VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 11, 852–856

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.99414

Efficacy of postsurgical medical therapy for infertile patients with deep endometriosis

David Skhirtladze[1], Jenara Kristesashvili[2], Ramaz Charekishvili[1]

[1]Department of Endoscopic Gynecologic Surgery, Clinic "Caraps Medline", Tbilisi, Georgia
[2]Department of Obstetrics, Gynecology, and Reproductology, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Objectives: Though laparoscopic surgery is effective for the treatment of deep endometriosis (DE), postoperative management remains controversial. Dienogest therapy after surgery may improve spontaneous pregnancy rates and decrease the severity of dysmenorrhea in infertile patients with DE. This study aims to determine the efficacy of postsurgical therapy with dienogest for improving fertility and reducing the intensity of dysmenorrhea in infertile patients with DE.

Material and methods: This open label, randomized controlled trial was conducted involving 88 women aged 21–38 years with infertility who underwent surgery for DE. Three patients were lost to follow-up. After surgery, eligible patients were randomly divided into two groups. Forty-four patients who received dienogest for three months following surgery were enrolled in group 1. The remaining 41 patients comprised group 2 and did not receive any postsurgical treatment over the same period. The primary outcome measure was the pregnancy rate calculated nine months after surgery, while the mean intensity of dysmenorrhea was measured before and nine months after surgery.

Results: The pregnancy rate in group 1 was significantly higher than in group 2 (47.7% vs 22%, $p = 0.013$) nine months following surgical intervention. Patients in group 1 exhibited a more statistically significant reduction in the mean score of dysmenorrhea intensity compared to group 2, from 8.7 to 2.8 vs 8.76 to 5.63, respectively ($p < 0.001$).

Conclusions: The use of dienogest as an add-on therapy for treating DE may show significantly higher effectiveness compared to surgical intervention alone for improving fertility and reducing the severity of dysmenorrhea.

Keywords: deep endometriosis (DE); infertility; dysmenorrhea; dienogest (DNG)

Ginekologia Polska 2024; 95, 11: 852–856

INTRODUCTION

Deep endometriosis (DE) represents a chronic, progressive disease commonly characterized by pelvic pain and infertility, leading to a decreased quality of life [1, 2]. Per definition, it is the presence of endometriotic nodules that extend over 5 mm beyond the peritoneal surface [3]. Though the exact prevalence of infertility in patients with DE is hard to estimate, according to the literature, it is higher in patients with moderate and severe disease (stage III–IV) than the overall rate, 36% vs 30% [4]. More than 95% of patients with DE experience severe pelvic pain [5].

Given the multifactorial etiology of endometriosis and its advancing, inflammatory course, only medical or surgical treatment is frequently insufficient to achieve a long-term and desired therapeutic effect [6]. Though laparoscopic surgery has become a treatment of choice for severe endometriosis-associated pain or failed medical therapy, the outcomes of surgical treatment of infertility associated with DE are inconclusive as the mechanism of infertility has not yet been fully identified. The postoperative management of the condition is still up for debate [7, 8].

The outcomes of surgical intervention concerning infertility related to DE oftentimes depend on other common coexisting conditions, including uterine fibroids, adenomyosis and pelvic adhesions. Only surgical intervention may not ensure the best treatment result. A high recurrence rate, which can reach 50% in the first five years after surgery, limits the therapeutic effectiveness of surgical treatment [8]. Therefore, to contribute to the improved management of DE, it is reasonable to consider other factors that may play a significant role in the pathogenesis of the disease. Some existing studies suggest that the use of selective

Corresponding author:
David Skhirtladze
Department of Endoscopic Gynecologic Surgery, Clinic "Caraps Medline", Tbilisi, Georgia
e-mail: davitge@yahoo.com

Received: 17.02.2024 Accepted: 20.04.2024 Early publication date: 25.07.2024

progestin — dienogest (DNG) may have a positive effect on improving endometriosis-associated pain, fertility rate and *in vitro* outcomes [9, 10]. A possible improvement in the prognosis may be attributed to the positive effect of dienogest on the eutopic endometrium, which is structurally altered in patients with endometriosis. Dienogest downregulates the expression of genes (PTPRR and AKAP13) present in the eutopic endometrium of patients with endometriosis [11]. In addition, it may improve the sensitivity of endometriotic tissue to progesterone by changing the ratio of progesterone (PR-A, PR-B) and estrogen receptor isoforms. Namely, dienogest reduces progesterone resistance by increasing the PR-B/PR-A ratio and decreasing the ratio of estrogen receptor-β to estrogen receptor-α, which are altered in patients with endometriosis [12].

As far as the best available evidence is inconclusive regarding the effectiveness of combined surgical and therapeutic approaches for the ultimate management of the disease, the rationale of our study was to investigate the effectiveness of dienogest as a postsurgical treatment therapy. Therefore, this study aimed to determine the efficacy of postsurgical medical therapy with selective progestin — dienogest for improving fertility and reducing pain in infertile patients with deep endometriosis.

MATERIAL AND METHODS

A total of 96 patients were assessed for eligibility to participate in the study, out of which 88 met inclusion criteria and were enrolled. We conducted an open-label, hospital-based randomized controlled trial involving 88 women with infertility aged 18–38 years who underwent surgical intervention for DE. It was a single hospital study carried out from March 2020 to December 2022 to observe changes within and between study groups.

The inclusion criteria involved infertile women with DE confirmed by laparoscopic visualization and histopathology reports. Also, the study included patients who had not undergone endometriosis-related surgical treatment for the past two years and had not received sex hormones for at least six months before surgery.

The exclusion criteria included patients who had undergone endometriosis-related surgical treatment for the past 2 years and had received sex hormones within six months before surgery; women with congenital or acquired hormonal disorders and congenital anomalies of the reproductive system, which have an adverse impact on reproductive function. Patients who had any clinical or ultrasound signs of adenomyosis were also excluded from the study.

Patients were prepared for laparoscopic surgical treatment after performing a preoperative clinical assessment along with transvaginal ultrasound (Voluson E8, General Electric USA) and, when necessary, other diagnostic modalities (CT and MRI). Surgery involved blunt and sharp dissection of the pelvic peritoneum and complete removal of deep endometriotic nodules through excision and shaving, following the recommendations of the working groups of ESGE, ESHRE and WES published in 2020 [7]. After undergoing surgery, patients who agreed to participate in the study were randomly divided into two groups using simple random sampling. Patients who received dienogest after surgery were enrolled in group 1 (treatment group, n = 44). The remaining patients who didn't receive medical therapy for the same period after surgery were allocated to group 2 (control group, n = 41), respectively. Three out of 88 initially included patients were lost to follow-up; consequently, 41 patients remained in group 2. The duration of adjuvant hormonal therapy with dienogest continued for three months in both groups with the following dosing regimen: 2 mg once daily, continuously after surgery. Barrier contraception was used during the study period in both groups. The final clinical data from 85 patients were analyzed.

The primary outcome measure was the pregnancy rate, which was compared between groups nine months after surgical intervention. The secondary outcome measure was the intensity of dysmenorrhea between and within groups by employing a validated numeric rating scale (NRS) measured before and nine months after surgery [13].

All persons participating in the study were informed in advance, the essence and goal of the study were explained and written informed consent for participation in the study was obtained. The principal investigator reassured participants that the privacy and confidentiality of data would be strictly protected from unauthorized parties. The Internal Ethics Committee of Clinic "Caraps Medline" granted approval to conduct the study (Ethics code: IEC.CCM.N00264. Date approved: March 4, 2020).

Descriptive and inferential statistical methods were employed to analyze the study data from 85 participants. The percentages, means and standard deviations for the data set were calculated by running descriptive statistics. The Chi-square test was used to measure the difference in pregnancy rates between the two groups and to look for the associations between the different phenotypes of endometriosis. The independent samples Student T test measured the difference between the mean dysmenorrhea intensity scores for both study groups. The mean pain score reduction within each group following the intervention was tested for statistical significance with paired samples Student T test. The Statistical Package for the Social Sciences (Version 21, IBM Corp) was used for all analysis with α value of 0.05 for determining significance.

Table 1. Participant characteristics per group

Characteristics	Group 1 (n = 44)	Group 2 (n = 41)	Total	p value
Mean age	31.25 ± 4.1	30.76 ± 5.07	31.01 ± 4.57	0.622
Mean pain score before treatment	8.7 ± 0.95	8.76 ± 1.04	8.73 ± 0.99	0.813
Isolated deep endometriosis	8 (18.2%)	9 (22.0%)	17 (20%)	0.664
Superficial peritoneal endometriosis	23 (52.3%)	20 (48.8%)	43 (50.6%)	0.748
Ovarian endometrioma	28 (63.6%)	27 (65.9%)	55 (64.7%)	0.831
Pelvic adhesions	22 (50.0%)	17 (41.5%)	39 (45.9%)	0.430

Data presented as n [%], mean ± standard deviation (SD), Student T test, Chi-square test

RESULTS

The mean age of study participants was 31 ± 4.57 standard deviation (SD) (range 21–38). The basic characteristics of patients didn't differ between groups. No statistically significant difference was observed between the groups with respect to age (p = 0.622), the mean score of dysmenorrhea intensity before treatment (p = 0.813), the presence different phenotypes of endometriosis (isolated deep endometriosis, superficial peritoneal disease and endometriomas) and pelvic adhesions (Tab. 1).

Out of 85 patients, isolated cases of DE were confirmed only in 17 patients (20%). More than 60% of patients had unilateral or bilateral endometrioma, while superficial endometrial disease accounted for about 50% of cases. In addition to a significant share of various forms of endometriosis, pelvic adhesions comprised a relatively large proportion of patients (39 patients).

The pregnancy rate for patients treated with oral dienogest was more than twice as high as that of treated with surgery only (p = 0.013) nine months after the intervention (Tab. 2). Also, patients who received postsurgical hormone therapy conceived earlier than those without treatment. Spontaneous pregnancy was documented in 14 patients out of 21 (66.6%) in group 1, as opposed to no pregnancies observed in group 2 within the first three months after cessation of hormone therapy and stopping barrier contraception. As for the intensity of dysmenorrhea, there was a statistically significant reduction in the mean pain scores in both groups (p < 0.001); however, compared to group 2, the patients in group 1 reported a higher mean score of pain intensity at nine months after surgery (p < 0.001) (Tab. 3). At nine months after surgery, 81.8% of patients in group 1 reported no or mild dysmenorrhea-related pain severity, as opposed to group 2, where only 17.1% of patients had mild or no pain. Higher moderate-to-severe mean score of dysmenorrhea intensity remained in patients with no adjunctive dienogest therapy compared with patients who received combined treatment (72.9 vs 18.2%).

Table 2. Pregnancy rates 9 months after surgical intervention

	Mean age ± SD	Pregnancy rate
Group 1 (pts. treated with dienogest)	31.25 ± 4.1	21 (47.7%)
Group 2 (pts. not treated with dienogest)	30.76 ± 5.07	9 (22.0%)
p value	0.622	0.013

Data presented as n [%], Student T test, Chi-square test; SD — standard deviation

DISCUSSION

As the precise pathogenesis of infertility associated with DE is a matter of further research, the outcomes of laparoscopic surgery remain controversial [14, 15]. Though the association between deep endometriosis and infertility is already well-established, the causal relationship is yet hard to determine [2]. It can be explained by the fact that the effectiveness of surgical treatment for DE in patients with infertility often depends on coexisting forms of endometriosis, such as superficial endometrial disease, ovarian endometrioma, or the presence of pelvic adhesions. They may serve as independent factors for female infertility. Our study data show no significant differences between the groups regarding DE and other disease phenotypes, including pelvic adhesions. Somigliana et al. [16] reported similar findings along the lines of DE, endometriomas, and superficial peritoneal endometriosis (6%, 50% and 61%, resp.). However, 74% of patients had concomitant pelvic adhesions, which is 1.6 times higher compared to our study results [16]. It may be explained by variations in treatment methods, differences during endometriosis, and other coexisting factors resulting in scar formation in the pelvis.

Endometriosis disrupts the normal response of endometriotic tissue to progesterone in the reproductive system and often results in progesterone resistance [17]. Resistance to progesterone is a sequel of alterations in the ratios of estrogen and progesterone receptor isoforms [12]. Recent reports have shown that the expression of progesterone

Table 3. Pre- and post-treatment mean scores of dysmenorrhea intensity 9 months after surgery by group

	Mean pain scores before	Mean pain scores after	p value
Group 1 (pts. treated with dienogest)	8.7 ± 0.95	2.8 ± 1.19	< 0.001
Group 2 (pts. not treated with dienogest)	8.76 ± 1.04	5.63 ± 1.93	< 0.001
p value	0.813	< 0.001	

Data presented as mean ± standard deviation (SD)

receptor isoform-B, which enhances endometrial response to progesterone, is downregulated while the activity of the inhibitor isoform-A is upregulated. Consequently, the PR-B/PR-A ratio is diminished [12, 18, 19]. Furthermore, in patients with endometriosis, the expression of estrogen receptor-α (ERα) is suppressed by estrogen receptor-β (ERβ) in endometriotic tissue reducing PR-B levels [20]. Abnormalities in eutopic endometrium may result in endometriosis-related infertility [21]. Positive effect of dienogest on the eutopic endometrium by changing PR-B/PR-A ratio may improve fertility prognosis and provide an enhanced treatment efficacy in patients with DE [12]. According to our study results, the pregnancy rate was more than twice as high in the group treated with dienogest compared to the group treated with surgery alone. Also, compared to group 2, spontaneous pregnancies occurred earlier in group 1. Some studies available in the literature have also reported an increase in pregnancy rates with the use of postoperative hormone therapy. In particular, the pregnancy rate was relatively higher in the group where hormonal treatment (other than dienogest) was used after surgery compared to the group where only surgery was performed (35–48% vs 34%) [22]. Furthermore, systematic reviews and meta-analyses showed that patients who received dienogest following endometriosis surgery had significantly higher odds of becoming pregnant (11.98 vs 4.05) [23]. This difference was not elicited in patients who received other medical therapy. Since there was no significant difference with respect to endometriosis-associated conditions in both groups, including pelvic adhesions, we may assume that the improved pregnancy outcomes, *i.e.*, fertility rate and earlier conception, observed in the dienogest group were caused by increased endometrial receptivity. Dienogest, as stated above, significantly reduces progesterone resistance in endometriotic tissue and intrinsic abnormalities in the eutopic endometrium. According to one retrospective study by Barra et al. [9], administering dienogest three months before in vitro fertilization improves fertility in patients with endometriosis [10]. Thus, even a short-term administration of dienogest in infertile patients may significantly improve pregnancy outcomes.

Dienogest also effectively reduces endometriosis-associated pain, according to numerous studies. Administration of progestogens in the postoperative period significantly lowers both menstrual and non-menstrual pelvic pain, improving the quality of life in patients affected by endometriosis [24, 25]. Our study results indicate that patients treated with oral dienogest after surgery exhibited almost twice the reduction in mean pain score of dysmenorrhea intensity at nine months compared to those treated only with surgery. Significant pain relief was seen in more than 80% of patients treated with dienogest after surgery, which is 4.8 times higher than in the group with surgery only. These results were comparable with the previous studies; there was a substantial reduction in the mean pain scores in patients who received dienogest following laparoscopic surgery. Patients who received long-term dienogest treatment elicited a significant reduction in dysmenorrhea pain intensity from 8.3 to 1.7 [26, 27]. Hence, dienogest administration in the postoperative period ensures effective treatment of pain associated with DE, leading to improved quality of life.

CONCLUSIONS

To the best knowledge, our study results have demonstrated that short-term postoperative use of selective progestin can even improve spontaneous pregnancy rates and reduce the intensity of dysmenorrhea in infertile patients with DE. More robust clinical trials, including multicenter studies, are needed to assess the effectiveness of the combined treatment option for DE. Dienogest as an add-on therapy for treating DE may show significantly higher effectiveness than surgical intervention alone for improving fertility and reducing dysmenorrhea-related pain intensity.

Article information and declarations

Data availability statement

The data that supports the findings of this study are available within the article. Additional data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

All persons participating in the study were informed in advance, the essence and goal of the study were explained and written informed consent for participation in the study

was obtained. The principal investigator reassured participants that the privacy and confidentiality of data would be strictly protected from unauthorized parties. The Internal Ethics Committee of Clinic Caraps Medline granted approval to conduct the study (Ethics code: IEC.CCM.N00264. Date approved: March 4, 2020).

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by David Skhirtladze, Jenara Kristesashvili and Ramaz Charekishvili.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Acknowledgments

All authors thank the team of the Department of Endoscopic Gynecologic Surgery of Clinic "Caraps Medline" for their support in carrying out the study.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Supplementary material

None.

REFERENCES

1. Marinho MCP, Magalhaes TF, Fernandes LF, et al. Quality of life in women with endometriosis: an integrative review. J Womens Health (Larchmt). 2018; 27(3): 399–408, doi: 10.1089/jwh.2017.6397, indexed in Pubmed: 29064316.
2. Bulletti C, Coccia ME, Battistoni S, et al. Endometriosis and infertility. J Assist Reprod Genet. 2010; 27(8): 441–447, doi: 10.1007/s10815-010-9436-1, indexed in Pubmed: 20574791.
3. D'Alterio MN, D'Ancona G, Raslan M, et al. Management challenges of deep infiltrating endometriosis. Int J Fertil Steril. 2021; 15(2): 88–94, doi: 10.22074/IJFS.2020.134689, indexed in Pubmed: 33687160.
4. Meuleman C, Vandenabeele B, Fieuws S, et al. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril. 2009; 92(1): 68–74, doi: 10.1016/j.fertnstert.2008.04.056, indexed in Pubmed: 18684448.
5. Koninckx P, Ussia A, Adamyan L, et al. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril. 2012; 98(3): 564–571, doi: 10.1016/j.fertnstert.2012.07.1061.
6. Becker CM, Gattrell WT, Gude K, et al. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril. 2017; 108(1): 125–136, doi: 10.1016/j.fertnstert.2017.05.004, indexed in Pubmed: 28668150.
7. Keckstein J, Becker CM, Canis M, et al. Working group of ESGE, ESHRE, and WES. Recommendations for the surgical treatment of endometriosis. Part 2: deep endometriosis. Hum Reprod Open. 2020; 2020(1): hoaa002, doi: 10.1093/hropen/hoaa002, indexed in Pubmed: 32064361.
8. Laganà AS, La Rosa VL. Multidisciplinary management of endometriosis: current strategies and future challenges. Minerva Med. 2020; 111(1): 18–20, doi: 10.23736/S0026-4806.19.06370-5, indexed in Pubmed: 31755676.
9. Barra F, Laganà AS, Scala C, et al. Pretreatment with dienogest in women with endometriosis undergoing IVF after a previous failed cycle. Reprod Biomed Online. 2020; 41(5): 859–868, doi: 10.1016/j.rbmo.2020.07.022, indexed in Pubmed: 32873492.
10. Chen I, Veth VB, Choudhry AJ, et al. Pre- and postsurgical medical therapy for endometriosis surgery. Cochrane Database Syst Rev. 2020; 11(11): CD003678, doi: 10.1002/14651858.CD003678.pub3, indexed in Pubmed: 33206374.
11. Poster viewing session. Endometriosis, endometrium, implantation and fallopian tube. Human Reproduction. 2011; 26(suppl_1): i202–i223.
12. Hayashi A, Tanabe A, Kawabe S, et al. Dienogest increases the progesterone receptor isoform B/A ratio in patients with ovarian endometriosis. J Ovarian Res. 2012; 5(1): 31, doi: 10.1186/1757-2215-5-31, indexed in Pubmed: 23113924.
13. Bourdel N, Alves J, Pickering G, et al. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update. 2015; 21(1): 136–152, doi: 10.1093/humupd/dmu046, indexed in Pubmed: 25180023.
14. Carneiro MM, Costa LM, Ávila Ide. To operate or not to operate on women with deep infiltrating endometriosis (DIE) before in vitro fertilization (IVF). JBRA Assist Reprod. 2017; 21(2): 120–125, doi: 10.5935/1518-0557.20170027, indexed in Pubmed: 28609279.
15. Koninckx PR, Ussia A, Adamyan L, et al. The epidemiology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear. Best Pract Res Clin Obstet Gynaecol. 2021; 71: 14–26, doi: 10.1016/j.bpobgyn.2020.08.005, indexed in Pubmed: 32978068.
16. Somigliana E, Infantino M, Candiani M, et al. Association rate between deep peritoneal endometriosis and other forms of the disease: pathogenetic implications. Hum Reprod. 2004; 19(1): 168–171, doi: 10.1093/humrep/deg513, indexed in Pubmed: 14688177.
17. Brosens I, Brosens JJ, Benagiano G. The eutopic endometrium in endometriosis: are the changes of clinical significance? Reprod Biomed Online. 2012; 24(5): 496–502, doi: 10.1016/j.rbmo.2012.01.022, indexed in Pubmed: 22417665.
18. Attia GR. Progesterone receptor isoform A but not B is expressed in endometriosis. J Clin Endocrinol Metab. 2000; 85(8): 2897–2902, doi: 10.1210/jc.85.8.2897.
19. Wu Y, Strawn E, Basir Z, et al. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in endometriosis. Epigenetics. 2006; 1(2): 106–111, doi: 10.4161/epi.1.2.2766, indexed in Pubmed: 17965625.
20. Trukhacheva E, Lin Z, Reierstad S, et al. Estrogen receptor (ER) beta regulates ERalpha expression in stromal cells derived from ovarian endometriosis. J Clin Endocrinol Metab. 2009; 94(2): 615–622, doi: 10.1210/jc.2008-1466, indexed in Pubmed: 19001520.
21. Liu H, Lang JHe. Is abnormal eutopic endometrium the cause of endometriosis? The role of eutopic endometrium in pathogenesis of endometriosis. Med Sci Monit. 2011; 17(4): RA92–RA99, doi: 10.12659/msm.881707, indexed in Pubmed: 21455119.
22. Chen I, Veth VB, Choudhry AJ, et al. Pre- and postsurgical medical therapy for endometriosis surgery. Cochrane Database Syst Rev. 2020; 11(11): CD003678, doi: 10.1002/14651858.CD003678.pub3, indexed in Pubmed: 33206374.
23. Liu Y, Gong H, Gou J, et al. Dienogest as a maintenance treatment for endometriosis following surgery: a systematic review and meta-analysis. Front Med (Lausanne). 2021; 8: 652505, doi: 10.3389/fmed.2021.652505, indexed in Pubmed: 33898487.
24. Tanmahasamut P, Saejong R, Rattanachaiyanont M, et al. Postoperative desogestrel for pelvic endometriosis-related pain: a randomized controlled trial. Gynecol Endocrinol. 2017; 33(7): 534–539, doi: 10.1080/09513590.2017.1296124, indexed in Pubmed: 28266234.
25. Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. Arch Gynecol Obstet. 2018; 298(4): 747–753, doi: 10.1007/s00404-018-4864-8, indexed in Pubmed: 30076546.
26. 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; 32(8): 646–649, doi: 10.3109/09513590.2016.1147547, indexed in Pubmed: 26890948.
27. 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; 12(6), doi: 10.3390/jcm12062400, indexed in Pubmed: 36983400.