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GENERAL GYNECOLOGY

Pain control and quality of life after laparoscopic en-block resection of deep infiltrating endometriosis (DIE) vs. incomplete surgical treatment with or without GnRHa administration after surgery

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Abstract
Purpose To evaluate the role of post-surgical medical treatment with GnRHa in patients with DIE (Deep Infiltrating Endometriosis) that received complete or incomplete surgery laparoscopic excision.
Methods Hundred fifty-nine patients with deep infiltrating endometriosis of the cul-de-sac and of the rectovaginal septum with pelvic pain undergoing laparoscopic surgery in academic tertiary-care medical center. Eighty patients underwent complete laparoscopic excision of DIE (Arm A) while 79 patients underwent incomplete surgery (Arm B). After surgery each surgical arm was randomized in two groups: no treatment groups 1A [40 pts] and 1B [40 pts] and GnRHa treatment for 6 months groups 2A [40 pts] and 2B [39 pts]. Pain recurrence and quality of life were evaluated in follow-up of 12 months and compared between groups.
Results No differences were observed between patient groups 1A and 2A. Groups 1A, 2A and 2B obtained significantly lower pain scores than those achieved by the group 1B undergoing incomplete surgical treatment and no post-surgical therapy. At 1-year follow-up patients treated with en-block resection (Groups 1A and 2A) showed the lowest pain scores and the highest quality of life in comparison with the other two groups (Group 1B and 2B).
Conclusion GnRHa administration is followed by a temporary improvement of pain in patients with incomplete surgical treatment. It seems that it has no role on post-surgical pain when the surgeon is able to completely excise DIE implants.

Keywords Incomplete surgery · Medical therapy · Quality of life · Endometriosis · GnRHa · Recurrences

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Introduction

Deep infiltrating endometriosis (DIE) is a form of endometriosis in which the pathologic tissue can penetrate up to 5 mm under the surface of the affected structure [1]. DIE can affect the retrocervical region, uterosacral ligament, rectum, rectovaginal septum, vagina, urinary tract and other extraperitoneal pelvic sites [2]. The incidence of DIE is reported in 20 % of all cases of endometriosis. Dysmenorrhea, deep dyspareunia, dyschezia and dysuria are the most frequently reported symptoms but even psychological symptoms have been reported [3]. Pain can be treated by excising deep nodules and ovarian cysts in laparoscopy [4, 5]. Recently even single port laparoscopy has been proposed for the treatment of ovarian and peritoneal endometriosis but it seems too complex for DIE excision [6, 7]. In most cases, women with chronic pelvic pain (CPP) thought to be due to endometriosis are initially treated empirically with non-steroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives. If these medications do not resolve the pain, laparoscopy is usually performed to determine a definitive diagnosis and possibly obtain a complete excision of all endometriotic implants

[4, 8, 9]. However, several times a complete excision of infiltrating endometriosis is not performed. The reasons are the difficulty in defining exactly the extent of the disease, the ability of the surgeon and, sometimes, the lack of the patient consent to a radical excision of all endometriotic implants due to the fear of possible complications (intestinal fistulae etc.) [10]. Moreover, many patients with chronic pain and infertility demand to the surgeon the excision of endometriotic implants to restore the reproductive function and possibly improve simptomatology but avoiding any risk of intestinal complications. In these cases, the rate of pelvic pain recurrence is very high and the request for medical therapy is frequent. GnRH agonist (GnRHa) is widely used for the treatment of endometriosis. It is clinically evident that GnRHa decreases the serum estrogen level by suppressing pituitary gonadotropin secretion and remarkably improves the subjective and objective symptoms of endometriosis [9–11]. GnRHa has been proposed as a postsurgical treatment to avoid recurrences after laparoscopic surgery. However, it is still not clear if GnRHa administration after surgery could prevent recurrences in patients with complete excision of endometriotic implants or it acts just in cases of incomplete surgery.

Parazzini et al. [12] reported that medical treatment with 400 μg/day nasal Naferelin for 3 months after surgery did not markedly improve short-term pelvic pain prognosis. Vercellini et al. [13] using survival analysis, reported that time to symptom recurrence was significantly longer in the GnRH analogue group. However, another study did not support the routine postoperative use of a 3-month course of GnRHa in women with symptomatic endometriosis stage III–IV. In fact, a significant longer relief of pain symptoms in women with symptomatic endometriosis stage III–IV was not observed [15].

Aim of our study was to investigate if GnRHa postsurgical treatment should be proposed to every patient with DIE who undergoes a laparoscopic treatment or if patients who receive an extensive excisional treatment do not need it in terms of pain and quality of life.

Sample size calculation

In calculating the sample size required, the primary assessment was the recurrence rates. A 31 % recurrence rate after laparoscopic reductive surgery and post-surgical treatment with a GnRH analogue has been reported (10). We expected a decrease in recurrence rates after laparoscopic complete excisional surgery, conservative surgery and postsurgical treatment with GnRHa. A difference of 25 % between the allocated treatments was considered signicant. To have a 90 % chance of detecting such a difference at an overall significance level of 5 %, 40 patients for each group were required.

Materials and methods

This randomized clinical trial compared the efficacy of GnRHa with no treatment in women with deep infiltrating endometriosis and chronic pain who underwent laparoscopic surgery with complete or incomplete excision of all endometriotic infiltrating implants. The study was conducted at the Department of Obstetrics and Gynecology of the University of Cagliari, Italy after approval by our institution's ethics committee and institutional review board.

The study population was selected from women with endometriosis who attended the Chronic Pelvic Pain Clinic of the our Department and were submitted to laparoscopy between January 2006 and December 2011. As usual all patients underwent a complete biochemical, ultrasonographic and MRI evaluation to characterize the site of the lesions and possible involvement of the bowel [16, 17]. All patients performed a preoperative diagnostic hysteroscopy [18, 19]. Deep infiltrating endometriosis (DIE) of the rectovaginal septum was classified according to Enzian score [20]. Pain was evaluated by using the modified Biberoglu and Behrman symptom scale as previously described [21], on which symptoms and signs are rated on a scale of 0 (no discomfort) to 3 (severe symptoms) in each of five categories, namely, dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness and indurations. Patients enrolled in this trial were required to have symptoms with a total score of at least 6 (of a possible 15), including a total of at least two in the symptoms of dysmenorrhea, dyspareunia and pelvic pain. As usual for the patients attending to our center, quality of life and health-related satisfaction were assessed with the Medical Outcomes Survey Short Form 36 (SF-36), which is the most widely used generic instrument to evaluate health-related quality of life [22].

All women were advised to use non-hormonal contraception throughout the study.

In conclusion, the criteria for inclusion were: (a) that the patients were of reproductive age and not >40 years old; (b) that the women had a laparoscopic diagnosis of deep infiltrating endometriosis with complete or incomplete surgical treatment; and (c) patient symptoms score before surgery was required to have a total score of at least 6 (of a possible 15).

Exclusion criteria were previous medical or surgical therapy for endometriosis, infiltration of the rectum >3 cm and/or rectal stenosis (Enzian score E4c), the presence of other disease that might cause pelvic pain and diagnosis of liver, endocrine or neoplastic disease.

Hundred fifty-nine out of 240 patients with surgical proven deep DIE of the rectovaginal septum entered the study after their written informed consent. Patients enrolled to this trial were divided in two arms (Arm A and Arm B).

Arm A (80 pts.) included the patients in which a complete excision of all endometriotic implant was achieved during surgery.

Surgical technique for the "complete" resection of the rectovaginalendometriotic lesions

Mechanical bowel preparation (low residue diet for 5 days prior to hospitalization; Selg 1000 [Promefarm, Italy] the day before surgery) and preoperative IV antibiotics were routine. Patients were counseled about the risks of entering the rectum, with the associated risk of laparotomy or laparoscopy with or without colostomy and gave their written informed consent to the surgical treatment and the follow-up evaluation. The goal of the operation was the radical exeresis of all endometriotic lesions and in particular of all fibrotic nodules of deep endometriosis, adhesions and all ovarian and peritoneal lesions. After clinical examination under general anesthesia, a uterine manipulator was positioned to displace the uterus anteriorly. A 10 mm trocar was introduced through the umbilicus to position the laparoscope (Karl Storz, Tuttlingen, Germany) and two 5 mm trocars were placed in the lower abdomen and one of 10 mm on the sovrapubic area. A sponge-holding forceps was inserted into the vagina to push up the posterior fornix and another one was placed into the rectum. Using these probes as guides the anterior rectum was separated from the posterior vaginal wall using 5 mm monopolar electrosurgical scissors, using preferentially sharp dissection starting with the dissection of the pararectal spaces with identification and lateralization of ureters in every case.

After identification of a cleavage plane between the anterior rectal wall and the nodule, it was excised without opening the rectal mucosa. In case of fibrosis of the submucosa, muscle layers were peeled with sharp dissection. The mucosal skinning of the rectal wall was reinforced by suturing the serous and muscularis mucosae in a single layer with Vycril suture 3-0. Hemostasis was achieved with bipolar electrodessication. All the recognizable lesions were removed and submitted subsequently to histological examination. The sponge holding forceps pushed in the vagina enabled the presentation of the posterior vaginal fornix that was opened and excised when involved by the nodule. Antibiotic vaginal suppositories were placed into the vagina very close to the suture for 7 days after operation to protect against ascending infections. In all cases, at the end of the procedure 100 ml air was inflated into the rectum to evidence any possible bowel lesion.

The Arm B (79 pts.) included the patients in whom surgery did not allowed a complete removal of all infiltrating implants for lack of patients consent to a radical excision.

Surgical technique in the "incomplete" resection of the rectovaginalendometriotic lesions

The preoperative preparation of patients was the same as in Arm A. Adhesions, ovarian, peritoneal and uterosacral ligaments endometriotic lesions were completely removed in every patient but the deep infiltrating nodules were not removed.

At the end of all laparoscopic procedures ("complete" and "incomplete") to possibly prevent or decrease the occurrence of post-surgical adhesions 500 cc of warm lactated Ringer's solution was instilled into the pelvis [23].

Randomization was achieved at the time of postoperative control (12 days after surgery) so that a definitive histological diagnosis of endometriosis was available.

In each arm the patients were randomized 1:1 in two group (group 1A, 2A and 1B, 2B) in accordance with a computer-generated randomization sequence to receive no therapy or triptorelin acetate (Gonapeptyl depot, Ferring, Italy) 3.75 mg given monthly by IM injection for 6 months. Patients were seen for a follow-up visit on a monthly basis, at which time a pelvic examination was performed. A patient diary, which included the endometriosis symptoms, was filled in by the patient every 3 months during 1-year period of the study. The SF36 was fulfilled by the patients before surgery and at 1-year follow-up.

Statistical methods

Data were analyzed with SPSS 10.1 (SPSS Inc, Chicago, IL). Data analysis included age, previous pregnancies, operative procedures, operating room time, intra and postoperative complications, length of stay and 30-day postoperative recovery. They were summarized as the mean and standard deviation for continuous data and frequency for categorical data. Within-group variations between baseline and follow-up values were evaluated using Wilcoxon matched pairs test. One-way repeated-measured of variance (ANOVA) was used to compare the results on the quality of life according to the SF36 results. Significance level was accepted at $p < 0.05$.

Results

The four groups of patients were similar with respect to their demographic and clinical characteristics. There were no significant differences with regard to age, fertility and deep endometriosis scores according to Enzian classification. No differences in baseline levels for pelvic pain were found among the groups. (Table 1).

Table 1 Characteristics of the patients

	Group 1A ($n = 40$) complete surgery no therapy	Group 2A ($n = 40$) complete surgery GnRH therapy	Group1B ($n = 40$) incomplete surgery no therapy	Group 2B ($n = 39$) incomplete surgery GnRH therapy	p
Age	24.2 ± 10	27.4 ± 8.2	25.6 ± 7.8	26.0 ± 10	NS
Enzian score					
E1(a–c)	18	15	16	17	NS
E2(a–c)	10	11	9	9	NS
E3(a–c)	10	13	8	10	NS
E4(a–bb)	2	1	3	3	NS
Cumulative pain scores	11.3 ± 3	10.0 ± 1.9	10.4 ± 1.8	11.0 ± 2.1	NS
Infertility	13	10	10	12	NS

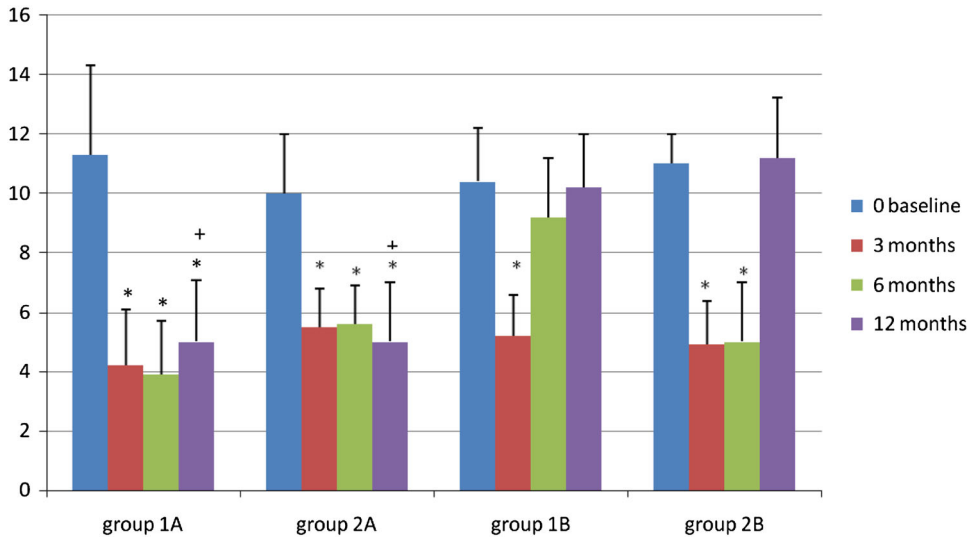

Fig. 1 Cumulative pain scores in the randomized groups, * $p < 0.01$ vs. baseline, $^{+}$ $p < 0.001$ vs. 6 months and 12 months in the incomplete excision group without GnRHa (group 1B) and vs. 12 months in the incomplete treatment with 6 months administration GnRHa (group 2B)

All the procedures were completed laparoscopically and no conversion to laparotomy was required. There were two complications at surgery in Arm A. One patient underwent rectal perforation and the rectum was repaired by laparotomy. In another patient, the left ureter was damaged during endometriosis excision and it was repaired during laparoscopic surgery. The mean operating time was longer in the patients who underwent a complete excision. The mean first operative day hemoglobin drop and white blood cell (WBC) increased, the need for analgesics and the hospital stay were not different in the two groups. We registered an intraoperative surgical complication in the incomplete excision group. During dissection, the ureter was cut and subsequently repaired in laparoscopy without any problem for the patient. All patients were fully recuperated in postoperative day 30.

At 3 and 6 months follow-up, the 80 patients treated with en-block resection of DIE (groups 1A and 2A) showed the highest reduction of cumulative pain scores for chronic pelvic pain, dysmenorrhea and dyspareunia. Moreover, groups 1A and 2A did not present any significant difference at 3 and 6 months follow-up.

Moreover, pain control did not differ significantly when these patients (groups 1A and 2A) were compared with the 39 patients undergoing incomplete surgery and post-surgical GnRHa treatment (Group 2B). Indeed, groups 1A, 2A, 2B obtained significantly lower pain scores than those achieved by the 40 patients (group 1B) undergoing incomplete surgical treatment and no post-surgical therapy ($p < 0.01$). After discontinuation of GnRHa and restoration of menstrual cycles, pain scores returned to pre-surgical levels in patients undergoing incomplete surgery and post-surgical medical treatment (group 2B) and were significantly different in comparison of the patients (group 1A and 2A) who received a complete excisional treatment ($p < 0.01$). Data are shown in Fig. 1.

Table 2 Differences in the patients quality of life as assessed by SF-36 before surgery and at 12 months follow up

	Group 1 baseline	Group 1 12 months	Group 2 baseline	Group 2A 12 months	Group 1B baseline	Group 1B 12 months	Group 2B baseline	Group 2B 12 months
General health	46.4 ± 12	60 ± 11.5$^{\#+}$	48 ± 11.2	63.1 ± 13$^{\#+}$	45.4 ± 14	43.2 ± 11	44 ± 16	46 ± 18
Physical function	51 ± 10	70 ± 12$^{\#+}$	53 ± 10.4	69 ± 11.1$^{\#+}$	48 ± 11	47 ± 14	53 ± 12	50 ± 10
Role (physical)	57.2 ± 12	55.8 ± 10	54.8 ± 14	55.9 ± 16	59 ± 14	60 ± 16	55.8 ± 14	57.8 ± 16
Role (emotional)	63 ± 10.8	62 ± 14	65.4 ± 15	64 ± 11.1	61 ± 12.8	60.2 ± 15	64 ± 14	62 ± 13.3
Mental health	57.4 ± 14	55.1 ± 11,8	56 ± 12	58.5 ± 14	53.1 ± 11.8	53.5 ± 11.5	59.5 ± 11.5	60.9 ± 15
Social function	55.8 ± 11	57.2 ± 14	56.2 ± 13	55.1 ± 15	57.8 ± 15	55 ± 15	59 ± 13	53.8 ± 14
Vitality	51.8 ± 13	65 ± 10$^{\#+}$	49.9 ± 11.3	68 ± 12$^{\#+}$	53 ± 10	53.1 ± 11	53.8 ± 12	52.1 ± 10
Pain	44.2 ± 13	68 ± 12$^{\#+}$	43,9 ± 11.4	67 ± 11$^{\#+}$	45.7 ± 16	45.1 ± 11.2	46.1 ± 15	42.1 ± 16

$^{\#}$ $p < 0.001$ vs. baseline, $^{+}$ $p < 0.001$ vs. 12 months incomplete excision and 12 months incomplete excision plus GnRHa

Ten patients dropped out in the arm A (six patients in group 1A and 4 in group 2A) because they got pregnant. Six patients in the group 1B and 1 patient in group 2B withdrew as they need hormonal treatment or repeated surgery for important recurrence of pain.

Table 2 shows data regarding the patient satisfaction with the treatments evaluated with the SF-36. This form consists of eight domains (physical function, physical role function, emotional role function, social function, general health, mental health, vitality and pain). At 1-year follow-up patients treated with en-block resection showed significant improvement in physical function ($p < 0.01$), general health ($p < 0.01$) (Fig. 2), and vitality ($p < 0.01$) in comparison to baseline and to 12 months follow-up of the patients who underwent an incomplete surgical treatment.

Discussion

Endometriosis is a common, hormone-dependent gynaecological disease that is characterized by the presence and growth of endometrial tissue outside the uterus and its pathogenesis is still not clear [24, 25]. Deep infiltrating endometriosis (DIE) frequently presents with pain and dyspareunia. Preoperative vaginal and rectovaginal examination is essential to identify the presence of extensive pelvic disease. Focal tenderness or nodularity of the cul-de-sac and uterosacral ligaments is the best means of identifying the disease that can be better characterized with transvaginal ultrasound [26]. Many recent studies support that complete excision of the endometriotic tissue provides the best long-term results [4, 27, 28].

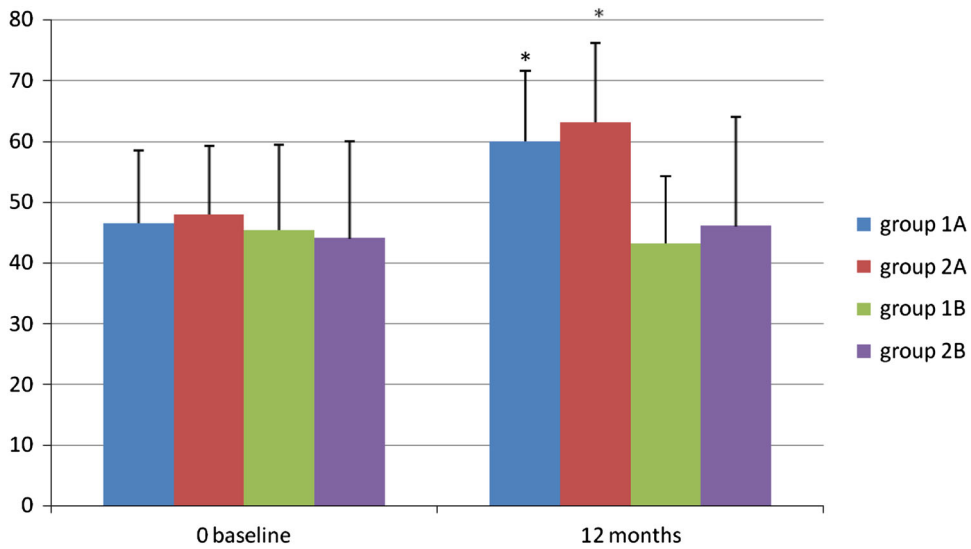

Fig. 2 Differences in the patients general health, as assessed by SF36, before surgery and at 12 months follow up, * $p < 0.001$ vs. baseline and vs. 12 months follow up in patients with incomplete excision with or without 6 months GnRHa administration (group 1B and 2B)

Since proper surgical management of the condition requires complete excision of all the lesions, careful palpation of any suspect lesion with a blunt probe to check for possible infiltration and nodularity is essential. Retraction of the rectosigmoid over the adenomyotic nodules in the cul-de-sac frequently obscures disease and can result in incomplete excision. The majority of patients with deep endometriosis present endometriotic lesions in the retrocervical position and in the higher portion of the rectovaginal septum as shown by MRI images and this seems to be the initial site of deep endometriotic invasion before progression to rectovaginal septum and rectum [29]. Effective management of the advanced stages of the disease poses big problems, in particular, related to the determination of the real extent of the infiltration, and another important issue is the risk of possible complications. A radical approach appears difficult and the duration of the operation is prolonged, but it can obtain the removal of all endometriotic implants. Leaving these implants may result in a high recurrence rate of pelvic symptoms. Our study has clearly shown that patients who underwent an incomplete excision present higher rates of pain recurrences and they need medical therapies and/or repeated surgery. The early pain improvement in group 1B (incomplete treatment) may be due to the removal of endometriotic cyst, adhesions, peritoneal endometriotic implants and nodules of the uterosacral ligaments, as well as a placebo effect. Nevertheless, at 6 months after surgery the pain relapsed if a complete excision had not been performed or if the patients did not receive a medical post-surgical treatment.

The surgical or medical approach to clinical recurrences is still a matter of debate. It is not still clear if a medical treatment after surgery should be suggested to all patients to avoid or at least delay such recurrences. GnRHa is widely used in the treatment of endometriosis symptoms. Several articles have been published reporting the results of various trials comparing treatment of endometriosis and its recurrences with GnRHa alone with GnRHa plus add back therapy [30–32]. Following these results many surgical units propose the adjuvant use of GnRHa after surgery in all patients with deep endometriosis for at least 6 months. However, the long-term use of GnRHa is associated with hypo estrogenic side effects and a substantial reduction in bone mineral density [33]. In particular the administration of medical therapy after surgery may have the detrimental effect to avoid the possibility of spontaneous pregnancy.

The aim of our study was to evaluate if the patients in whom a complete excisional treatment of all detectable endometriosis nodule have any advantage of receiving a post-surgical therapy with such drugs or the benefits are limited to the patients with incomplete excisional treatment. All the patients included presented severe symptoms and confirmed deep infiltrating endometriosis at surgery. Our results support that a postsurgical treatment with GnRHa may be useful in reducing pain and in delaying recurrences of symptoms in patients with incomplete treatment. This is not a minor finding as many patients with deep infiltrating endometriosis receive such a surgery. In fact laparoscopy is widely diffuse in the gynecological units and women with chronic pelvic pain are promptly submitted to laparoscopy without referring to specialized centers. The surgical treatment in these units is limited to adhesiolysis and to the excision of endometriomas in the deep infiltrating nodules without any treatment or only partial resection. These patients can benefit of a hormonal suppressing therapy to delay symptom recurrence. Unfortunately, our study has clearly shown that symptom reappear as soon as there is the discontinuation of the medical therapy. On the contrary, patients who receive a complete surgical excision of deep endometriosis implants do not need a postoperative administration of GnRHa. The laparoscopic approach in patients with DIE is often demanded not only to resolve pain, but also to obtain pregnancies. It has been previously shown that surgical treatment of DIE improves pregnancy rates [27, 28]. Consequently, in patients with reproductive desire the use of GnRHa after complete excisional treatment of DIE may not only be unnecessary, but also delay the possibility to obtain a requested pregnancy.

The major limitation of this study was the short length of follow-up (1 year). It is clear, that the rate of recurrence increased with an increase in the follow-up period. It might be argued that increasing the follow-up period, even the patients with complete excisional surgery but without post-surgical medical treatment could develop clinical recurrence. Moreover, our surgical approach to the bowel involvement consisted in the shaving of all visible lesions that could result in an incomplete excision of microscopic implants which could increase recurrences in the long-term follow-up in some patients [34]. It has been clearly demonstrated that long-term administration of estroprogestins markedly prevents endometriosis recurrence [35]. Nevertheless, the medical treatment may prevent pregnancy and our study clearly showed that in the 1-year follow-up, patients extensively excised do not need it.

In conclusion, complete surgical excision of deep endometriosis improves the quality of life with a long-lasting outcome. GnRHa administration is followed by a temporary improvement of pain in patients with incomplete surgical treatment, although, following discontinuation of treatment, symptoms tend to recur. It seems that it has no role when the surgeon is able to completely excise deep endometriosis implants at least for one year.

Conflict of interest The authors report no conflict of interests.

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