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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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Abstract

Study objectives:

Besides the pain, there are two further problems in the management of endometriosis: the high recurrence rate of 10% per year and the high rate of impaired fertility. The pathogenesis, of these two factors, is not completely investigated.

Design:

This is a cohort retrospective study and aim of this study is to evaluate the complete excision of endometriotic lesions including posterior compartment peritoneum considering postoperative outcome, focusing on pain devolution, fertility rate and recurrence rate.

Setting:

Charité University clinic, Department of Gynaecology, Endometriosis research Centre.

Patients:

54 patients were enrolled in this study, with severe deep infiltrating endometriosis (scored by ENZIAN) and superficial endometriosis, as well as endometriomas (rASRM I=3; II-15; III-10; IV-26).

Intervention:

Posterior compartment peritonectomy (visible endometriotic lesions and inflamed altered peritoneum) was performed in all patients as a part of the complex surgery: complete excision of endometriosis.

Measurement and Main Results:

Postoperative outcome was evaluated, based on the post-operative follow-up (up to 5 years) from 54 investigated patients. In 36 women (66%) pre-operative complaints were eliminated. Furthermore, from 28 women seeking fertility, pregnancy was reported in 13 cases (46%). Remarkably, in 7 (54%) cases pregnancy occurred spontaneously and in the remainder with assisted fertilization. Additionally, long-term follow-up demonstrated a recurrence rate in 1.8% of

patients.

Conclusion:

Overall, the number of complaints was significantly reduced. Only in the case of persisting adenomyosis patients suffered from ongoing postoperative complaints, as in reproductive aged women keeping the uterus was highly required. Although this pilot study about systematic posterior peritonectomy showed improved recurrence rate and fertility rate, the main question remains: does this surgical technique appropriate better results and outcomes in the future. This question has to be addressed in a prospective randomized study.

Key words: Endometriosis, pelvic pain, infertility, laparoscopy, peritoneum, Posterior compartment peritoneum, peritonectomy, long-term follow-up, recurrence rate.

The aim of this study is to evaluate the efficiency of the posterior compartment peritoneum peritonectomy in the pathogenesis of endometriosis. Analyzing postoperative outcome, including severity of EN-related complaints, fertility rate and recurrence rate.

Introduction

Endometriosis is a complex gynecological disease, affecting 10-20% of women within their reproductive age [1]. It is a relevant clinical issue since it often causes pain, dysmenorrhea, dyspareunia, non-cyclical pelvic pain, infertility and bleeding disorders.

The pathogenesis of two further factors of this enigmatic disease, infertility rate and recurrence rate, is yet to be completely investigated.

Peritoneum became a signature factor for endometriosis after the establishment of laparoscopic surgery, due to possible visual diagnosis and surgical therapy. The pelvic peritoneum is the most common site for endometrial implants, distribution of the lesions on anterior compartment: vesico-uterine pouch and posterior compartment: pouch of Douglas, ovarian fossae and Sacro-uterin ligament. However, 80% of lesions disseminate on the area of Cul-de-sac, including ovarian fossae [2]. One of the theories, concerning the pathogenesis of peritoneal endometriosis is retrograde menstruation, with subsequent implantation on and growth in [3]. On the another hand, retrograde menstruation occurs in 76%–90% of women and not all cases have a clear manifestation of endometriosis [4]. Therefore, there might be further factors involved in the pathogenesis of endometriotic lesions. One further important factor seems to be a possible change of the mesothelial cells in patients with endometriosis. A recent in vitro co-culture experiment demonstrated the invasion of peritoneal mesothelial cells by human stromal cells in women with endometriosis, while the invasion was resisted in women without endometriosis. Moreover, after stromal cell invasion peritoneal mesothelial cells disappeared due to apoptosis [5]. Many theories explain the process of endometriosis progression in mesothelium, but this topic remains controversial. One of theories about mesothelium invasion is tissue remodeling. Here, matrix metalloproteases promote the digesting and remodeling of the extracellular matrix (ECM) and cytoskeleton reorganization, leading to the ECM facilitating ectopic endometrial cells to bind [6].

Nevertheless, mesothelial cell morphology changes can be caused by the immune system response by the inflammatory process. Significant increase of macrophages in peritoneal tissue of patients with endometriosis [7], prostaglandins [8] and pro-inflammatory cytokines [9, 10] support that notion. This complex inflammatory cascade is considered to play the central role in the establishment and progression of endometriosis. Remarkably, the release of pro-

inflammatory cytokines affects not only endometriotic lesions, but also surrounding tissues and causes inflammatory process of the whole area [11], followed by stimulation of cell proliferation [12] and neovascularization, which is also considered to be the indicator of the pelvic pain in women with endometriosis [13],[11]. Furthermore, some studies have highlighted histological demonstration of endometriosis in macroscopically healthy peritoneum, in endometriosis patients, with impaired infertility and chronic pelvic pain (CPP) [14-19]. These investigations lead to the statement that alterations in peritoneum around the peritoneal endometriotic lesions (pEL) are larger than generally believed.

Nowadays, surgeons concentrate on excision or coagulation of visible EM lesions, reporting theoretically better long-term symptom relief, but many cases require further surgical interventions postoperatively, i.e. physicians are facing the recurrence problem[20, 21]. The higher manifestation of recurrent endometriotic lesions in the border of the excised lesions indicates a possible role of invisible altered tissue in recurrence [22, 23]. Furthermore, the current study showed the endometriotic lesions as major regulators and promoters for systemic inflammation in endometriosis and the recurrence of the condition. As long as, removal of the altered tissue was directly proportional to the decrease of inflammatory factors in endometriosis patients postoperatively[10].

Considering the wide spread inflammatory process in endometriosis-affected peritoneum, our study aims to analyze the role of the removal of the complete posterior peritoneum compartment, as part of the big complex surgery, regarding postoperative symptoms, recurrence and fertility rate. As long as the data referring this particular topic is missing.

Materials and methods

In this retrospective study, 54 patients with severe endometriosis manifestation were consecutively investigated. Each patient underwent laparoscopy for pain or infertility symptoms in Charité University Clinic, Campus Benjamin Franklin in Berlin, encompassing five-year data, starting in 2011 and ending in 2016. Endometriosis was laparoscopically and histopathologically confirmed in all 54 patients, intra-Operatively scored by the revised American Society for Reproductive Medicine (rASRM) score and the ENZIAN-score (Tab.2), a definition of the deep infiltrating endometriosis [24-26]. Intra-operative findings were recorded and analyzed. Patients

have signed written informed consent prior to enrollment in this study and the institutional ethical board of the clinic approved the research. A pre-operative questionnaire (VAS based) was collected in our gynecological outpatient clinic regarding endometriosis related symptoms such as dysmenorrhea, dysuria, dyschezie, dyspareunia, chronic pelvic pain, cyclical pelvic pain and infertility. Exhaustive historic data from previous medical and surgical therapy for endometriosis was reviewed and recorded. The purpose of the complex surgical treatment was the complete excision of endometriotic lesions, including peritonectomy of the total pelvic posterior compartment (visible endometriotic lesions and inflamed peritoneum), i.e a complete cytoreduction of the posterior peritoneum of the pelvis, including cul-de-sac (pouch of Douglas) and ovarian fossae (Fig.1). Follow-up represents pre- and postoperative verbal questionnaire and data review, based on the questioner, visual analogue scale (VAS) and numerical rating scale (NRS) for postoperative surveillance, including subsequent medical history, complaints, fertility and recurrence rate. To analyze the difference between pre and postoperative symptoms, quality of life and fertility rate, there were used stacked bar graphs.

History of the disease:

Follow up data of all 54 patients were available. The mean age of the patients was 35 year (21-55) at the time of surgery, n=45 (83%) of women were nulliparous, n=2 (4 %) were uniparous and n=7 (13%) multiparous. Preoperatively, n=30 (56%) women had taken at least one form of hormonal treatment, composed of combined oral contraceptives, progesterone and contraceptive vaginal ring. Hormonal treatment was interrupted 2 months prior to surgery. N=34 women were already operated in the past and the rest 20 Patients had no previous surgical interventions (Tab.1). Out of these 34 women, n=25 were operated once, n=7 had undergone two and n=2 three previous surgical procedures: n=10 diagnostic laparoscopy, n=20 laparoscopic excision of EM-lesions, n=4 laparoscopic coagulation of EM-lesions and n=2 laparotomic excision.

Primary indications

Impaired fertility was a mainstream problem in n=28 (52%) of women. Twenty-five (46%) of the

patients suffered from the endometriosis associated complaints, like dysmenorrhea in N=50 (93 %), dyspareunia n=39(72 %), dysuria in n=11(20 %), dyschezia n=30(56 %), chronic pelvic pain in n=32 (59 %), cyclic pelvic pain n=44(81 %) and sciatica (pain affecting leg, lower back and hip) in n=9 (17 %) of the cases (Fig.2).

Intra-operative findings

During the surgery, majority of women n=29(54 %) presented to be with stage IV endometriosis, classified by rASRM score, n=10(19 %) indicated stage III, n=16 (30%) stage II and only n=3 (6%) stage I (Tab.2).

Intra-operatively, was defined the character and localization of the deep infiltrating endometriosis according to the ENZIAN score (Tab.2) [24]: infiltration of rectovaginal septum, the posterior pelvic wall, uterus, Sacro-uterin ligament, inguinal region, bowel, bladder, ureter, diaphragm and lungs.

Posterior compartment peritonectomy was a part of complex surgical procedure, including cyst-excision, hysterectomy, partial bowel resection, partial bladder resection, neurolysis and ureterolysis. (Tab.1)

Statistical analysis

Difference between pre and postoperative endometriosis associated pain scores and quality of life were analyzed using computed-based software Prism (version 5.00; Graph Pad Software). Data was assessed with *t* tests and non-parametric statistical tests including Kolomogov-Smirnov test, D'Agostino's K-squared test, Shapiro- Wilk normality test and Mann-Whitney test. It is a pilot prospective study, excluding the control group of the patients.

Results of long-term follow-up

Fertility rate

Preoperatively, n=28 women (50%) presented the history of infertility, out of n=7 (25%) with secondary and n=21 (75%) primary infertility. Mean time of the prior infertility was 3 years (min 1 year and max 10 years.) After the surgery n=22 infertile patients underwent supportive hormonal treatment in the mean time of 3 months (Tab.3).

Significant results were reported postoperatively in fertility rate. Within the specified timeframe between performed surgeries to follow-up, n=13 (46%) women became pregnant in the mean time of 6 months, followed by the live birth. Remarkably, n=6 (46 %) by assisted fertilization and n=7 (54%) after spontaneous conception (Fig.3).

Post-operative pain outcome

Post-operative data showed a remarkable improve of the quality of life in majority of patients. Accordingly, n=36(67%) cases reported symptom free status and in rest n=18(33%) of women endometriosis associated symptoms remained, but VAS (range 0-10) reported significant decrease of the pain scale (Fig 3). To understand the efficacy of the surgery, univariate and multivariate analysis were performed with relevant preoperative complaints for each of the previously described postoperative endometriosis associated symptoms.

Totally, n=43 of the patients underwent hormonal supportive treatment after the surgery, including dianogest, combined hormonal contraceptives, Gonadotropin-releasing hormone modulator and hormonal Intrauterine device (Tab.3). The mean time of hormonal treatment was 6 months after surgery. In some cases, n=15 there were used two different hormones, as a result of side effects or bad tolerance to the primary therapy. From these patients n=28 were symptom free postoperatively and in n= 15 patients EN related complaints still remained, but significantly improved.

Postoperative questionnaire reported n=11(20%) dysmenorrhea cases ($p\text{-value} < 0.0001$), n=9(17%) dyspareunia ($p\text{-value} < 0.0001$), n=2 (4%) dysuria ($p\text{-value} < 0.006$), n=6(11%) dyschezia ($p\text{-value} < 0.0001$), n=1(2%) cyclic pelvic pain ($p\text{-value} < 0.0001$), n=9 (17%) chronic pelvic pain($p\text{-value} < 0.0001$) and n=4 (7%) of sciatica ($p\text{-value}=0,1$) cases (Fig.2).

Recurrence rate

With the 5-year follow-up, the evidence of recurrence was represented only in one case. The patient required further surgical intervention. She was re-operated in our clinic, with evidence of endometriosis, histologically confirmed. Remarkably, the initial surgery was followed by in-vitro

fertilization, performed four times. Subsequent surgery procedure showed progression of the disease from rASRM stage I to stage II, including sacral plexus, parametrium and Uterus. Therefore, surgical treatment involved radical Hysterectomy, sacral roots neurolysis and total Parametrectomy.

Discussion

Usually in case of complex endometriosis, surgeons are trained to excise the visible endometriotic lesions. Often the endometriosis associated inflammation leads to severe conglomerate tumor and usual procedure is dissection of the organs and the excision of fibrotic and inflamed peritoneum is not standard procedure in this kind of surgery. The surgeons may not remove the fibrotic inflamed peritoneum as they are mainly focused on removal of deep infiltrated Endometriosis (DIE). Besides, many studies report the mechanisms of peritoneal endometriosis, but very less is known about surgical treatment and its subsequent outcomes. To date, there are no clear literature, explaining the exact surgical technique, representing recurrence rate, fertility rate and pain relief improvement.

Peritoneal endometriosis is widespread complex disease, with the wide range of immunological environment, rich of macrophages, increased number of macrophage-secreted pro-inflammatory cytokines and growth factors [12, 17, 18, 27-29]. These products, such as IL-6, IL-8, TNF α , IL-1 β and TGF- β take part in remodeling of peritoneal cells structure, which could be the easy pathway for adherent endometrial cells to infiltrate the peritoneal surface, by elimination of the tight junctions [10, 18, 29, 30]. Demonstrating the nerve fibers in peritoneal endometriosis [13] [31], improves the character of neurogenic inflammatory processes in peritoneum, leading to the pain generation as well. Furthermore, pEL can stimulate nerve growth factor (NGF) expression, which modulates the nerve fiber growth in endometriosis [11] (fig.2). Moreover, peritoneal endometriotic lesion leads to reactions in the surrounding tissue and, therefore, is larger than generally believed, as EM-associated nerve fibers and smooth muscle-like cells were identified in surrounding tissues of infiltrated areas [11].

Consequently, in many cases microscopically inflammatory-altered peritoneum is presented without typical endometriotic lesions. So far it is unclear, what to do with these inflamed, affected tissues.

The summary of these distinct ideas was the origin of our surgical treatment.

Nowadays, surgeons primarily focus on excision of DIE and the peritoneum has in such a complex infiltration only a matter of secondary importance, so the treatment of peritoneal lesions usually is coagulation or excision of altered pEL, visually exposed with red, white, brown or black lesions. However, the golden standard is not defined so far. The studies confirmed a comparable postoperative pain relief; however, the data about the improvement of the fertility rate or the recurrence rate are very controversial. In our study we included n=34 (63 %) women with recurrent disease, primarily operated by excision or coagulation of endometriosis lesions. This could reflect the high recurrence rate in patients with endometriosis. Generally, surgical treatment of endometriosis remarkably rises the pregnancy rate [32], but doesn't guarantee the decrease of recurrence rate, as occult endometriosis of the peritoneum still remains untouched [14, 18, 19]. Moreover, few other studies demonstrated significantly high rate of recurrence, occurring in 37% [22], 56% [33], 21% [34] of the operated endometriosis patients and support our surgical effort to eliminate the endometriotic lesions completely, to keep the recurrence rate low. Furthermore, the consequent interruption of the hormonal therapy two months prior to surgery might be a good approach in order to make endometriotic lesions even more visible preoperatively [35]. Our goal was not only removing peritoneal lesion, but literally act on widely spread inflammatory process and remarkably decrease the chances of recurrence. Another point was postoperative supportive hormonal treatment, in order to stop reflux menstruation and avoid further recurrence, giving the time to the targeted surface to recover without new infiltrations. As the follow-up demonstrated, even in infertile patients the concept of combining surgical treatment with supportive HT was successful. As for 22 infertile patients taking HT postoperatively in the mean time of 3 months, n=7 achieved pregnancy in the mean time of 6 months (Tab.3). Moreover, from all n=43 patients who were given postoperative supportive HT reported totally symptom free status as well. Lastly, our study demonstrated only one case of recurrence. Remarkably, in this patient was performed four cycle of in-vitro fertilization postoperatively. Current research demonstrated high influence of IVF on endometriosis recurrence rate, exposing the high level of estradiol [36, 37]. Another study reported that, repeated ovarian hyperstimulation during IVF stimulates the endometriotic lesion expansion [38]. Considering that, in this case four cycle IVF could have been the recurrence indicator.

Although, Vercellini [39] critically analyzed gaining popularity of laparoscopic surgery in

endometriosis patients with subfertility, till nowadays surgery is considered to be the only golden standard in endometriosis treatment. Bergqvist demonstrated, that there was lower amount of oestrogen and progesterone receptors in ectopic tissue than in endometrium. Therefore regulation of endometriotic tissues by oestrogen and progesterone could be more difficult, once they are formed [40]. Accordingly, the single hormonal treatment could not be the only benefit for peritoneal endometriosis. Moreover, it presents a big problem for the patients with impaired fertility, as their aim is to conceive. Besides, particular data demonstrated the strong influence of endometriosis not only on receptivity of endometrium, but also development of the oocyte and embryo [41].

However, our postoperative follow-up suggests the efficacy of complete posterior peritonectomy as part of the surgical procedure in fertility rate; achieving the pregnancy in 43% of patients, with impaired fertility, remarkably in the median time range of 6 months (Fig. 4). Furthermore, 50% of pregnancies appeared spontaneously, followed by live birth. Likewise, other studies demonstrate the same fertility rate after removing multiple endometriosis lesions by deep infiltrating endometriosis [32, 42, 43]. Considering peritoneal endometriosis, as neurogenic inflammatory disease, capable of covering nearby tissues [11], removing the complete inflamed area could be a good basement for the successful fertility outcome in these patients. Since, the process was detained completely, avoiding the recurrence in future and therefore making chances of postoperative pregnancy higher[44].

Appropriately, our study shows, that total peritoneal excision as part of the surgical procedure offers possible reduction of recurrence rate and improving fertility rate.

Significant improvement of pain relief in postoperative outcome supports the efficiency of this surgical technique, as well. As, neurogenic process in peritoneum is considered to be the main pain indicator in these patients. Median time of 2 years follow-up revealed 67% absolutely symptom-free patients, with extremely improved quality of life. Remarkably, in the rest 33% of the patients endometriosis associated symptoms remained postoperatively, although the pain scale was significantly reduced (Fig.2). We have to consider that majority of these patients (n=11) had a severe form of Adenomyosis and removing the uterus was not an option, due to impaired fertility and reproductive age.

Accordingly, leaving the Uterus in terms of Adenomyosis means that endometriosis process was not removed completely. Moreover, it could have been the main etiological factor of remained

EM-associated postoperative symptoms [45] and possibly difficult to treat without hysterectomy[46].

It is absolutely clear that, not only total peritoneal peritonectomy served the improvement of pain relief, but also other procedures performed simultaneously, as the most surgeries were complex, including cyst-excision, hysterectomy, partial bowel resection, partial bladder resection, neurolysis and ureterolysis. Nevertheless, on another hand, many medical groups could not avoid the recurrence rate of 20%-45%, after performing complex surgery on patients with DIE [47-50]. The main bias in this study is that we did the peritonectomy as part of a complex surgical procedure, however for a first pilot study we thought it was more acceptable to do this when the retroperitoneum was still open. The peritonectomy was performed as the main procedure in three cases, where the peritoneum was strongly affected, but there was no deep infiltrating endometriosis present. More and more data demonstrates that the peritoneum, as an important organ playing a huge role in endometriosis pathogenesis, development and pain generation [11, 13, 52], consequently peritonectomy should be acknowledged as a mainstream procedure for successful postoperative outcome.

Therefore, the complete excision of DIE, with total posterior compartment peritonectomy could be the surgical treatment of choice in order to decrease the post-operative pain relief, improve quality of life and prevent recurrence in future. Nevertheless, we have to point out the complications, which can follow this complex surgical approach. As the inflammation process in our study was mostly complex and involving several organs simultaneously the chance of complications, such as hemorrhages, neuropathy, urinary leakages, adhesions, infections etc. are possible, since the anatomy of the pelvic floor is very complex and requires technically skilled and trained surgeon. In fact, in our study group demonstrated single early-postoperative complication - urinary leakage after extensive ureterolysis in case of ureteral infiltration accompanied by hemorrhage, which required re-laparoscopy. So, this complication was not related to peritonectomy. In light of this, extensive investigation of postoperative outcomes of posterior peritonectomy as a part of complex surgery, including indications and complications, might be a possible factor in managing these patients in the future, without increasing complication risk.

To our knowledge, there is only one presentation demonstrating the postoperative outcome, after total posterior compartment peritonectomy, including posterior cul-de-sac and

ovarian fosse (Trehan 2003). However, this topic remains controversial. As long as this study excludes the control group, in future it will be valuable to perform further prospective randomized studies in order to understand better the efficiency of this method.

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Legends:

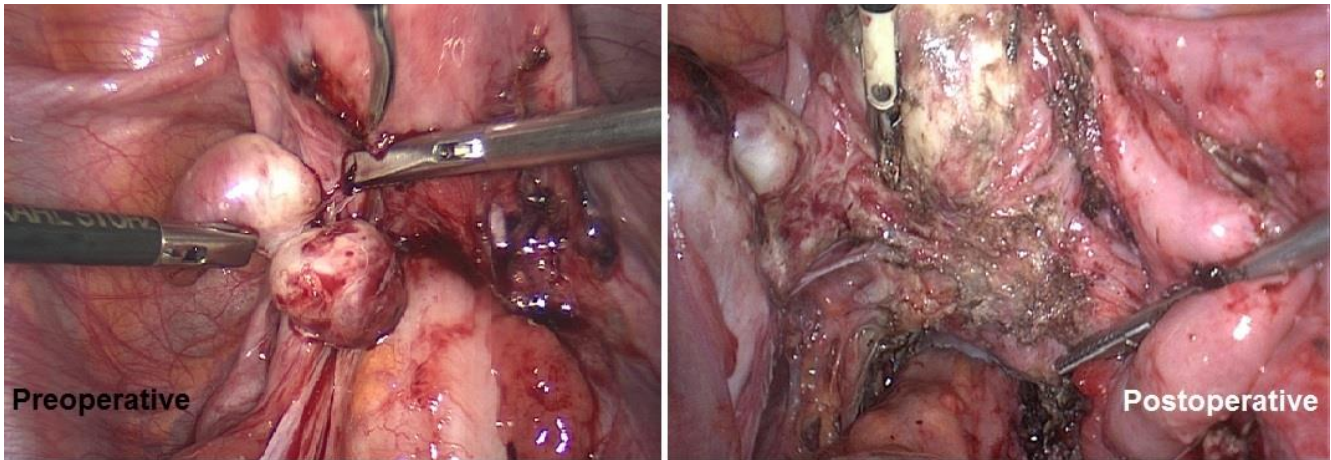


Figure 1:

- a) Laparoscopic picture of deep infiltrated endometriosis, as a conglomerate tumor, involving posterior compartment peritoneum of the pelvis, cul-de-sac (pouch of Douglas) and ovarian fossae.
- b) Posterior compartment after laparoscopic complete posterior peritonectomy, as a part of complex surgery, including cul-de-sac (pouch of Douglas) and ovarian fossae.

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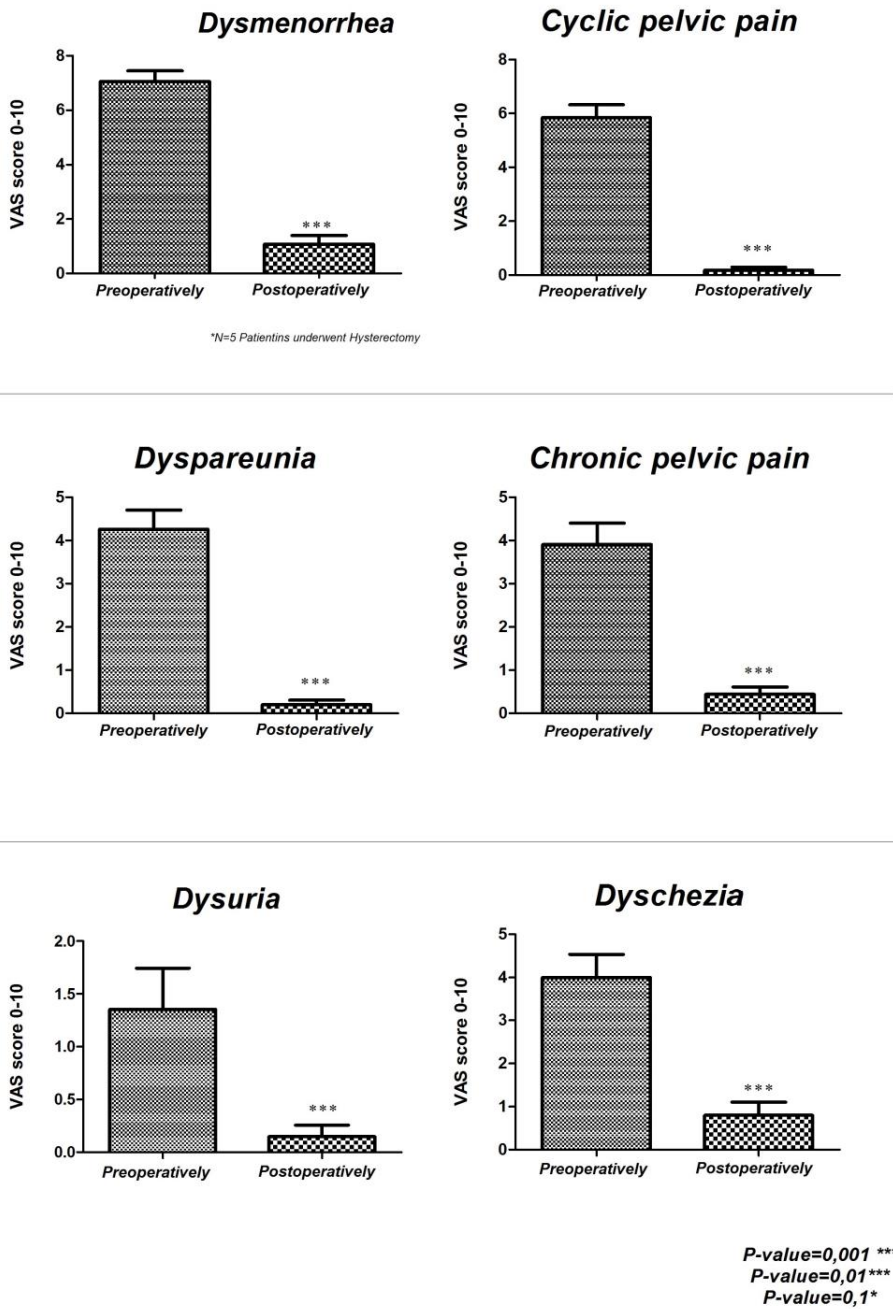


Figure 2:

VAS score analyzed statistically by KS, D’Agostino & Pearson omnibus, Shapiro-Wilk normality test. Graphs presenting mean of the pre- and postoperative complaint’s VAS score and significance of the operation related to the pain reduction. (VAS: visual analogue scale)

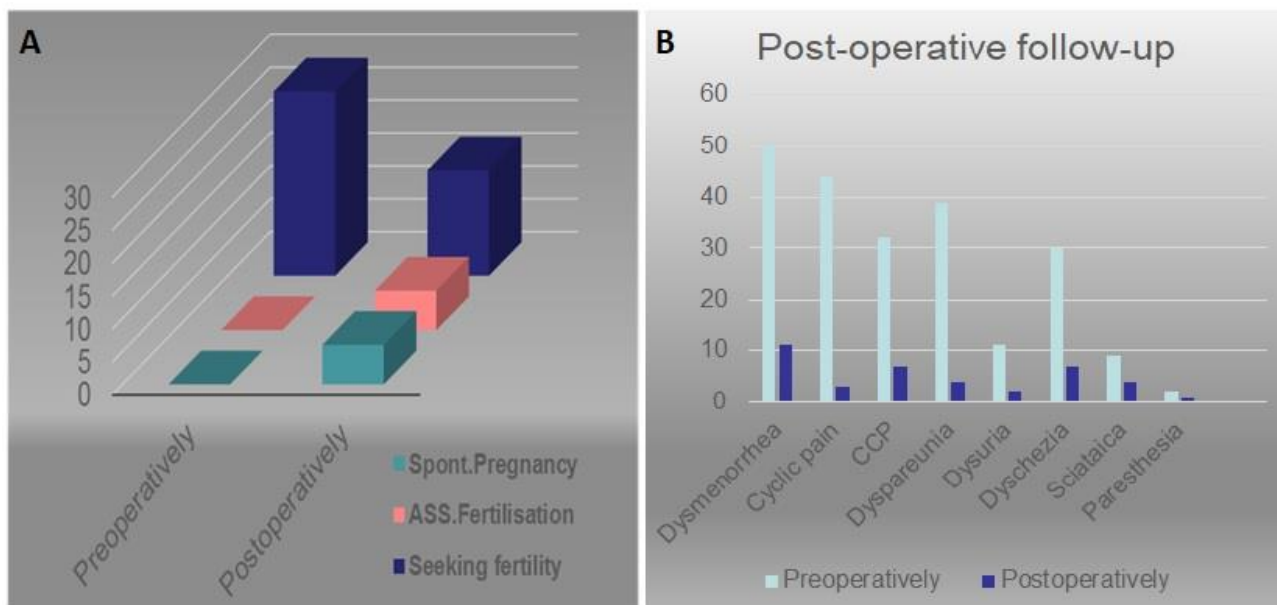


Figure 3:

- a) Infertility rate pre- and postoperative, with the correlation of conception type in numbers.
- b) Stacked bar graphs demonstrating the comparison of pre- and postoperative endometriosis-related symptoms in numbers.

Table 1: Details of procedures and follow-up (54 patients)

Table.1.	
Mean time of the follow-up, mo (±SD)	29 ±15
Mean age of the patients, yr (±SD)	35 ± 7
Preoperative hormonal treatment, n (%)	30 (56)
Mean duration of infertility, yr (±SD)	3 ± 2,1
Previous surgery for endometriosis, n (%)	34 (63)
Preoperative Adenomyosis n(%)	40 (74)
<i>Procedures</i>	
Posterior peritonectomy n(%)	54(100)
Cyst-excision n(%)	13 (24)
Hysterectomy n(%)	5 (11)
Partial bowel resection n(%)	27 (50)
Partial bladder resection n(%)	7 (12)
Neurolysis n(%)	18 (33)
Ureterolysis n(%)	32 (59)
Complete removal of the disease, n (%)	18 (33)

Mean time of the follow-up, mo (\pm SD)	29 \pm 15
Symptom free status postoperatively n(%)	36 (67)
Fertility rate n (%)	13 (46)
Recurrence, n (%)	1(1,8)
Complication (%)	1(1,8)
Postoperative Adenomyosis	36 (67)
SD - standard deviation	

Table 2: rASRM and ENZIAN interaction

Table 2. rASRM/ENZIAN	ENZIAN 1 <1cm			ENZIAN 2 1-3cm			ENZIAN 3 >3m			ENZIAN F				
	A	B	C	A	B	C	A	B	C	FA	FB	FU	FI	FO
rASRM I n=3(6%)	0	0	0	1	2	1	0	1	0	1	1	0	1	1
rASRM II n=16(30%)	1	0	0	3	3	3	6	10	5	8	6	0	5	2
rASRM III n=10(19%)	1	0	0	4	4	0	0	5	1	7	4	1	1	3
rASRM IV n=29(54%)	0	0	0	3	5	5	11	23	16	22	10	1	18	12

Table 3: Postoperative Hormonal Treatment.

Postoperative Hormonal Treatment n=43	Symptom free	Preoperatively seeking fertility/ Postoperative Pregnancy	Preoperatively seeking fertility/ no postoperative pregnancy
Dianogest n=16	N=10	N=2	N=5
combined hormonal contraceptives n=8	N=4	N=1	N=4
Gonadotropin-releasing hormone modulator n=5	N=3	N=1	N=4
Gonadotropin-releasing hormone modulator and Dianogest n=9	N=8	N=3	N=1
combined hormonal contraceptives and	0	0	0

Dianogest n=1			
combined hormonal contraceptives and IUD n=1	N=1	0	0
IUD and Dianogest n=3	N=2	0	N=1

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