DAVID SKHIRTLADZE [1], JENARO KRISTESASHVILI [1], RAMAZ CHAREKISHVILI [2]

POSTOPERATIVE PROGESTIN THERAPY FOR PAIN RELIEF IN PATIENTS WITH DEEP ENDOMETRIOSIS

[1] Iv. Javakhishvili Tbilisi State University, Faculty of Medicine, Department of Obstetrics, Gynecology and Reproductology; [2] Evex Medical Corporation, Tbilisi, Georgia

Doi: https://doi.org/10.52340/jecm.2023.05.28

დავით სხირტლაძე [1], ჯენარო ქრისტესაშვილი [1], რამაზ ჩარექიშვილი [2]

პოსტოპერაციული თერაპია პროგესტაგენით პაციენტებში ღრმა ენდომეტრიოზით გამოწვეული ტკივილის დროს

[1] ი. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტის მედიცინის ფაკულტეტის მეანობა-გინეკოლოგია-რეპროდუქტოლოგიის დეპარტამენტი; [2] სს „სამედიცინო კორპორაცია ევექსის ენდოსკოპიურ-გინეკოლოგიური დეპარტამენტი; თბილისი, საქართველო.

რეზიუმე

შესავალი. ღრმა ენდომეტრიოზი წარმოადგენს პროგრესირებად დაავადებას, რომელსაც ახასიათებს ტკივილი მენჯის არეში, რაც მნიშვნელოვნად აქვეითებს ცხოვრების ხარისხს. მიუხედავად იმისა, რომ ლაპაროსკოპიული ქირურგია წარმოადგენს ღრმა ენდომეტრიოზით გამოწვეული ტკივილის მკურნალობის წამყვან მეთოდს, ხშირ შემთხვევაში მხოლოდ ქირურგიული ჩარევა არ არის საკმარისი სასურველი თერაპიული ეფექტის მისაღწევად. დღესდღეობით არსებული ლიტერატურული მონაცემების თანახმად პერსპექტიულად შეიძლება განიხილოს სელექტიური პროგესტაგენის - დიენოგესტის გამოყენება ენდომეტრიოზთან დაკავშირებული ტკივილის ხანგრძლივ მართვაში. ვინაიდან ლიტერატურული მონაცემები კომბინირებული ქირურგიული და თერაპიული მკურნალობის ეფექტურობის შესახებ არის ხშირად არაერთგვაროვანი, შესაბამისად კვლევის **მიზანს** წარმოადგენდა პოსტოპერაციულ პერიოდში დიენოგესტით მკურნალობის ეფექტურობის დადგენა პაციენტებში ღრმა ენდომეტრიოზით გამოწვეული ტკივილის დროს.

მასალა და მეთოდიკა. ჩატარდა პროსპექტული, ღია კვლევა, რომელშიც მონაწილეობდა 21-38 წლის 46 ქალი, რომლებსაც ჩაუტარდათ ქირურგიული ჩარევა ენდომეტრიოზთან დაკავშირებული ტკივილის მკურნალობის მიზნით. პაციენტები დაიყო ორ საკვლევ ჯგუფად რანდომიზაციის გზით. 27-მა პაციენტმა მიიღო პრეპარატი დიენოგესტი პოსტოპერაციულად 3 თვის განმავლობაში, ხოლო დანარჩენ 19 პაციენტზე, რომლებმაც არ მიიღეს დიენოგესტი, მოხდა დაკვირვება იმავე დროის ინტერვალით. კვლევის ძირითად გამოსავალს წარმოადგენდა დისმენორეის ინტენსივობის შეფასება, როგორც ოპერაციამდე, ასევე ოპერაციიდან 9 თვეში, ვალიდირებული რიცხვითი შეფასების სკალის (NRS) გამოყენებით. ქირურგიული ტექნიკა მოიცავდა მენჯის პერიტონეუმის დისექციას, ბლაგვი და ბასრი წესით, ღრმა ენდომეტროიდული უბნების ამოკვეთით ESGE, ESHRE და WES სამუშაო ჯგუფის რეკომენდაციების შესაბამისად.

შედეგები. კვლევის შედეგად, ორივე საკვლევ ჯგუფში ინახა დისმენორეის ინტენსივობის საშუალო ქულის სარწმუნო შემცირება ($p<0.01$). თუმცა პაციენტებში, რომელთაც ქირურგიული მკურნალობის შემდეგ ჩაუტარდათ ჰორმონული თერაპია დიენოგესტით, აღენიშნებათ ტკივილის ინტენსივობის სარწმუნოდ მაღალი შემცირება იმ ჯგუფთან შედარებით, რომელთაც ჩაუტარდათ მხოლოდ ქირურგიული მკურნალობა.

დასკვნა. მიღებული შედეგების ანალიზის საფუძველზე შეგვიძლია დავასკვნათ, რომ ოპერაციული ჩარევის შემდგომ ჰორმონოთერაპია დიენოგესტის გამოყენებით წარმოადგენს ენდომეტრიოზით გამოწვეული ტკივილის მკურნალობის ეფექტურ საშუალებას, მხოლოდ ქირურგიული ჩარევის მეთოდთან შედარებით. შესაბამისად, ჩვენი მონაცემების მიხედვით პერსპექტიულად შეიძლება განიხილოს აღნიშნული კომბინირებული თერაპიის მეთოდის პრაქტიკაში დანერგა.

Introduction. Deep endometriosis, also referred to as deep infiltrative endometriosis, is an advanced and highly aggressive phenotype of endometriosis. It is a progressive, recurrent condition often resulting in severe pelvic pain and infertility [1,2]. Deep endometriosis is defined as the presence of

endometriotic tissue invading the space beyond the peritoneal layer by more than 5mm. It is estimated that of all cases of endometriosis the share of patients suffering from deep disease constitutes 20% [3]. Though pain is the main symptom of endometriosis, about 20-25% of patients may be fully asymptomatic, which makes it hard to recognize [2]. Pain symptoms associated with endometriosis can be clinically manifested in various forms encompassing dysmenorrhea, non-menstrual pelvic pain, dyspareunia, dysuria or dyschezia. In more than 95% of cases, deep endometriosis is associated with severe pelvic pain [4]. The main anatomic sites affected by endometriosis include uterosacral and cardinal ligaments, anterior and posterior cul-de-sacs, posterior vaginal fornix, bladder, bowel and rectovaginal septum [3]. In about 90% of cases, rectovaginal lesions are present also affecting other organs such as the colon, ureters, and bladder [5]. Considering the involvement of multiple sites by the deep disease, it's becoming a routine practice to include multidisciplinary team in the treatment of deep endometriosis to ensure effective and comprehensive surgical care.

As endometriosis represents a chronically progressive disease with considerably high recurrence rate, in many cases, only medical or surgical treatment options fall short of accomplishing sustained and desired therapeutic outcome [6]. Although laparoscopic surgery has become a standard of care for severe endometriosis-associated pain, postsurgical management of the disease remains subject to discussion [7,8]. The effectiveness of surgical treatment is often dependent on concomitant medical conditions such as leiomyoma, adenomyosis, pelvic adhesions, etc., and surgery alone may not be sufficient for the ultimate management of the disease. The therapeutic effectiveness of surgical or medical treatment of deep endometriosis is also limited by its high recurrence rate reaching 50% in the first 5 years after operative intervention [9].

Owing to its multifactorial etiology, other contributing factors should also be considered that may take part in the pathogenesis endometriosis that pose challenges to the successful management of the disease. According to some studies, selective progestin–dienogest has a positive effect on improving endometriosis-related pain. It's been proven to be more effective and safe treatment option compared to other hormone therapies [10-16]. As such, in one study, Vannuccini et al., which evaluated medical therapy for endometriosis-associated pain, dienogest was more efficacious for alleviating pelvic pain in contrast to other hormone medicines such as medroxyprogesterone, goserelin and danazol [17]. Postoperative administration of progestins significantly reduces both menstrual and non-menstrual pelvic pain, leading to improved women's functional capacities in the patients with endometriosis [18,19]. Reduction in pain intensity with the use of dienogest is associated with its effect on pro-inflammatory mediators and cytokines as it downregulates the expression of COX-2, mPGES-1, IL-8, IL-6, monocyte chemoattractant protein (MCP)-1, VEGF, NGF and PGE_2, which hat are synthesized in endometriotic cells [20].

According to literature review, existing research findings remain a matter of dispute regarding the effectiveness of combined surgical and therapeutic approaches for the comprehensive management of deep endometriosis-related pain. Therefore, the aim of our study was to determine the effectiveness of selective progestin–dienogest as postsurgical add-on therapy for pain relief in patients with deep endometriosis.

Materials and Methods. A prospective, open-label, hospital-based study was carried out involving 46 women ages 21-38 who underwent surgical intervention for endometriosis-associated pain. Pre-post quasi-experimental design was selected for the study. The diagnosis of deep endometriosis was made based on laparoscopic findings and postoperative pathology report. The study was carried out at Clinic Caraps Medline, Medical Corporation EVEX JSC, Tbilisi Georgia.

The following inclusion criteria were used: patients who hadn't undergone surgical treatment for endometriosis for the past 2 years and had not received hormone therapy 6 months before the laparoscopic intervention, no clinical and ultrasound signs of adenomyosis. As for the exclusion criteria, it encompassed women with congenital or acquired hormonal disorders and congenital anomalies of the reproductive system, which negatively impact women's reproductive function.

Preoperative clinical evaluation as well as transvaginal ultrasound (Voluson E8, General Electric USA) was performed to prepare patients for the surgical intervention. When necessary, other diagnostic

studies (CT and MRI) were utilized for the diagnostic purposes. The surgical technique entailed sharp and blunt dissection of the pelvic peritoneum through the use of standard endoscopic instruments to exercise deep endometriotic lesions per recommendations of the working group of ESGE, ESHRE and WES [21] (Fig.1.). Following the surgical treatment, based on willingness of patients to take part in the study, a simple random sampling was used to divide the patients randomly into two groups. 27 patients who received dienogest therapy after surgery were enrolled in group 1, while the remainder 19 patients received no treatment and were observed over the same time interval comprised group 2. Continuous add-on dienogest therapy was prescribed with a daily dose of 2mg for the duration of 3 months shortly after surgery. There was no loss of follow-up. To prevent pregnancy, barrier contraception was used in both groups throughout the study period.

The intensity of dysmenorrhea, the main outcome, was assessed by measuring the pain intensity in both groups before and six months after cessation of hormone therapy. A validated numeric rating scale (NRS) was used to measure the intensity of dysmenorrhea [22]. The following categories were defined according to the severity of pain: no or mild pain (0-3), moderate pain (4-6) and severe pain (7-10).

All study participants were given detailed information in advance regarding the essence and goal of the study. Written informed consent forms were signed and obtained from all persons enrolled in the study. The Ethics Committee of "Clinic Caraps Medline" granted approval for carrying out the study.

Results: The mean age of study participants was 31±4.57 SD (range 21–38) with no difference in basic characteristics in both groups. There was no statistically significant difference between the groups regarding the intensity of dysmenorrhea before the surgical treatment (p=0.689). A statistically significant reduction in RNS pain score for dysmenorrhea was seen in both groups (p<0.01). However, the patients who had been treated with oral dienogest after surgery exhibited more statistically significant reduction of pain score at 9 months after surgery compared with the patients with surgery alone (p<0.05) (Table 1). At nine months after surgery, 85.2% of patients in group 1 experienced no or mild pain symptoms (dysmenorrhea) in contrast to group 2, where only 15.9% of patients reported mild or no pain symptoms in patients with no adjuvant dienogest therapy, higher moderate-to-severe mean pain scores remained compared to patients who received combined medical and surgical therapy (84.2 vs. 14.8%, p<0.05). (Fig.2, Fig.3.).

Figure 1. Numeric Rating Scale (NRS). Laparoscopic Surgical Instruments for Dissection

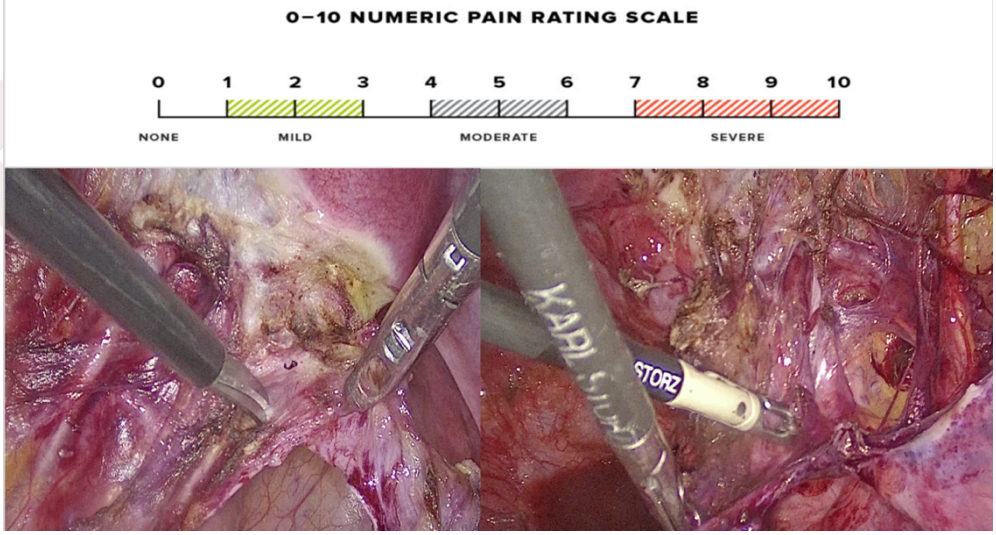


Table 1. Pre- and Posttreatment Mean Dysmenorrhea Pain Intensity by Study Group

Group	n	Mean Pain Score before	Mean Pain Score after	*p*
Dienogest add-on (Gr. 1)	27	8.6 (SD 1.18)	2.2 (SD 1.31)	<0.001
Surgery only (Gr. 2)	19	8.5 (SD 0.83)	6.2 (SD 0.99)	<0.01
p	n/a	0.689	<0.01	

Figure 2. Dysmenorrhea Pain Intensity Per Group Before and After Intervention

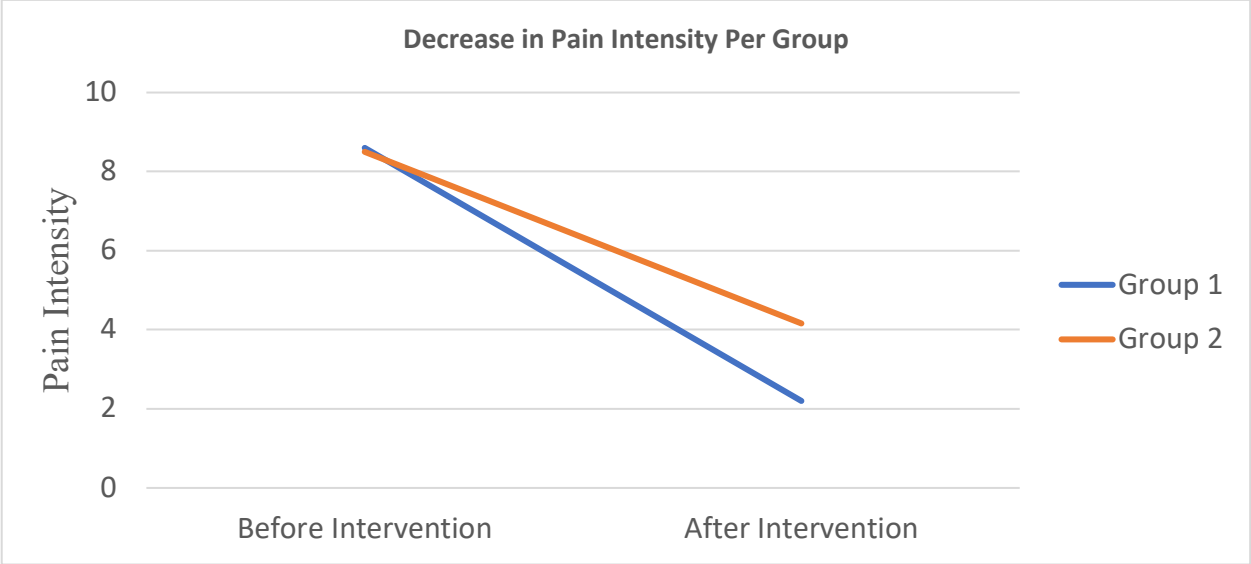
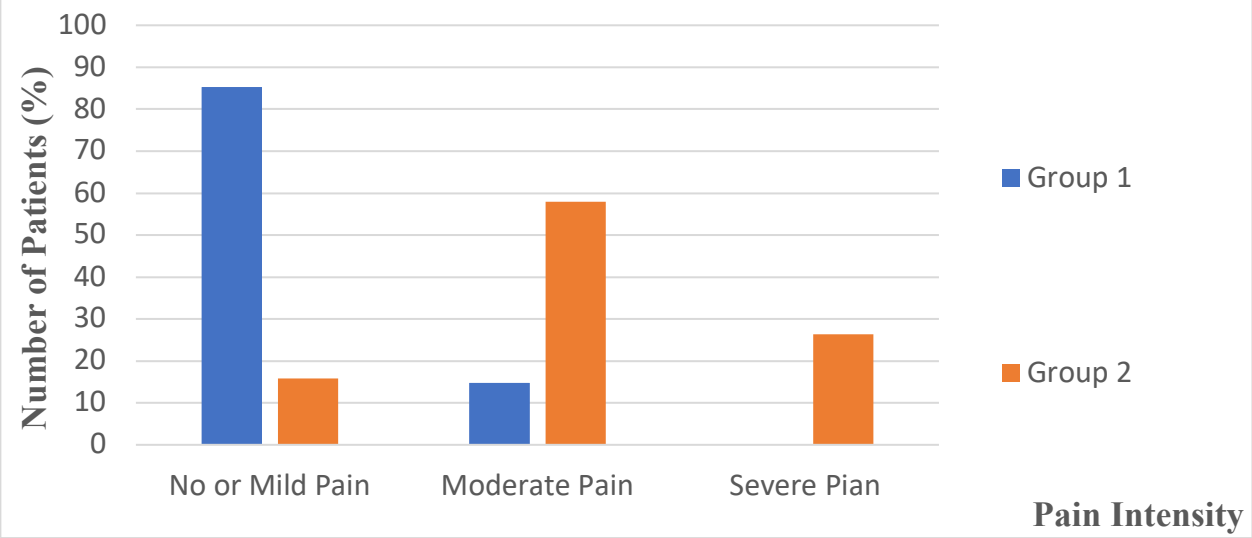


Figure 3. Pain Intensity Per Group 9 Months After Surgical Treatment



Discussion. According to various studies, dienogest therapy is effective in reducing endometriosis-related pain. The use of progestins as a maintenance therapy after surgical treatment significantly relieves both menstrual and non-menstrual pelvic pain and thus improves the quality of life in patients suffering from endometriosis [23,24]. Our study results revealed that patients who received oral dienogest after surgery reported almost twice the reduction in dysmenorrhea pain score at nine months compared to patients treated with surgery alone. Significant pain relief was observed in more than 85% of patients treated with combined therapy, which is almost 5.5 times higher than in group 2. These results were comparable to the previous studies; namely, the patients receiving dienogest after surgical intervention experienced a significant reduction in pain scores. In patients who received long-term treatment with dienogest, there was a significant reduction in dysmenorrhea pain intensity from 8.3 to 1.7 [25,26). Therefore, the use of dienogest in postoperatively is an effective treatment option for deep endometriosis-associated pain, resulting in improved quality of life.

Conclusion: The study results have demonstrated that postoperative add-on therapy with dienogest seems to be more effective for reducing the intensity of dysmenorrhea in patients with deep endometriosis compared to surgical intervention alone. Our research outcomes along with existing research data provide the rationale to support the combined treatment option an attempt to contribute to improved management of endometriosis-associated pain.

References

1. Marinho MCP, Magalhaes TF, Fernandes LFC, et al. Quality of Life in Women with Endometriosis: An Integrative Review. J Womens Health (Larchmt). 2018 Mar;27(3):399-408.
2. Bulletti C, Coccia ME et al. Endometriosis and infertility. J Assist Reprod Gen. 2010 Aug;27(8):441-7.
3. D'Alterio, M. N., D'Ancona, G., Raslan, M., et al. Management Challenges of Deep Infiltrating Endometriosis. International journal of fertility & sterility, 2021;15(2), 88–94.
4. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril. 2012 Sep;98(3):564-71.
5. Wild, M., Miskry, T., Al-Kufaishi, A. et al. Medical management of deeply infiltrating endometriosis - 7 year experience in a tertiary endometriosis centre in London. Gynecol Surg 16, 12 (2019).
6. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertility and sterility 2017;108:125-136.
7. Working group of ESGE, ESHRE, and WES, Joerg Keckstein, Christian M Becker, et al., Recommendations for the surgical treatment of endometriosis. Part 2: deep endometriosis, Human Reproduction Open, Volume 2020, Issue 1, 2020,
8. Laganà AS, La Rosa VL. Multidisciplinary management of endometriosis: current strategies and future challenges. Minerva Med. 2020;111(1):1820.
9. WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125-136.
10. Barra, F., Scala, C., Ferrero, S. Current understanding on pharmacokinetics, clinical efficacy and safety of progestins for treating pain associated to endometriosis. Expert Opin. Drug Metab. Toxicol. 2018; 14: 399–415.
11. Maiorana A, Incandela D, et al. Efficacy of dienogest in improving pain in women with endometriosis: a 12-month single-center experience. Arch Gynecol Obstet. 2017 Sep;296(3):429-433.
12. Safety and Effectiveness of Dienogest (Visanne®) for Treatment of Endometriosis: A Large Prospective Cohort Study: effective in the treatment of endometriosis Cho B, Roh JW, Park J, Jeong K, Kim TH, Kim YS, Kwon YS, Cho CH, Park SH, Kim SH. Safety and Effectiveness of Dienogest (Visanne®) for Treatment of Endometriosis: A Large Prospective Cohort Study. Reprod Sci. 2020 Mar;27(3):905-915.
13. Murji A, Biberoğlu K, Leng J, et al. Use of dienogest in endometriosis: a narrative literature review and expert commentary. Curr Med Res Opin. 2020 May;36(5):895-907.
14. Bizzarri, N., Remorgida, V., Leone Roberti Maggiore, U., et al. Dienogest in the treatment of endometriosis. Expert Opin. Pharmacother. 2014; 15: 1889–1902
15. Ferrero, S., Remorgida, V., Venturini, P.L., Bizzarri, N. Endometriosis: The effects of dienogest. BMJ clinical evidence. 2015; 2015:0802.
16. Morotti, M., Sozzi, F., et al. Dienogest in women with persistent endometriosis-related pelvic pain during norethisterone acetate treatment. Eur. J. Obstet. Gynecol. Reprod. Biol. 2014; 183: 188–192
17. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 2022 Jun;23(3):333-355.
18. Tanmahasamut P, Saejong R, et al. Postoperative desogestrel for pelvic endometriosis-related pain: a randomized controlled trial. Gynecol Endocrinol. 2017 Jul;33(7):534-539.
19. Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. Arch Gynecol Obstet. 2018 Oct;298(4):747-753. doi: 10.1007/s00404-018-4864-8. Epub 2018 Aug 3. Erratum in: Arch Gynecol Obstet. 2019 Jan;299(1):293. PMID: 30076546.
20. Lai, Z.Z., Yang, H.L., Ha, S.Y., Chang, K.K., et al. Cyclooxygenase-2 in Endometriosis. International Journal of Biological Sciences, 2019;15(13), 2783-2797.
21. Working group of ESGE, ESHRE, and WES, Joerg Keckstein, Christian M Becker, et al. Recommendations for the surgical treatment of endometriosis. Part 2: deep endometriosis, Human Reproduction Open, Volume 2020, Issue 1, 2020

22. Bourdel N., Alves J., Pickering G., Ramilo I., Roman H., Canis M. Systematic review of endometriosis pain assessment: How to choose a scale? Hum. Reprod. Update. 2015;21:136–152.
23. Tanmahasamut P, Saejong R, et al. Postoperative desogestrel for pelvic endometriosis-related pain: a randomized controlled trial. Gynecol Endocrinol. 2017 Jul;33(7):534-539.
24. Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. Arch Gynecol Obstet. 2018 Oct;298(4):747-753. doi: 10.1007/s00404-018-4864-8. Epub 2018 Aug 3. Erratum in: Arch Gynecol Obstet. 2019 Jan;299(1):293. PMID: 30076546.
25. Adachi K, Takahashi K, Nakamura K, et al. Postoperative administration of dienogest for suppressing recurrence of disease and relieving pain in subjects with ovarian endometriomas. Gynecol Endocrinol. 2016 Aug;32(8):646-649.
26. Khashchenko EP, Uvarova EV, Chuprynin VD, et al. Pelvic Pain, Mental Health and Quality of Life in Adolescents with Endometriosis after Surgery and Dienogest Treatment. J Clin Med. 2023 Mar 20;12(6):2400.

DAVID SKHIRTLADZE [1], JENARO KRISTESASHVILI [1], RAMAZ CHAREKISHVILI [2]

POSTOPERATIVE PROGESTIN THERAPY FOR PAIN RELIEF IN PATIENTS WITH DEEP ENDOMETRIOSIS

[1] Iv. Javakhishvili Tbilisi State University, Faculty of Medicine, Department of Obstetrics, Gynecology and Reproductology; [2] Evex Medical Corporation, Tbilisi, Georgia

SUMMARY

Background. Deep endometriosis is an advanced phenotype of endometriosis characterized by pelvic pain often leading to decreased quality of life. Though laparoscopic surgery has become a treatment of choice for patients with deep disease suffering from persisting endometriosis-associated pain, postsurgical management remains a subject of discussion. Some studies suggest that the use of selective progestin–dienogest has a positive effect on improving the pain associated with deep endometriosis. However, the current available evidence is inconclusive regarding the effectiveness of combined surgical and therapeutic approaches for the ultimate management of the disease. Therefore, the aim of the study was to determine the effectiveness dienogest as postsurgical add-on therapy for pain relief in patients with deep endometriosis.

Materials and Methods. A prospective, open-label study was conducted involving 46 patients, ages 21-38 years, who underwent surgical intervention for endometriosis-associated pain. They were randomly divided into two groups depending on their desire to participate in the study. 27 patients received dienogest 3 months after surgery, while the remainder 19 patients received no treatment over the same time interval. The main outcome measure was the intensity of dysmenorrhea assessed before and after surgery employing validated numeric rating scale (NRS). The surgical technique entailed sharp and blunt dissection of pelvic peritoneum per recommendations of the working group of ESGE, ESHRE and WES.

Results: There was statistically significant reduction in the mean dysmenorrhea pain score in both groups ($p<0.01$). However, patients who had been treated with oral dienogest after surgery exhibited greater statistically significant reduction of pain score at 9 months compared to the patients who only underwent surgery.

Conclusion: Postoperative add-on therapy with dienogest seems to be more effective for pain relief in patients with deep endometriosis compared to surgical intervention alone. Our study results support postsurgical use of dienogest for endometriosis-associated pain as an attempt to contribute to improved quality of life.

Keywords: Deep endometriosis, dysmenorrhea; dienogest.