial umbilical resection $n=1$ (5%) (Table 1).

In all patients with RCE ($n=15$), a single laparoscopy was performed. Uterine manipulator was applied to displace the uterus anteriorly and push up the posterior fornix better. The procedure started with adhesiolysis and opening of the retroperitoneal space, presenting the ureter on the both sides in some cases ($n=13$); followed by the preparation of pararectal spaces, exposing superior hypogastric nerves and pelvic splanchnic nerves. The final step was the peritonectomy of the complete posterior compartment, with the excision of the cervical nodule in one en bloc sample. The RCE surgical procedure was also extended, along with partial bowel resection 10 (66% out of $n=15$ RCEP), partial bladder resection 2 (13%), neurolysis 15 (100%) including hypogastric nerve, partial nerve resection $n=6$ (40%) counting five hypogastric nerve and one plexus sacralis, ureterolysis 13 (88%), peritonectomy 12 (80%), appendectomy 1 (6%), diaphragm resection 2 (13%). All specimens were sent for histopathological examination and endometriosis was proven histopathologically. Table 1 demonstrates an overview of the performed surgical procedures (Table 1).

Post-operative follow-up was evaluated during visits in our outpatient clinic and by phone interview. During the interview, patients were asked questions about symptoms related to dysmenorrhea, dyspareunia, dyschezia, recurrence and postoperative pregnancy, rated by the VAS and NRS as well.

Statistical analysis

Data analysis included age, pre-operative and postoperative complaints, operative procedures, recurrence rate, complications, fertility rate. The mean and standard deviation (SD) for indications and postoperative follow-up were taken. Divergence between pre- and postoperative status was investigated by Graph pad Prism 5 using p value test and t nonparametric test.

Table 2 Summary of preoperative and intraoperative rASRM classification in patients with RVE and RCE

rASRM staging	RVE	RCE
rASRM I $n=4$	3	1
rASRM II $n=9$	7	2
rASRM III $n=4$	1	3
rASRM IV $n=17$	8	9

Table 3 The intraoperative classification of endometriosis with ENZIAN score for RVEP and RCEP

	ENZIAN 1 < 1 cm			ENZIAN 2 1–3 cm			ENZIAN 3 > 3 m			ENZIAN F				
	A	B	C	A	B	C	A	B	C	FA	FB	FU	FI	FO
RVE	2	1	1	8	1	6	5	1	4	14	4	0	2	3
RCE	2	0	0	0	3	4	5	0	7	12	2	1	2	2
Total $n=$	4	1	1	8	4	10	10	1	11	26	6	1	4	5

Results

Indications

As our study was focused on the women in their reproductive age, with current and prospective family planning, the mean age of the patients with RVE was $34 (\pm 5.4)$ and $31 (\pm 4.8)$ for RCEP (Table 1). RVE was presented in 55% (19) of the patients and RCE in 45% (15). All 34 patients took non-steroidal anti-inflammatory drugs (NSAID) preoperatively. Previous hormonal therapy had been taken in $n = 12/19$ (63%) RVEP and in $n = 7/15$ (47%) RCEP, including combined oral or vaginal contraceptives and progesterone-only pills. Surgical treatment was recommended in cases of infertility and ongoing symptoms or with a progression of the symptoms while taking hormonal treatment, which was interrupted 2 months prior to surgery. $N = 19/34$ (56%) of the women were operated on one or more times prior to our surgery, recorded in $n = 10/19$ RVEP and in $n = 9/19$ RCEP. Of this group, $n = 2/9$ RVEP and $n = 3/9$ RCEP underwent a single diagnostic laparoscopy. In $n = 4/10$ RVEP and in $n = 5/9$ RCEP, visible EL were partially resected or coagulated, reporting ongoing EM-related complaints. Preoperatively, an incomplete excision of RVE endometriosis was performed in $n = 4/10$ RVEP and an excision of RCE was done in $n = 1/9$ RCEP; accordingly, these cases indicated a recurrence/progression of RVE and RCE EM. Endometriosis-related complaints were similarly recorded in the RVEP and RCEP. Dysmenorrhea was present preoperatively in $n = 17$ (89%) RVEP and in $n = 12$ (80%) RCEP. Cyclic pelvic pain was reported in $n = 16$ (84%) RVEP and $n = 11$ (73%) RCEP, chronic pelvic pain in $n = 9$ (47%) RVEP and in $n = 9$ (60%) RCEP. $N = 17$ (89%) RVEP and $n = 11$ (73%) RCEP suffered from dyspareunia, and $n = 15$ (79%) RVEP and $n = 7$ (47%) RCEP from dyschezia. Dysuria was documented in $n = 3$ (15%) RVEP and in $n = 3$ (20%) RCEP. Impaired fertility was presented in $n = 8$ (42%) RVEP, with $n = 7$ cases of primary sterility and one case of miscarriage in an early phase. From $n = 9$ (60%) RCEP seeking fertility, $n = 7$ cases of primary sterility, one case of secondary sterility and one case of miscarriage were documented.

Intraoperative status

The intraoperative staging of the EN manifestation is presented in Tables 2 and 3. The vaginal assisted laparoscopy was performed in 16/19 (84%) RVEP. The remaining three patients (16%) with RVE underwent a single laparoscopy, $n = 2/19$ with laparoscopic vaginal dissection and $n = 1/19$ without. All 15 women with RCE received a

single laparoscopy. Rectosigmoid resection was performed on 64% (20) of women, including 10/15 RCEP and 10/19 RVEP. The mean distance of the anastomosis above the anus was 8 cm in both groups, with a minimum distance of 6 cm and maximum 10 cm, similar for both groups. All of these 10 RVE patients underwent vaginal dissection as well, applying a suture vaginally in eight cases and laparoscopically in two cases. No vaginal dissection was carried out in case of RCE. In case of very deep rectum resection, there was constructed protective ileostomy in 6/34 (18%) patients, within 4 RCEP and 2 RVEP (Table 1). In most cases, the excision of RV and RC lesions was a consequence of deep infiltrating endometriosis (Tables 2, 3.) and required complex surgery. The classification of the infiltration, width and depth of the infiltration and, location of endometriosis was made by the ENZIAN score and rASRM staging as previously noted (Table 2, 3.). More than 50% of the patients reported rASRM stage IV (Table 2), which also infiltrated nearby organs. RVE was present in the infiltration of rectosigmoid junction ($n = 10$), bladder ($n = 2$), nerves ($n = 8$), appendix ($n = 1$), lymph nodes ($n = 1$), umbilicus ($n = 1$). In patients with RCE, the pouch of Douglas was partly or totally obliterated, involving rectosigmoid junction ($n = 11$), bladder ($n = 2$) fallopian tubes ($n = 4$), ovaries ($n = 8$), nerve fibers ($n = 8$), appendix ($n = 1$), diaphragm ($n = 2$) in the process.

Early post-operative complications

Our investigation reported no minor postoperative complications, but two cases of major complications in the early post-operative period: one patient with RVE and another with RCE. The first patient presented a significant hemoglobin drop on the second postoperative day. Suspecting the intraabdominal bleeding, computerized tomography (CT) scan was taken and a laparoscopic revision was performed. Intraoperatively, the bleeding source could not be identified, coagel was removed and no evidence of vaginal or bowel suture insufficiency was determined. Afterwards, on the third postoperative day, an increased creatinine value in the intraabdominal drainage was revealed. A CT urography confirmed a urinary tract leakage on the left side handled conservatively with urethral stent inserted under cystoscopy. This patient was discharged from the clinic in subjective well-being.

The second patient with RCE demonstrated anastomotic leakage on postoperative day nine with increased infection parameters and suspicious fluid in the intraabdominal drainage, which was the immediate indication for surgical intervention. Intraoperatively was detected a vaginal fistula, as a result of anastomotic insufficiency with local infection. In terms of already existing urethral stent (applied during first operation), the ureter suture insufficiency was identified.

Laparotomy was finished by the closure of the vagina, reanastomoses of the ureter and application of the colostomy (Hartmann situation), which was closed 1 year later.

Follow-up

Postoperatively, every patient $n = 16$ (47%) with no reproductive concern took supportive hormonal treatment (HT) $n = 11$ RVEP and $n = 5$ RCEP, except one patient who refused to take HT because of nicotine abuse. HT included progestogen-only pills, combined hormonal contraceptives, gonadotropin-releasing hormone agonists and hormonal intrauterine device (Table 4). Patients with subfertility were divided in two groups, $n = 11$ patients with adenomyosis, who took HT: $n = 7$ gonadotrophin-releasing hormone agonists (GnRHa) and $n = 4$ dienogest shortly (3 months) postoperatively in non-stop modus as a therapeutic purpose to improve the chances of upcoming in vitro fertilization (IVF). And second group with $n = 6$ patients, where HT was not required. Totally HT was taken in $n = 27$ (77%) of all the patients, out of them $n = 12$ RVEP and $n = 9$ RCEP (Table 4).

In general, postoperative follow-up revealed an apparent reduction of EN-related symptoms. Dysmenorrhea disappeared postoperatively in $n = 16/17$ (94%) RVE and $n = 9/12$ (75%) RCE patients (Fig. 2). Here, we have to mention that one RVEP with remaining postoperative dysmenorrhea had no postoperative HT, as the patient was seeking fertility. Three RCEPs with postoperative dysmenorrhea did not undergo postoperative HT as well, as one was seeking fertility and rest two patients declined recommended postoperative HT. In fact, this group of patients with remaining dysmenorrhea reported decrease of pain intensity according to the VAS score (from 0 to 10 scale system of the pain level), for one RVEP from level 5 to level 4 and for RCEPs from mean level of 8 to mean level of 6. As for the rest $n = 16$ RVEP and $n = 9$ RCEP without postoperative dysmenorrhea, every patient from this group underwent postoperative supportive HT in non-stop modus, except $n = 3$ RVEPs those seeking fertility. However, terminating menstrual bleeding in this group could indicate the absence of postoperative dysmenorrhea. In general, the mean intensity of postoperative persisting symptoms was significantly decreased from level

7 to level 4 (Fig. 2). The postoperative database reported only one case/11 of cyclic pelvic pain in RCEP. Postoperative chronic pelvic pain (CPP) was reported only in $n = 4/9$ RVEP, out of them $n = 3$ took postoperative HT. CPP was reported in one/9 RCEP; this patient was under HT postoperatively as well. There were representative changes in patients with dyspareunia 28 (91%), including $n = 17$ RVEP and $n = 11$ RCEP. This group postoperatively reported only $n = 2/17$ (6%) cases of dyspareunia, significantly only in RVEP. Dyschezia 22 (64%) was one of the main complaints in RVEP 15 (79%) and RCEP 7 (47%), postoperatively reporting only in $n = 3/15$ (21%) RVEP and $n = 4/7$ (57%) in RCEP. From six (18%) women preoperatively suffering from painful urination, $n = 3$ (15%) RVEP and $n = 3$ (20%) RCEP, only $n = 1/3$ RVEP reported dysuria (Fig. 2).

Fertility rate

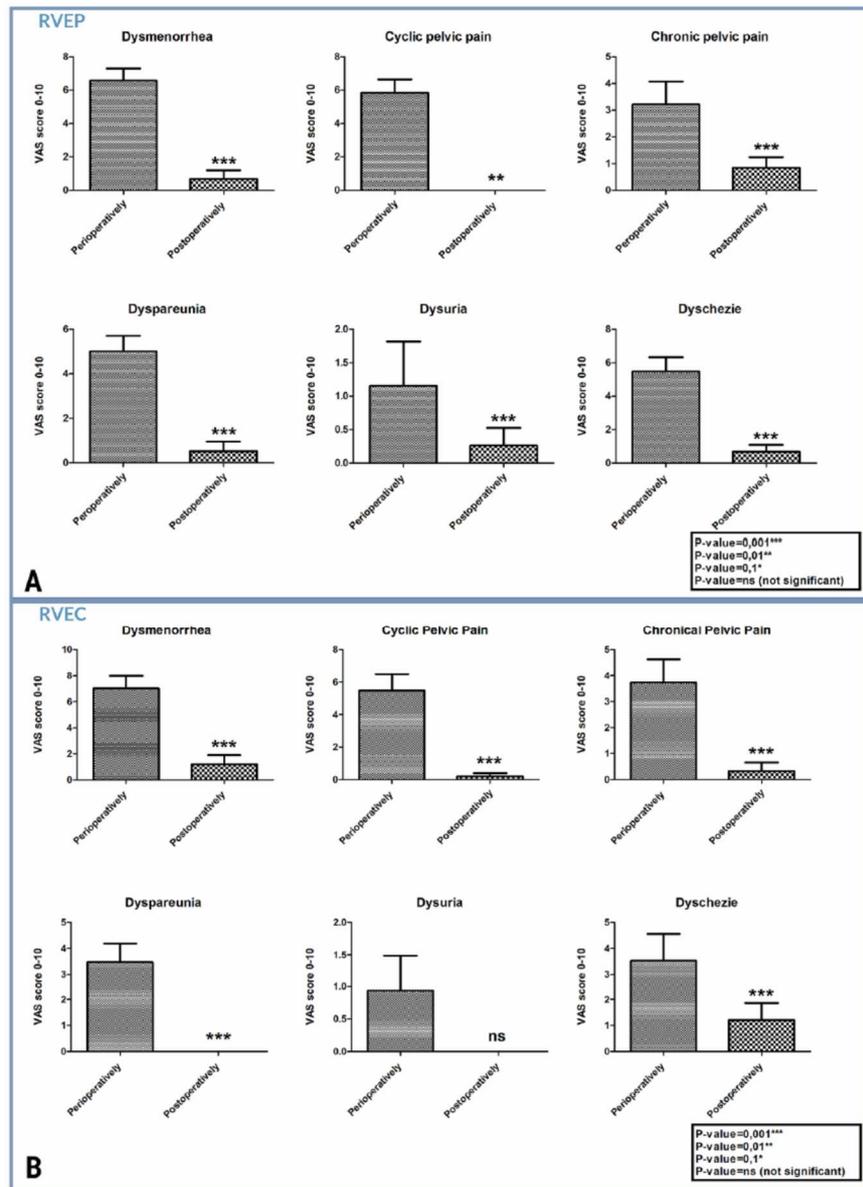
The analysis demonstrated an increase in postoperative fertility rate. Preoperatively, $n = 17$ (50%) women suffered from impaired fertility, $n = 8/19$ (42%) RVEP and $n = 9/15$ (60%) RCEP. The median duration of infertility for RVEP was 2 years and 3 years for RCEP. $N = 14/17$ (82%) had a history of primary sterility, $n = 7$ with RVE and $n = 7$ with RCE. The remaining $n = 3/17$ patients suffered from secondary sterility, of which $n = 2/3$ reported a miscarriage in the early weeks of pregnancy, one RVEP and one RCEP, and $n = 1/3$ RCEP reported secondary sterility after childbirth. Postoperatively, $n = 12/17$ (71%) women got pregnant in a mean time of 6 months (Fig. 3), $n = 7/10$ RVEP and $n = 5/10$ RCEP. In $n = 5/11$ pregnancy developed spontaneously, in $n = 4/5$ RVEP and $n = 1/5$ RCEP. Another six patients achieved pregnancy after artificial reproduction treatment (ART) including $n = 3/5$ RVEP and $n = 4/5$ RCEP. In these cases, pregnancy was followed by the delivery of healthy newborns.

A paired T-test demonstrated no statistically significant difference in pain relief, postoperative complications or organ dysfunction, fertility rate and recurrence rate between RVE and RCE. (Fig. 4).

Table 4 Postoperative hormonal treatment in patients with and without subfertility

	Dienogest <i>N</i> =	COC <i>N</i> =	Desogestrel <i>N</i> =	Desogestrel /Mirena <i>N</i> =	Single GnRHa <i>N</i> =	Mirena <i>N</i> =	GnRHa followed by Dienogest <i>N</i> =
RVEP \emptyset subfertility	7	3	0	1	0	1	0
RCEP \emptyset subfertility	3	0	0	0	0	0	1
RVEP with subfertility	2	0	0	0	1	0	0
RVEP with subfertility	4	0	1	0	3	0	0

Fig. 2 VAS score analyzed statistically by Graph pad Prism 5 using p-value test and t non-parametric test. Graphs present the pre- and postoperative complaint's considering VAS score, reporting the pain reduction postoperatively in both groups: **a** RVEP and **b** RCEP



Discussion

In this study group, with a mean age of 32 years, the women are of reproductive age and need an accurate surgical treatment with organ sparing techniques, i.e., the most possible radical excision of the lesions while preserving the functionality of the organs. This was very challenging. Women who had a hysterectomy were excluded from this study.

Furthermore, the larger the EN nodule, the higher the risk of complication [12]. On another hand, the danger of recurrence is higher in cases of incomplete excision of EL

[9]. Moreover, a delay in first-line surgical treatment may lead to irreparable consequences in young women seeking fertility [13] such as the future evolution of the disease, reduced ovarian reserve, severity of symptoms and radical surgery (hysterectomy). The complete excision is essential to improve the fertility rate in these women [13–15].

Another relevant topic is achieving a “correct” preoperative diagnosis of the endometriosis. The exact detection of the EM nodules is of utmost importance in managing patients with RVE and RCE, as these patients are suffering from extensive pain for many years before they

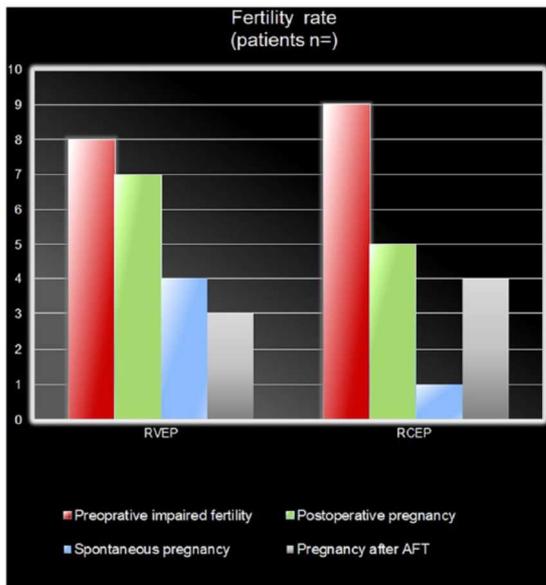


Fig. 3 Fertility rate in RVEP and RCEP pre- and postoperatively

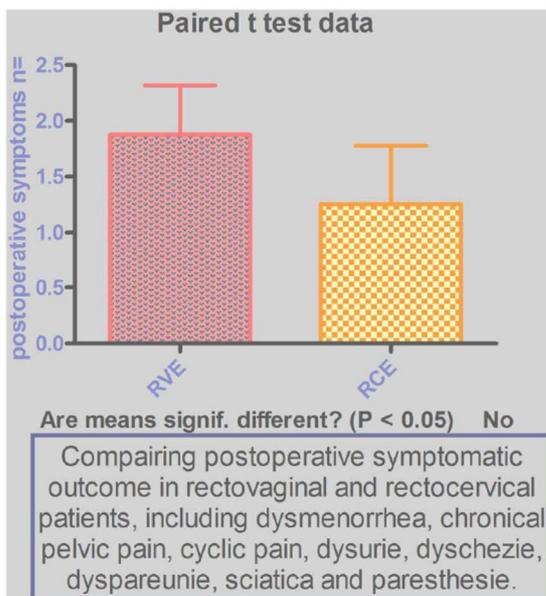


Fig. 4 The analysis of postoperative results, presenting no significant difference between RCE and RVE

receive suitable treatment [17]. Differentiating between rectovaginal endometriosis and retrocervical endometriosis is vital [6]. During ordinary gynecological examination, the rectosigmoid segment has to be palpated [10] to

determine the location and then extension of endometriotic lesions. Moreover, the posterior vaginal fornix should be inspected with a speculum, to exclude EM infiltration in vagina, and in terms of infiltration analyze the area of involvement. Several studies highlight the importance of the transvaginal sonography (TVS) as a non-invasive tool for diagnosis of DIE preoperatively [16, 17]. Visualization of sonoanatomical changes in the pelvis is essential [7, 8]. Demonstration of endometriotic involvement/nodules in the recto-vaginal septum represents RVE, and the identification of hypoechogenic irregular structures (EN infiltration) on the cervix involving the upper part of the posterior vaginal fornix determines RCE. Therefore, combining bimanual examination with TVS helps to understand the true localization of DIE. Endosonography and MRI provide further opportunity to expose EN localization [18–20]. In our patients, preoperative rectal examination identified 20 cases with bowel infiltration, which were then verified intraoperatively in the estimated extension.

Generally, RVE and not RCE is believed to present with rectal wall infiltration [6, 21], but our study also reported ten (66%) cases of RCE with rectal lesions, correlated and reported with ENZIAN score and rASRM classification (see Tables 2, 3). Therefore, a clear definition for RVE can be considered as the involvement of the vagina and rectovaginal septum, independent of the bowel infiltration. However, the question is which surgical technique is most optimal for RVE and RCE?

This study involves patients with very complex cases, affecting adjacent organs (bladder, intestines, nerve fibers, lymph nodes, and peritoneum) (Tables 2, 3). In these circumstances, the surgical technique is preoperatively unpredictable, and it is more challenging than usual. In the case of RCE without vaginal wall infiltration, it was reasonable to adopt a single laparoscopy. Moreover, applying a uterine manipulator was better highlighting anatomy of the posterior fornix and preventing excessive vaginal dissection. This method avoids possible damage of cervix and therefore improves the chance of successful pregnancy. RVE presented with different anatomical dissemination of endometrial lesions, including rectovaginal septum and vagina itself. Therefore, for RVE treatment was performed vaginal assisted laparoscopy to access the vaginal wall lesions easily, open the rectovaginal septum [10], dissect the infiltration completely and finally reconstruct the wall with an intravaginal suture. Previously, several groups avoided to resect presented vaginal nodules, concerning that excision would make more harm than EL itself [22]. This study presented 28 (91%) of women, RVE ($n=17$) and RCE ($n=11$), preoperatively suffering from dyspareunia, but postoperatively identifying only in two (6%) RVEP. Few studies have shown a huge impact of vaginal resection on the improvement in sexual activity postoperatively, reporting more than

80% women with a significant decrease in the presence and severity of dyspareunia [9, 23, 24].

Although some authors see vaginal openings as a main risk factor for complications [12, 25], this method might be of lower risk for patients with a partial bowel resection. As with applying two sutures at the same time on the intraabdominal side, an intestinal and vaginal suture might increase the chances of complications [26], like suture insufficiency, leakages or fistulas [27, 28]. Therefore, applying the suture intravaginally might be a factor for decreasing the friction between two sutures by having them on separate sides. In this study, from the 10/17 RVEP with partial bowel resection, only one case reported early post-operative complication, but without any evidence of vaginal or bowel suture insufficiency, intraoperatively demonstrating an unclear abdominal bleeding and later ureter leakage. Another case of RCE demonstrated a vaginal fistula in the early postoperative period because of anastomotic insufficiency, although no vaginal dissection was performed. The complete dissection of rectovaginal and retrocervical EL, including bowel resection and anastomosis, may appear too radical and tricky, resulting in high risk of postoperative complications [29] as various studies demonstrated postoperative complications rated from 10 to 18%, including anastomosis insufficiency, anastomotic stricture, urinary dysfunction and massive bleeding in patients after vaginal and partial bowel resection [30–33]. In this study, the bowel infiltration was presented from 6 cm till 10 cm above the anus. It is a very low anatomical localization for the bowel resection. Consequently, applying the protective ileostomy (PI) in patients with deep rectal bowel resection could have minimized the chances of these complications and led to the better recovery. Several studies question efficiency of temporal PI in EN patients with rectal resection [34, 35], although a lot of experienced gynecologists demonstrated improved postoperative outcome after applying PI [34, 36–38]. In this study, no patient with ultralow rectal resection and temporal PI reported any postoperative anastomosis-related complications. Nevertheless, the removal of all endometrial nodules carrying out the nerve structures could lead to the improvement of EN-related symptoms and reduced recurrence rate as well. These are important factors for pain generation in these patients [23, 39–41]. Moreover, endometriotic lesions can create their own autonomic and sensory innervation [41, 42] which can, therefore, be associated with hyperalgesia.

This presented approach to this disease seems to be effective, as the overall results of this study show a significant improvement in pain, fertility rate, quality of life, functionality of bladder and bowel postoperatively (Fig. 2), low rate of complications and recurrence rate (Table 1). 62% ($n = 21$) of the women reported symptom-free status, $n = 12/19$ with RVE and $n = 9/15$ RCE. It must be noted that 74% ($n = 25/34$) of these women took supportive hormonal

treatment postoperatively, to avoid recurrent disease and to treat persisting dysmenorrhea (in uterus sparing management). It is an interesting finding, as the preoperative hormonal treatment was not efficient for these same patients. In this study, $n = 19/34$ (56%) women received hormonal treatment prior to surgery and reported insufficiency of the HT whilst 12/19 RVEP (63%) and $n = 8/19$ RCEP (42%) had ongoing severe EN-related complaints. In the case of hormonal insufficiency, the indication of the surgical approach appears to be more effective and beneficial for the treatment of RCE and RVE [5, 9, 10, 43]. Moreover, surgery allows us to remove altered area and additional supportive HT terminates the further expansion of the endometriosis. Accordingly, this leads to an efficient postoperative outcome and improved quality of life. Furthermore, $n = 11$ women suffering from infertility took HT postoperatively in nonstop modus for a period of 3 months, including GnRHa ($n = 2$ RVEP; $n = 5$ RCEP) and dienogest ($n = 2$ RVEP; $n = 2$ RCEP), as for the period of wound healing after the excessive surgery and for the therapeutic purpose before IVF in order to achieve successful pregnancy [44]. The follow-up revealed $n = 6/11$ ($n = 3$ RVEP; $n = 3$ RCEP) postoperative successful pregnancies in these women. Although the remaining $n = 13$ (38%) of the women demonstrated postoperative EN-related complaints, the study reported a significant decrease in severity of symptoms and in the recurrence rate in this group (Fig. 2). $N = 8$ of this group took supportive hormonal treatment postoperatively, instead they had symptoms like CPP, dyspareunia, dyschezia, sciatica and paresthesia, and intensity of the symptoms was decreased from preoperative mean level of 8 (according to VAS score scale) to level 4 postoperatively. Another $n = 5$ patients from this group did not have HT when trying to conceive, their symptoms were dysmenorrhea, cyclic pelvic pain, dyschezia, but also with significant pain relief from preoperative mean level of 8 to level 5. Finally, postoperative statistical analysis reported no significant difference in postoperative outcome, between RCEPs and RVEPs (Fig. 4).

This study, in agreement with other studies, confirmed that the resection of the DIE in cases of RVE and RCE can be efficient in terms of successful pregnancy [13–15, 45]. Postoperatively, $n = 12$ (71%) patients seeking fertility achieved pregnancy in a mean time of 6 months, of which $n = 7$ with RVE and $n = 5$ with RCE (Fig. 3). Interestingly, 50% of conceptions happened spontaneously.

In conclusion, our aim was to demonstrate the importance of planning and performing surgery, respectively, to rectovaginal and retrocervical endometriosis, as well as how the preoperative indication can have a huge impact on the postoperative follow-up and complication rate.

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Compliance with ethical standards

Conflicts of interest All authors of this work declare that they have no conflict of interest.

Ethical issues All procedures performed in this study were in accordance with the ethical standards of the Charité ethics committee. The study was approved by the IRB of Charité ethics committee (EA).

Informed consent Informed consent was obtained from all the patients.

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Laparoscopic Neuronavigation for Deep Lateral Pelvic Endometriosis: Clinical and Surgical Implications.

Vito Chiantera, Marco Petrillo, Elene Abesadze, Giulio Sozzi,

Margherita Dessole, Mariano Catello Di Donna, Giovanni Scambia, Jalid Sehouli and Sylvia Mechsner.

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When and how should peritoneal endometriosis be operated on in order to improve fertility rates and symptoms? The experience and outcomes of nearly 100 cases

A. M. Dückelmann¹ · E. Taube² · E. Abesadze³ · V. Chiantera⁴ · J. Sehoul¹ · S. Mechsner¹

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Abstract

Purpose To analyze the follow-up results of patients suffering from symptomatic early-stage endometriosis after a consistent laparoscopic peritoneal stripping of the altered peritoneum (peritoneal endometriosis and surrounding inflamed tissue) was performed. This type of endometriosis is resistant to medical therapy and/or impairs fertility.

Methods Using our prospectively maintained database, we were able to identify all symptomatic women with the suspicion of only peritoneal endometriosis who underwent laparoscopy at our endometriosis center over a period of 5 years. All procedures were carried out in a standardized fashion by one single surgeon, who is highly experienced in minimal invasive surgery, and included a suspended hormonal pretreatment for 2 months. Postoperative outcomes including complications, fertility and recurrence rates were analysed.

Results Laparoscopic peritonectomy was performed on 94 women. Follow-up data were available in 87% of these cases. At the time of surgery, almost all patients tested showed signs of stage I or II endometriosis (44.7 and 48.9%, respectively). More than three-quarters of the women reported pain relief, inter alia, due to the post-surgical hormonal therapy. About one-third of the patients wanted to have children after the procedure. 62% of them became pregnant and the majority did so without the need for assisted reproductive therapy. In seven women a re-operation was performed.

Conclusion According to our data, a consistent excision of altered peritoneum followed by adjuvant hormonal therapy and multimodal concepts results in better outcomes for the patient, particularly in regards to pregnancy and recurrence rates.

Keywords Peritoneal endometriosis · Peritonectomy · Laparoscopic surgery · Pelvic pain · Infertility

Introduction

Endometriosis is a benign chronic inflammatory disease affecting millions of women worldwide during their reproductive years [1, 2]. The pathogenesis is still under debate,

however, most likely, stem cell such as cells from retrograde menstruation adhere to the peritoneal surface and develop into peritoneal endometriotic lesions [3, 4]. Apart from the establishment of such ectopic lesions, numerous and brisk immune cell infiltrates were found within the microenvironment of these lesions, indicating acute immunological reactions [5, 6]. Both pathways are linked to each other. Macrophages are in the peritoneal fluid as well as in the peritoneal lesions and in the unaffected peritoneum from women with endometriosis, secreting a variety of pro-inflammatory cytokines and chemokines in the peritoneal fluid [7, 8]. Neurotrophins and neuronal guidance molecules and their receptors are most highly expressed in the glands of endometriotic peritoneal lesions [9]. The release of nerve growth factors leads to changes in the peritoneal innervation [8]. This includes the hyperinnervation of sensory nerve fibers and the hypoinnervation of sympathetic nerve fibers with an imbalance of pro- and anti-inflammatory neurotransmitters

✉ S. Mechsner
sylvia.mechsner@charite.de

¹ Department of Gynecology, Charité-Universitätsmedizin Berlin Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

² Department of Pathology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

³ Department of Gynecology, Vivantes Clinic Berlin Hellersdorf, Myslowitzerstr. 45, 12621 Berlin, Germany

⁴ Department of Gynecologic Oncology, University of Palermo, Piazza Marina, 61, 90133 Palermo, Italy

[10, 11]. As more nerve fibres were found in the areas where increased numbers of macrophages were identified, the density of macrophages seems to correlate with the number of nerve fibres, which in turn correlates with the development of endometriosis-related symptoms [8, 12]. Endometriosis-associated immune cell infiltrates might be a trigger for a neurogenic inflammatory reaction and a critical point where cyclical pain becomes acyclical pelvic pain [10, 11, 13–15].

Pain is the main symptom of endometriosis patients with a very heterogenous variation of several symptoms including dysmenorrhoea, cyclical and acyclical pelvic pain, dysuria, dyschezia, dyspareunia etc. [16]. These symptoms have a negative impact on the physical, mental, and social well-being of patients [17]. The severity of pain is independent of the stage/extent of the disease and the appearance and location of endometriosis deposits [18–22]. However, pain generation is very complex and the impact of peritoneal lesions on pain generation is difficult to understand and differentiate from symptoms caused by other kinds of illness, like adenomyosis, deep infiltrating lesions, endometrioma or adhesions [23]. Many patients suffer from a combined manifestation of lesions and present a combination of symptoms [23].

The first step in the treatment of patients with suspected endometriosis symptoms should be hormonal treatment. If this fails then surgery should be indicated as the next treatment option [24–28]. The therapeutic approach of peritoneal endometriosis worldwide is very heterogenous. Many patients receive laparoscopy for the diagnostic purpose only. So residual foci are left behind, which should be avoided as an outcome depending on the completeness of the surgical treatment. Compared to diagnostic laparoscopy only, the surgical management of mild endometriosis seems to be more effective in treating the symptoms of pain and improving the quality of life for women with endometriosis as well as improving their pregnancy rate [29–33].

In a randomized, placebo-controlled trial by Abbott et al. comparing immediate excision with delayed surgery on 39 women, of whom about 50% had rAFS stage I and II,

surgery was associated with a 30% placebo response rate, not dependent on the severity of the disease. Approximately 20% of women did not report an improvement after surgery for endometriosis [34]. In another classical study by Sutton et al. on the same question (but on women with mostly stage I disease receiving laparoscopic ablation) the nonresponse rate was 38% [35]. Recently a review showed that many women only gain limited or intermittent benefits from long-term treatment [36].

As a consequence, early stage surgical intervention in endometriosis should be limited to patients with painful symptoms and contraindications or ones who show a poor response to medical therapies or in cases of subfertility [32]. Hormonal treatment as therapeutic attempt should always be performed before surgery, in particular in the absence of any sonographic evidence of endometriosis, to clarify the cause of pain and identify patients with symptomatic peritoneal endometriosis. The surgical approach should be reserved for clearly defined objectives: to reduce pain, increase patient's pregnancy rate, exclude advanced stages of endometriosis or malignant adnexal masses and delay recurrence for as long as possible [37].

Aside from invasiveness, morbidity and complication risks, the recurrence of symptoms or lesions after surgery is highly concerning [38–40]. According to a review the 2 years recurrence rate is estimated to be 21.5% [41]. The association between disease relapse and rARSM stages is still under debate, recurrence is, however, markedly prevented by the administration of estrogen-progestins [41–45].

Sharp excision, bipolar diathermy and ablation by CO₂-laser are the most common techniques in laparoscopic surgery for endometriosis. The question of which techniques should be preferred to manage superficial peritoneal disease has not yet been answered [46] (see Table 1).

In practice, there is a tendency for gynecologic surgeons to prefer to perform ablation because it is considered easier. Theoretically, excision is advantageous because it ensures that the entire lesion or pathologic tissue is removed.

Table 1 OP technique

	Kind of study	OP technique	Number of patients	Outcome
Healey et al. [73]	RCT	Excision vs ablation with CO ₂ laser	178	No significant difference at 12 months (improvement of patients' symptoms in both arms). Trends in improvement of dyschezia and dyspareunia
Wright et al. (75)	Prospective randomized	Excision vs ablation	24	No significant difference (symptom relief at 6 months in both arms)
Radosa et al. (74)	Retrospective	Excision vs coagulation	79	Coagulation group better for dysmenorrhea and the number of recurrence with subsequent surgical intervention (2.8 vs 18.6%)
Riley [71]	RCT	Excision vs ablation by using an argon beam coagulator	73	Ablation group better for dyspareunia at 6 months only. No significant difference at 12 months

In our opinion, there is a lack of studies regarding the indication for surgery of peritoneal endometriotic lesions and the surgical procedure to treat them. This paper focuses on our experience and presents the follow-up results after laparoscopic peritoneal stripping of the altered peritoneum (peritoneal endometriosis and surrounding inflamed tissue).

Materials and methods

We analysed our prospectively maintained database to identify all women who underwent laparoscopy at our endometriosis center from January 2014 to June 2019. Women with a sonographic exclusion of complex endometriosis manifestation and symptomatic endometriosis and/or impaired fertility older than 18 years were included. Indication for surgery was only given for typical symptoms of endometriosis after the failure of sufficient hormonal treatment (amenorrhoea > 6 months) with ongoing acyclical pelvic pain. The estimated endometriotic lesions were peritoneal lesions (with or without adenomyosis). Patients were not excluded if they had already been diagnosed with endometriosis. An initial survey of the pelvis was performed, and any patient found to have ovarian cysts or endometriomas, retrospectively, or any signs for deep infiltrating endometriosis, was excluded. Exclusion criteria included further intraoperative bilateral salpingo-oophorectomy and hysterectomy for adenomyosis. The goal was to concentrate on women with only peritoneal endometriosis.

The database contained all information about demographic and clinical characteristics, medical examination, imaging and surgical therapy. The preoperative pelvic pain severity was assessed by a 10-point visual analog scale (VAS) that was routinely performed at preoperative visits and covered different types of pain: dysmenorrhea, cyclic pain, complex chronic pain, dyspareunia, dysuria and dyschezia. VAS scores were a validated way to measure pain and used to measure overall pelvic pain as well as the different types of visceral pain [47]. We stated all clinically relevant symptoms with a score ≥ 5 .

All procedures were carried out in a standardized fashion by one single surgeon, who is highly experienced in minimal invasive surgery for endometriosis. A suspended hormonal pretreatment for 2 months followed the surgery [48]. In all cases, a careful evaluation of the whole abdominal cavity was performed. The clinically suspected diagnosis was verified intraoperatively and all visible endometriosis implants and/or inflammatory altered peritoneum were radically excised (peritonectomy) including the removal of around two cm of the surrounding normal-appearing tissue (wide excision). For classification, we used the revised score of the American Society of Reproductive Medicine (rARSM) [49]. Excision was carried out by grasping the peritoneum

with the endometriotic lesion, thus distancing it from the underlying tissue. Using laparoscopic scissors, the lesion along with a border of normal peritoneum was extracted [48]. We did not use barrier methods to prevent adhesions. Excised lesions were submitted for histological examination to confirm the diagnosis and analyse the status of inflammation and fibrosis. After surgery, long-term hormonal therapy was offered at the hospital to all women not trying to become pregnant.

The primary outcome was the confirmation of diagnosis, a change in pain symptoms, quality of life assessment and pregnancy in cases of patients who wanted children at the follow-up visit. A therapeutic response defined a > 50% reduction in symptoms. Patients who did not visit our outpatient clinic were contacted by telephone at least three times.

Data evaluation and statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software, version 26 (IBM Corporation, Armonk, NY, USA). If data are missing, the total number of cases with available information is referred to. Categorical variables are reported as frequencies and percentages. Continuous variables are reported as the mean and standard deviation. Spearman's correlation coefficient was used to compare non-normally distributed variables. A within-group comparison was undertaken with the Wilcoxon rank-sum test for non-parametric data. We performed a stepwise backward logistic regression to assess potential clinical characteristics independently associated with pain scores. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 94 patients, who showed symptoms resistant to medical treatment and had received peritonectomy within a time period of 5 years at our endometriosis center, were included in this study. The follow-up data of 82 patients (87.23%) were available.

The average age of the patients was 29.40 years (± 6.751) at the time of surgery, 84.9% of women were nulliparous, 15.1% were uni- or multiparous. 42.6% completed a preoperative questionnaire, while the other patients were questioned in detail during a personal interview.

The vast majority (91.2%) of women had taken pain medication (non-steroidal anti-inflammatories or spasmolytics) before surgery without sufficient pain relief, and 68.1% women had taken at least one form of hormonal treatment (combined oral contraceptives, progesterone only pills or a contraceptive vaginal ring) (Table 2). Hormonal treatment was interrupted at least 2 months prior to surgery in all cases.

Table 2 Characteristics of the patients included

Age (years) ± SD	29.40 ± 6.751
Nulliparous ^{*86}	73 (84.9%)
Multiparous ^{*86}	13 (15.1%)
Pain killer preop. ^{*57}	52 (91.2%)
Hormonal treatment preop. ^{*91}	62 (68.1%)
Vegetative symptoms ^{*64}	38 (59.4%)
Nicotine ^{*38}	13 (34.2%)
Depression ^{*88}	15 (17%)
Adenomyosis sonographically ^{*82}	62 (75.6%)
Normal pelvic situs ^{*82}	15 (18.3%)
Other pathological finding ^{*82}	5 (6.1%)
First surgery	47 (50%)
Surgery for other reasons (such as appendectomy, ovarian cysts and emergency diagnostic laparoscopy)	6 (6.4%)
Previous surgery for EM	41 (43.6%)
EM diagnosed preop. ^{*93}	49 (52.7%)
Child wish ^{*93}	61 (65.6%)
Impaired fertility ^{*61}	29 (47.5%)

*n = number of women included in this subanalysis, variation due to missing data

The majority of women had vegetative symptoms (59.4%), such as nausea, vomiting, headache, migraine, diarrhea and obstipation. About one-third (34.2%) indicated nicotine abuse while nearly one-fifth (17%) suffered from depression (Table 2).

Primary surgical treatment was performed in one-half of cases. 43.6% of patients had previous abdominal surgical interventions for endometriosis. Accordingly, in about one-half of the patients' endometriosis was diagnosed preoperatively.

Primary indications

Ultrasound examinations preoperatively revealed adenomyosis in three-quarters of the patients and any other pathological findings, such as the suspicion of extra ovarian cysts or a malformation of the uterus, were found in 6.1%. In 18.3% a normal pelvic situs was diagnosed (Table 2).

86% of patients disclosed that they suffered from dysmenorrhea, 67.4% had cyclic pain, 55.9% reported complex chronic pain, 62.4% dyspareunia, 21.5% dysuria and 35.5% dyschezia. For pain levels please see Table 3.

65.6% of women said they wanted to have a child preoperatively and impaired fertility was seen in about one-half of these patients (Table 2), out of these three had further problems complicating/aggravating fertility, namely Asherman, PCO and adrenogenital syndrome.

Table 3 Presurgical symptoms

Dysmenorrhea preop. ^{*93}	80 (86%)
Cyclic pain preop. ^{*92}	62 (67.4%)
CCP preop. ^{*93}	52 (55.9%)
Dyspareunia preop. ^{*93}	58 (62.4%)
Dysuria preop. ^{*93}	20 (21.5%)
Dyschezia preop. ^{*93}	33 (35.5%)
Strength of dysmenorrhea preop. average and max. (median)	7 and 9
Strength of cyclic pain preop. average and max. (median)	5 and 7
Strength of chronic pain preop. average and max. (median)	5 and 8
Strength of dyspareunia preop. average and max. (median)	4 and 7
Strength of dysuria preop. average and max. (median)	2 and 6
Strength of dyschezia preop. average and max. (median)	4 and 7

*n = number of women included in this subanalysis, variation due to missing data

Intraoperative findings

Endometriosis was clinically confirmed in all cases on the basis of a conspicuous peritoneum. At the time of surgery, almost all women showed stage I or II endometriosis (44.7 and 48.9%, respectively) as classified by the rASRM score. 6.4% indicated stage III, in 17% of patients, in addition to pelvic peritoneal lesions, extragenital endometrial lesions were found outside of the pelvis, mainly on the diaphragm (Table 4). Of the 73 patients who underwent chromoperutubation, a bilateral fallopian patency was seen in 76.7% of cases, unilateral patency in 32.9% and no patency was found in 4.1%. There were no complications reported for the duration of the whole study. Residua of endometriosis had to be left for various reasons in seven women: missing

Table 4 Intraoperative findings

Tubal patency	73 (87.7%)
No patency ^{*73}	3 (4.1%)
Patency both sides ^{*73}	56 (76.7%)
Patency one side ^{*73}	24 (32.9%)
rARSM I	42 (44.7%)
rARSM II	46 (48.9%)
rARSM III	6 (6.4%)
EM genitalis externa	16 (17%)
Histological diagnosis: EM ^{*90}	25 (27.8%)
Histological diagnosis: EM and inflammation ^{*90}	54 (60%)
Histological diagnosis: inflammation ^{*90}	11 (12.2%)

*n = number of women included in this subanalysis, variation due to missing data

informed consent in case of unexpected incidental endometriosis of the diaphragm (two times) and superficial lesions on the large intestine (three cases), which were coagulated, or unsuspected deep infiltrating endometriosis on the sigma (two times).

88% had histologically confirmed endometriosis combined with chronic inflammation, and fibrosis, and the remaining patients had signs of peritoneal inflammation/fibrosis only (Fig. 1).

Post-operative outcome

The mean time after which the follow-up questionnaire was completed was 14.86 months (± 12.792 , range 2–59 months).

Postoperative data showed a remarkable improvement in the quality of life of the majority of patients. More than three-quarters of women reported pain relief (Fig. 2). Of these patients, 23.8% reported symptom-free status and in 52.5% of the women endometriosis-associated symptoms improved greatly. Significant results were reported postoperatively in fertility rates. Within the specified timeframe between performed surgeries to follow-up, 62.07% (18/29) of women with infertility problems became pregnant post surgically, seven women had already delivered, six women had an ongoing pregnancy, four patients had an abortion, one

patient had a biochemical pregnancy (Fig. 3). Only three out of these 18 women needed assisted reproductive technology (ART).

Despite our insistent recommendation only 29.87% (23/77) of patients took postoperative hormonal treatment (HT), 11 women rejected the hormonal therapy, seven women did not tolerate therapy, in one patient the gynecologist refused to prescribe HT. In six women multimodal pain therapy was proposed. Twenty-nine patients wanted to get pregnant and consequently opted against HT (Table 5).

Symptoms decreased significantly after surgery in the majority of patients ($Z = -4.330$, $p < 0.000$). In comparison to the group of women without HT post surgically, there was a significant decrease of pain in the HT-group (Figs. 4, 5). After analyzing the effect of pre-operation on the outcome, there were no significant differences between the two groups. In seven women a re-operation was performed (see Table 6). The evidence of recurrence was confirmed in only two patients, one of which wished to conceive. This patient underwent fertility treatment for the last 2 years and due to the progression of symptoms and the status of the fallopian tubes we decided to do laparoscopy again. She became pregnant (biochemical pregnancy) after our second intervention. The other patient rejected post-surgical hormonal treatment. The main problem facing the other women

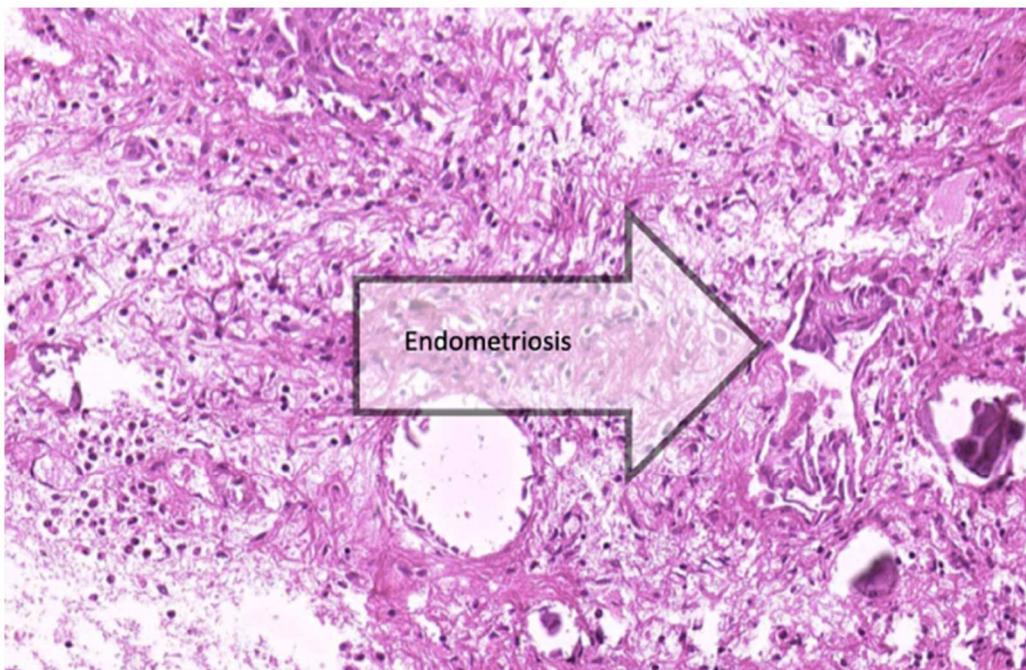


Fig. 1 some acute and chronic inflammatory cells, psammomatous calcification

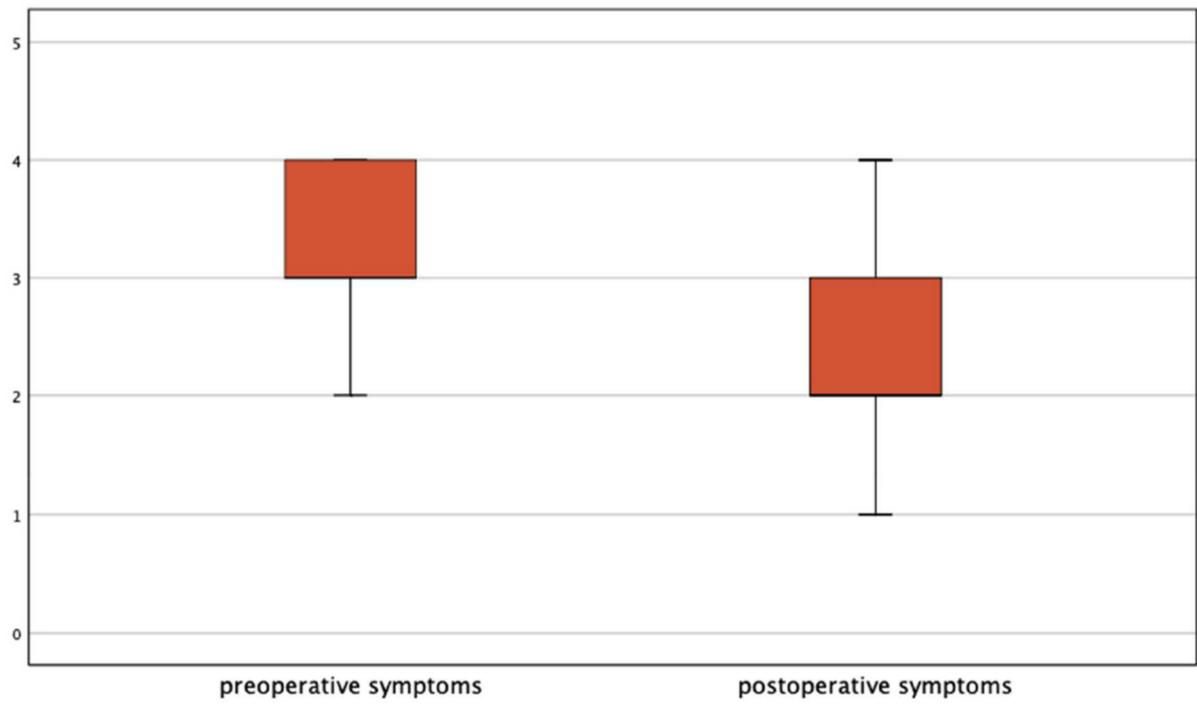


Fig. 2 Significant difference between symptoms before and after surgery presented by box-plots. Pain score divided into 4 categories: 4: severe (VAS 8–10), 3: modeste (VAS 5–7), 2: mild (3–4), 1: no pain

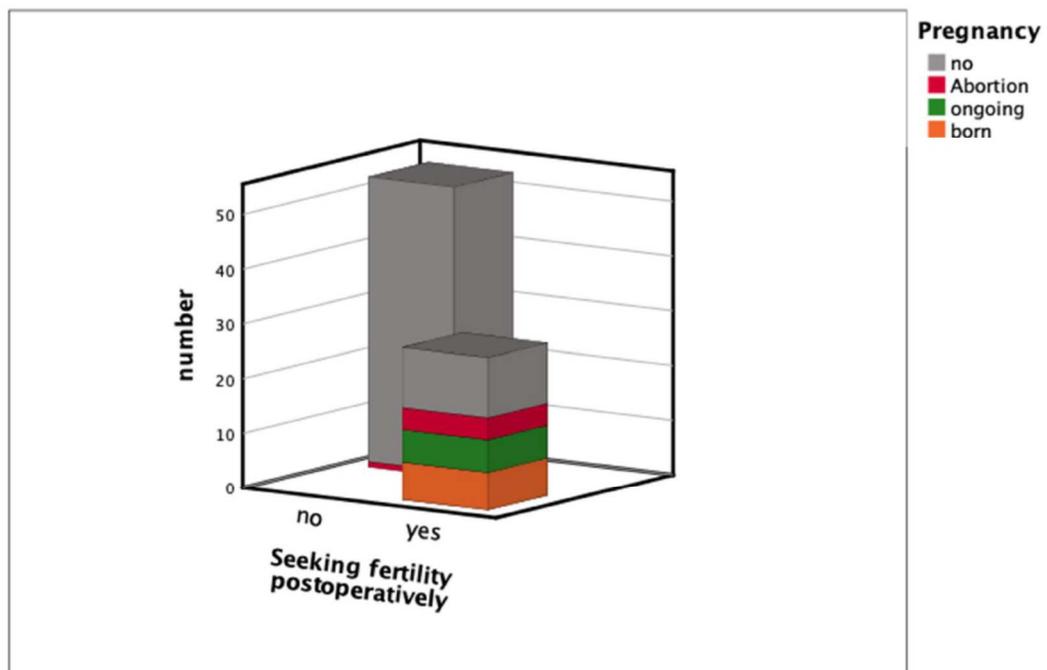


Fig. 3 Fertility rate after surgery

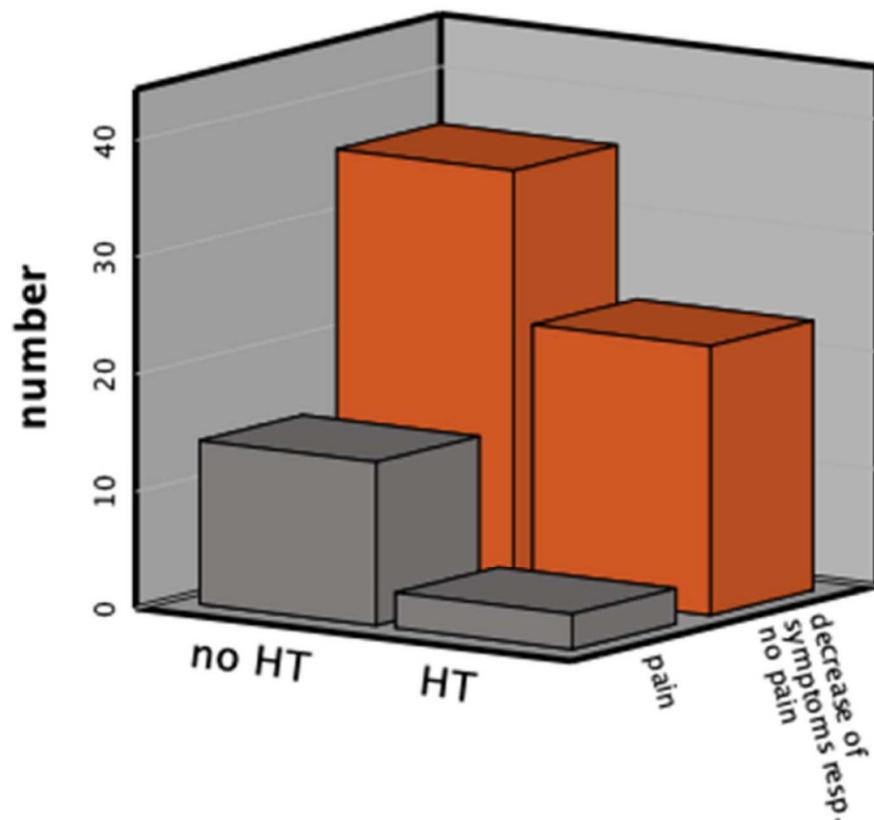
Table 5 Follow-up

Time of follow-up (range)	14.86 ± 12.792 (2–59)
Re-operation ^{*83}	7 (8.4%)
No pain after surgery ^{*80}	19 (23.8%)
Symptoms improved after surgery ^{*80}	42 (52.5%)
Symptoms unchanged/worse after surgery ^{*80}	19 (23.8%)
Child wish post surgically ^{*81}	29 (35.80)
Deliveries ^{*29}	7
Ongoing pregnancies ^{*29}	6
Abortion ^{*29}	5
ART ^{*18}	3 (16.7%)
Hormonal therapy (HT) after surgery ^{*77}	23 (29.87%)
HT rejected ^{*77}	11 (14.29%)
HT not tolerated ^{*77}	7 (9.09%)
Multimodal pain therapy ^{*77}	6 (7.8%)

*n = number of women included in this subanalysis, variation due to missing data

was severe adenomyosis. At re-operation, we could see the intact/regrown peritoneum without any signs of inflammation (Fig. 5). We did not detect an excessive presence of adhesions.

Fig. 4 Symptoms post surgically according to hormonal therapy



Correlation analysis and logistic regression revealed no effect on the influential parameters of the pain scores and postoperative symptoms.

Discussion

In summary, endometriosis was clinically confirmed in all cases and laparoscopic excision in our cohort was beneficial in reducing pain, thus improving the patient's quality of life and enhancing the chance of pregnancy of women in the early stages of endometriosis for more than 1 year following the check-up. However, to achieve these objectives, a well-considered selection for surgery in endometriosis patients is crucial and adequate timing guarantees the highest benefit [50]. Endometriosis has to be understood as a chronic disease which needs individual concepts. Especially the first surgery has to be planned and performed very carefully [51]. Early and recurrent surgeries due to inadequate evidence have to be avoided, as it is well known that endometriosis patients generally need multiple surgeries and have a poor physical and mental health status, and there is a higher chance that disease recurrence happens [52].

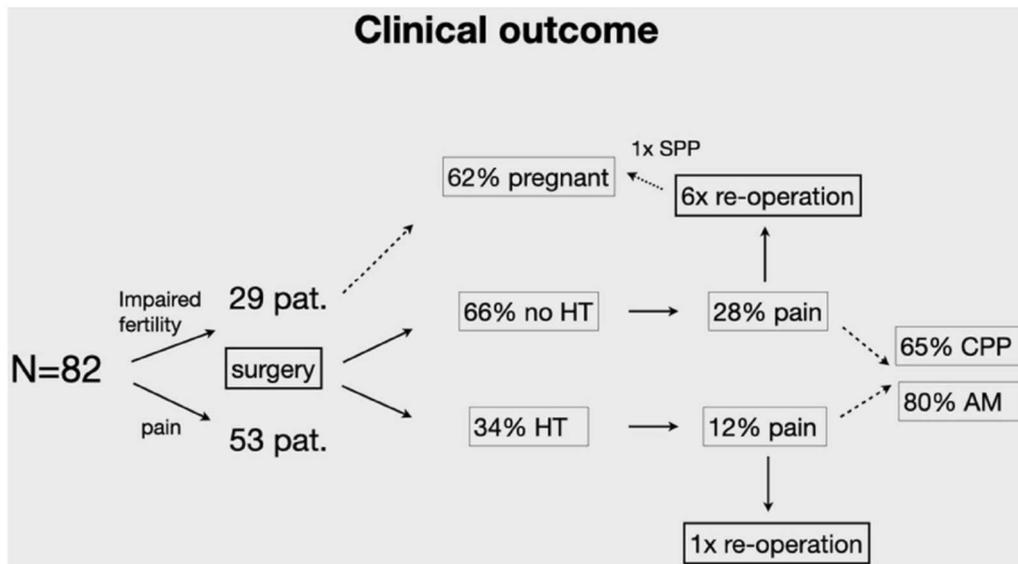


Fig. 5 Description of cohort of patients. *HT* hormonal therapy

The success rates for reducing the characteristic symptoms of endometriosis have been stated in the literature and are similar to the results we found in our study. Almost 25% were non-responders in a recent study by Ghai et al. on 102 women with superficial endometriosis, independent on the surgical method (excision or ablation) [53]. Interestingly, women were more likely to be non-responders if treated for early-stage endometriosis compared with those with severe endometriosis. One reason for this might be that surgeries are often done under hormonal treatment like combined oral contraception, so the extent of peritoneal endometriosis is underestimated and implants are left. One study by Strowitzki et al. clearly showed a downstaging of peritoneal endometriosis under hormonal treatment with dienogest [54]. However, data on presurgical suspended hormonal therapy are usually missing.

The pelvic peritoneum appears to play a key role in the development and maintenance of endometriosis. The attempt of hormonal therapy before surgery helps to identify patients with exclusively acyclic pain resistant to hormonal treatment as an indication for the occurrence of peritoneal lesions with neurogenic inflammation. Such patients might have a benefit from the excision of these lesions. Accordingly, it was shown that the removal of peritoneal lesions remarkably decreased not only the pain level, but the low pain threshold went back to the normal level of healthy controls [55–57]. Another benefit of excision is the histologic confirmation of the disease. Nearly 100% of our patients had an altered peritoneum with a histologically proven disease and/or inflammation.

Histologic diagnosis is, however, dependent on pathologist's experience [58].

The patients' hormonal therapy had been stopped before surgery (minimum 2 months prior to surgery) due to the chance of failure. So, the altered peritoneum was more visible and glassy lesions and inflammation could be removed. Interestingly not only the endometriotic lesions could be confirmed, but also the presence of inflammation in nearly 75% of cases. This extended inflammatory reaction might be underestimated as an essential part of pain generation. However, certain patients suffered from persistent pelvic pain after the excision of endometriosis. This might also be associated with adenomyosis, a main cause of dysmenorrhea. During sonography examinations, it was discovered that three-quarters of women in our cohort had adenomyosis. It is well known that in up to 90% of the cases, endometriosis and adenomyosis appear at the same time [59].

In more than 20–25% of patients, pain still remains a part of their daily life despite the well processed surgical or hormonal treatment [60]. Similarly, in our cohort 23.7% of patients experienced no benefit after surgery (Table 5). However, 11 of them (57.9%) rejected adjuvant hormonal treatment.

Our renewed surgery rate is low (8.54%) compared to the probability of a further surgical procedure of about 15–20% according to literature and this may be attributed to the correct suspicion of peritoneal endometriosis and the adequate excision of all areas of abnormal peritoneum (peritoneal lesions and inflamed altered tissue without hormonal downregulation) with a sufficient safety margin in all cases

Table 6 Recurrence

	Surgery before our surgery?	Time interval between surgeries	Indication	Surgery	Intraop. findings	Postop. therapy	Outcome
Case 1	No	2 years	Persistent pain, increased tension of pelvic floor	2nd: diagnostic (performed in another hospital), 3rd: peritonectomy	No EM at 2nd surgery. rARSM I and AM at 3rd surgery	Multimodal pain therapy, HT after 1st surgery. Fertility treatment (2×IVF) after 2nd surgery	Biochemical pregnancy after 3rd surgery
Case 2	1 year before our surgery, not clear if HT	2 years	Cyclic pain, dysmenorrhea	Peritonectomy	rARSM II	Rejects HT, takes cortisone therapy	1 year after surgery again incipient neurogenic pain
Case 3	No	1 1/2 years	Upon request (to prevent HT)	Diagnostic, removal of isthmocele	Severe AM, no EM. Ovula nabothii in isthmocele	HT	1 year after surgery again incipient cyclic pain (because of retroperitoneal fibrosis?)
Case 4	7 years before our first op, not clear if HT	2 years	Emergency for acute pain	Diagnostic	AM, no EM	HT	After hysterectomy (performed in another hospital) now improvement of symptoms
Case 5	1 year before our first op, long-term treatment with IUD	1/2 year	Upon request	Hysterectomy	Severe AM, no EM	No therapy	Symptoms improved after hysterectomy
Case 6	no	4 1/2 years	Persistent pain, spinal hyperalgesia	Diagnostic, IUD	Severe AM, no EM	Rejects therapy	Asks for hysterectomy
Case 7	1 year before our surgery, not clear if HT	2 years	Upon request	Diagnostic	No EM	HT	

[61–63]. An earlier report demonstrated that one-quarter of the patients with proven peritoneal endometriosis already had microscopic endometriotic implants in their peritoneum that were otherwise deemed normal [64]. And others showed recurrent endometriotic lesions especially in the margin of earlier resection areas [65]. We recommend hormonal treatment following surgery to all our patients with the aim to prevent recurrence [66, 67].

In patients who received further surgery after extensive peritonectomy, all but two had no evidence of endometriosis, neither macroscopically nor histologically at the time of re-operation. This does not signify that endometriosis has not been the cause of pelvic pain but proves the concept of chronic long-term pain which may be a consequence of the up-regulation of pain sensitization and not recurrent disease. Such pain may not go away even after hormonal and/or surgical therapy [68]. These chronic pain patients suffer from spinal hyperalgesia, myofascial pain syndrome or pelvic floor muscle imbalance. Chronic pain is an interplay

of pathophysiological, psychological and social factors. The complexity of pain sensation and perception have to be addressed. We recommend multifaceted care models including pain management programs, nutrition advice, counseling and education, osteopathy, and psychological therapies alongside gynecologic treatments to affected women [69].

Based on two older contradictory studies and a Cochrane review comparing laparoscopic surgical treatment with diagnostic laparoscopy only in minimal and mild endometriosis, the laparoscopic surgery had better results for pregnancy after 20 weeks, regardless of the surgical method [29–31]. The odds ratio of 1.65 and the number needed to treat of 12 are though viewed critically [61]. In a comparison of the basic chance of pregnancy of about 20% our pregnancy rate is pleasantly more than three times higher. In our view, the surgical removal of peritoneal implants with a safety margin address the nociceptive as well as the neurogenic inflammatory pathway of pain caused by endometriosis. Maybe the excision of

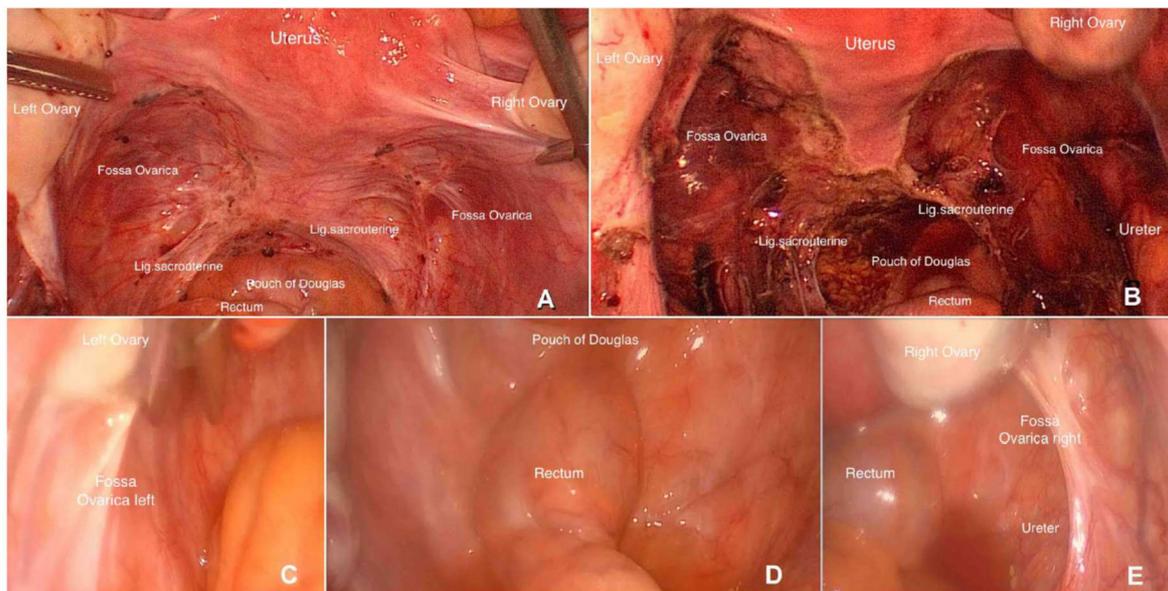


Fig. 6 Surgical site before surgery (a), after surgery (b) and at re-operation (c–e)

the inflamed tissue affects fertility. We recommend timely and comprehensive surgical management and determined fertility treatment in patients wishing to conceive considering the higher chance of conception within 2 years of surgery and the negative impact of repeated surgery on fertility outcomes [50] (see Fig. 6).

Strengths

One methodological strength of this study is the standardized documentation of clinical data and pain history on a dedicated questionnaire in the majority of cases. Surgery was done with the expectation of peritoneal endometriotic lesions and good and uniform preparation of the patients. All interventions were done by a single high-volume minimally invasive gynecologic surgeon with a focus on endometriosis. Consistent techniques were performed throughout the duration of the study. All patients had to discontinue their choice of standard medical suppression treatment for endometriosis at least 2 months before surgery. All women were evaluated and treated by physicians with long-standing and extensive expertise in the management of endometriosis. This is indirectly confirmed by the observation that endometriosis was confirmed in all cases. In addition, the follow-up interviews were performed mainly face-to-face, reducing the risk of recall bias. Our follow-up rate was high compared to other studies (61.61% in Yeung et al., 60.3% in Riley et al. [70, 71]).

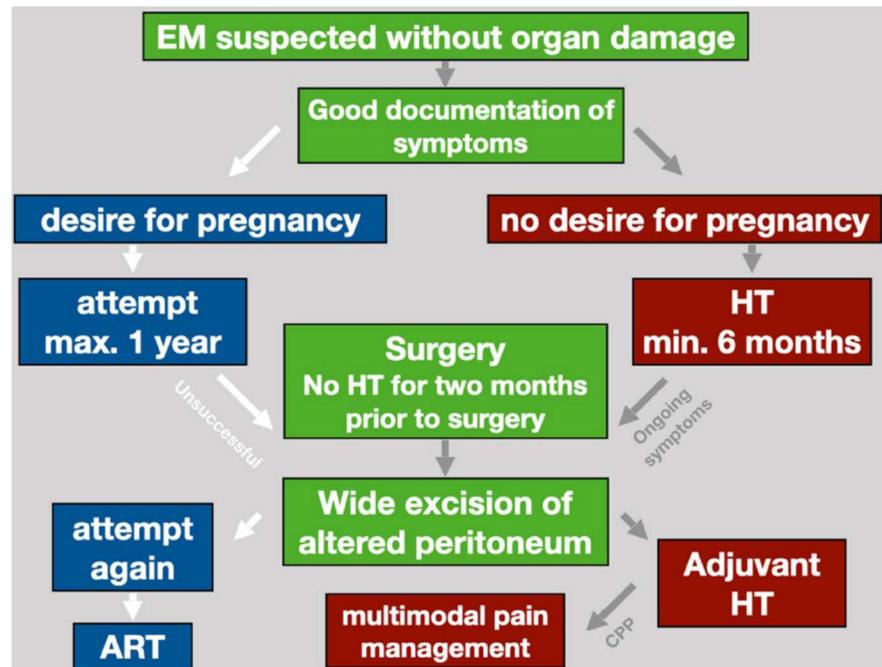
Limits

Regarding the limitations of this study, many women (43.6%) had previously been operated on due to symptoms of endometriosis, prior to having surgical excision. It is possible that this may bias the outcome, with women being pre-selected because they had had a previously failed therapy. This highlights two points: the first is that the perfect treatment has yet to be found. All current available treatments have a significant “failure rate” as noted by the recurrence of pain and the desire for further treatment. The second is that endometriosis is a very individual chronic disease requiring different treatments depending on the patient’s particular phase of life. Interestingly our surgeries on women, who had been operated previously, were as successful as first time interventions. One possible explanation could be that the first operations had been performed under hormonal therapy (Fig. 7).

The design was one cohort and the time of follow-up was inconsistent. With the given sample size of the study, it cannot be excluded that some of the observed effects could be clouded by subsequent medical or surgical treatment not reported by patients or recorded in our medical files.

We do not have the post-surgical VAS scores of symptoms. An important change for the patient may be one that represents a meaningful reduction in symptoms or improvement in HRQoL from her point of view. Vincent et al. suggest that the definition of a responder in endometriosis corresponds to a > 30 or > 50% reduction in symptoms [72]. We

Fig. 7 Standard of procedure in our hospital



classified trial participants as a responder who called themselves a responder by having had a subjectively satisfying response to therapy (> 50% reduction in symptoms).

It is possible that the results of this study may be affected by the 12.77% of women who were not reached for follow-up, since subjects lost to follow-up notoriously have a worse prognosis [43]. We compared responders with non-responders. Based on this analysis it is unlikely that the results would be significantly altered by women who were not included in the follow-up cohort.

Summary

We understand endometriosis as a complex and multifactorial disease. Patients with endometriosis need individual management of the disease regarding the personal situation (symptoms and family planning). Early and recurrent surgeries for diagnosis only without any therapeutical concept have to be avoided [50, 51]. Long-term treatment with hormones and multimodal concepts are needed.

Author contributions AD: Data collection, management and analysis, manuscript writing. ET: Data collection, manuscript editing. EA: Data collection, manuscript editing. VC: Manuscript editing. JS: Manuscript editing. SM: Project development, data analysis, manuscript editing.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AD, ET and EA. The first draft of the manuscript was written by AD. All authors read and approved the final manuscript.

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Data availability Data will be available upon request.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethics approval The study was performed in line with the principles of the Declaration of Helsinki. It was approved by the local Institutional Review Board and all participants provided written informed consent (to participate and for publication).

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10 Lebenslauf

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

11 Publikationsliste

1. When and how should peritoneal endometriosis be operated on in order to improve fertility rates and symptoms? The experience and outcomes of nearly 100 cases.
Dückelmann AM, Taube E, Abesadze E, Chiantera V, Sehouli J, Mechsner S.
Arch Gynecol Obstet. 2021 Feb 3. doi: 10.1007/s00404-021-05971-6.
2. Post-operative management and follow-up of surgical treatment in the case of rectovaginal and retrocervical endometriosis.
Abesadze E, Chiantera V, Sehouli J, Mechsner S.
Arch Gynecol Obstet. 2020 Oct;302(4):957-967. doi: 10.1007/s00404-020-05686-0.
3. Possible Role of the Posterior Compartment Peritonectomy, as a Part of the Complex Surgery, Regarding Recurrence Rate, Improvement of Symptoms and Fertility Rate in Patients with Endometriosis, Long-Term Follow-Up.
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J Minim Invasive Gynecol. 2020 Jul-Aug;27(5):1103-1111. doi: 10.1016/j.jmig.2019.08.019.
4. Laparoscopic Neuronavigation for Deep Lateral Pelvic Endometriosis: Clinical and Surgical Implications.
Vito Chiantera, Marco Petrillo, Elene Abesadze, Giulio Sozzi,
Margherita Dessoie, Mariano Catello Di Donna, Giovanni Scambia, Jalid Sehouli and Sylvia Mechsner.
J Minim Invasive Gynecol. 2018; 25, 1217-1223. <https://doi.org/10.1016/j.jmig.2018.02.015>.
5. How to understand the complexity of endometriosis related pain. A review.
V. Chiantera, E. Abesadze, S. Mechsner
J Endometr Pelvic Pain Disord 2017; 9(1): 30 – 38 DOI:10.5301/je.5000271
6. Abdominal Wall Endometriosis: Myofibroblasts as an evidence of metaplasia. A case report
M.G. Ibrahim, E. Delarue, E. Abesadze, M. Haas, J. Sehouli, V. Chiantera, S. Mechsner.
Gynecol Obstet Invest. 2017;82(1):96-101. doi: 10.1159/000452101. Epub 2016 Nov 4
7. An atypical manifestation of inguinal endometriosis in the extra pelvic part of the round ligament: A case report.
V. Chiantera, E. Abesadze, M.G. Ibrahim, A.M Dückelmann, S. Mechsner.
Int J Reprod Contracept Obstet Gynecol. 2016; 5(9): 3202-3207

Berlin, den 07.04.2021

12 Die Liste ausgewählter Publikationen:

1. Post-operative management and follow-up of surgical treatment in the case of rectovaginal and retrocervical endometriosis.

Abesadze E, Chiantera V, Sehouli J, Mechsner S.

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