Experimental
&
Clinical Article

Reproductive Medicine; *Endocrinology and Infertility*

Impact of Dienogest Alone or in Combination with Ethinylestradiol on the Quality of Life of Women with Endometriosis: A Prospective Cohort Study

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ABSTRACT

OBJECTIVE: We aim to compare the effectiveness of oral contraceptives and dienogest, primarily by considering the quality of life scale. We also aim to compare the Cancer Antigen-125 and Anti-mullerian Hormone values.

STUDY DESIGN: Gynecological examination findings evaluated based on ESHRE and ASRM Guideline criteria are compatible with endometriosis, or a previous surgery pathology result is consistent with endometriosis, and patients whose imaging report was compatible with endometriosis were selected. Among the patients who were recommended medical treatment, patients selected as Dionegest 2mg+Ethinylestradiol 0.03 mg (Dienelle) treatment were considered Group 1, and patients deemed suitable for treatment with treatment 2mg Dionegest (Visanne) were considered Group 2. Pre-treatment Cancer Antigen-125/Anti-mullerian Hormone values and SF-36 were recorded.

RESULTS: There was no significant difference between drug groups in terms of education status, body mass index, family history, smoking, alcohol consumption, age, age at menarche, menstruation pattern, duration of menstruation, infertility, gestational status, job loss due to pain complaints, operation, and MRI findings (p>0.05). There was no significant difference between the drug groups regarding the quality of life before and after treatment (p>0.05). There was no significant difference between drug groups regarding endometrioma size, Cancer Antigen-125, and anti-mullerian hormone findings (p>0.05).

CONCLUSION: Evaluating our data, the efficacy and success of the two treatment protocols were the same. It seems more logical to prefer cost-effective oral contraceptive treatments with a low side-effect profile than high-cost Dionegest. Following the guidelines accepted step therapy in treating mild or moderate endometriosis, cyclic oral contraceptives may be recommended as first-line therapy.

Keywords: Anti-mullerian Hormone, Cancer, Antigen-125, Dienogest, Endometriosis, Life-long treatment, Low-cost treatment, Oral contraceptives, SF-36 quality of life scale

Gynecol Obstet Reprod Med 2023;29(3):196-205

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Submitted for Publication: 04.12.2023 Revised for Publication: 12.12.2023
Accepted for Publication: 14.12.2023 Online Published: 18.12.2023

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Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2023.1453

How to cite this article: *Canday M. and Salman S. Impact of Dienogest Alone or in Combination with Ethinylestradiol on the Quality of Life of Women with Endometriosis: A Prospective Cohort Study. Gynecol Obstet Reprod Med. 2023;29(3):196-205*

Introduction

Endometriosis is a chronic inflammatory and benign disease whose etiology is not precise (1). Genetic predisposition and hormonal and immunological changes are critical in developing the disease (2). Endometriotic implants usually cause adhesions in the pelvic organs and peritoneum, ovarian endometriotic cysts (endometrioma), and extensive fibrosis (3). With its estrogen-dependent nature, this disease peaks between the ages of 25-30 and affects approximately 10% of women of reproductive age (4).

Although the pathognomonic finding of endometriosis is chronic pelvic pain, 20-25% of patients may be asymptomatic (5,6). Also, endometriosis should be considered in patients with dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, abnormal uterine bleeding, infertility, chronic fatigue, and the presence of non-gynecological symptoms such as

dyschezia, dysuria, hematuria, rectal bleeding, and shoulder pain (7,8).

Symptoms of endometriosis negatively affect patients' quality of life by creating conditions that hinder their daily, work, and educational life, social relationships, and sexual and mental health (9,10). However, it is known that as the severity of symptoms increases, the scores in the quality of life scales decrease (11,12). Improving the patient's quality of life can be achieved with adequate control of the symptoms of the disease. In this respect, the treatment to be chosen is of great importance. Endometriosis treatment should be personalized and modified according to the clinical presentation, the severity of the symptoms, the patient's age, fertility expectation, tolerance of treatment's side effects, and cost-effectiveness (13,14). Although the efficacy of both oral contraceptive pill (OCP) and dienogest (DNG) in the treatment of endometriosis is accepted, it can be claimed that there are differences in terms of cost-effectiveness and side effects, which was the purpose of doing this study.

Quality of life assessment studies show that these women with endometriosis are negatively affected in many aspects, such as their work and education life, social and family relationships, and social functions due to the symptoms of the disease (11,12,15,16).

Our study aimed to compare the effectiveness of oral contraceptive and dienogest treatments, which are most frequently used as first-step therapy, primarily by considering the quality of life scale and secondarily by comparing the treatments by evaluating the CA-125 and AMH values.

Material and Method

Our study was organized as a prospective cohort study. Following the ethical committee's (10217170) approval, patients aged 18-45 who applied to our gynecology outpatient clinic for two years are evaluated.

Our study complies with the Declaration of Helsinki, the principles of Good Clinic Practice, and does not conflict with the ethical rules of the subject research (17). All patients who participated in our study, having been thoroughly informed about the study, have provided their informed consent, confirming their willingness to participate.

2.1. Patient selection with inclusion and exclusion criteria

Patients who applied with endometriosis symptoms were included if TAUSG/TVUSG/MRI results were compatible with endometrioma or previous operation pathology result was reported as peritoneal endometriosis or endometrioma. It has been suggested that approximately 1/3 of the patient group cannot be treated with low-dose POPs (Progestin Only Pills) and low-cost progestin therapy (18). The possibility of this patient group having a deep pelvic endometriosis (DPE) diagnosis was considered. In addition, considering factors such as treatment resistance, the possibility of having received treatment recently, or the possibility of preferring surgical treatment to medical treatment in the diagnosis of DPE, patients diagnosed with DPE were not included in the study (18). Among the patients included in the study due to the exclusion of the DPE group, those who had undergone surgery were included in the stage 1-2 group, among patients compatible with endometriosis with peritoneal ovarian involvement. The socio-demographic characteristics of the patients identified as the study group and the presence of the symptoms were investigated. Among the patients with high first measured CA-125 values, patients with a heterogeneous adnexal mass, solid area, papillary protrusion, or pathological blood flow with Doppler in favor of malignity were excluded from the study. IOTA Simple Rules 5 malign features were taken into account while making the evaluation (19). Patients were excluded if they had autoimmune disease, malignancy, hematological and similar diseases, or severe systemic disease and high morbidity. Our study did not include patients if GnRH analog and OCP treatments were used in the last six months. The study did not include those with mental/psychiatric diseases, neuropathy, and fibromyalgia-like diseases that may prevent the evaluation of pelvic pain scoring. Patients with systemic disease that may cause false elevation of CA-125 value or patients with ovarian insufficiency findings that may cause errors in evaluating AMH values were excluded from the study group.

2.2. Treatment protocol

Patients whose demographic characteristics matched were divided into treatment groups. Group 1 was Dienogest 2mg+ Ethinylestradiol 0.03 mg (Dienelle), and group 2 was 2mg Dienogest (Visanne). Acyclic use of their drugs was recommended to the patients. Pre-treatment CA-125/AMH values and quality of life assessments were recorded with the SF-36 QLS. After six treatment cycles, SF-36 QLS was applied to the patients, and CA-125 and AMH measurements were repeated.

2.3. Evaluation of treatment's efficacy

Control SF-36 evaluations, CA-125, and AMH values were evaluated in the sixth month. Patients who could not be followed up at six months or had missing data and did not comply with the recommended treatment protocol for six months were not included in the study. SF-36 QLS was considered a primary variable in the evaluation of treatment protocols. The SF-36, a quality-of-life scale, has its validity and reliability confirmed for the Turkish version (20). The secondary efficacy result was on CA-125 and AMH levels. CA-125 has been investigated so far and is suggested to be associated with endometriosis. CA-125 is used alone or with different biomarkers to diagnose and follow up on endometriosis (21). Also, studies show that AMH values indicating ovarian reserve can be detected low in endometriosis (22), or high

AMH values can be detected in large endometriomas (greater than 6 cm) (23). The changes in CA-125 and AMH values, which are associated with current studies of endometriosis with treatment protocols, were determined as the secondary variables of our study regarding treatment effectiveness. CA-125 (U/mL) and AMH (ng/mL) were measured with the ELISA at baseline and end of cycle six. The tests were performed with standard methodology in our institution during the non-menstruating phase. In addition, the change in cyst sizes of patients with a cystic structure compatible with endometrioma in the examinations was also recorded to evaluate the effectiveness of the drugs. TVUSG/TAUSG was performed with General Electric Voluson 730 by Dr. Canday for each patient. The endometrioma's maximum diameter (D1) with the diameter orthogonal to D1 (D2) was measured. Volume was calculated by the formula (D1+D2 X ½) 3 X0.52 because of the spheroid shape of endometriomas. If patients have more than one endometrioma, the total volume is recorded. Three groups were created as increased (more than 15%), unchanged (±15%), and reduced (more than 15%) according to changes in cyst volume from pre-treatment and end of cycle six.

2.4. Statistical analyses

The sample size was calculated by G-Power 3.12; an alpha of 0.05 with 90% power gave an effect size of 0.7, requiring a minimum of 33 subjects per group (24).

While evaluating the findings obtained in the study, the SPSS 24.0 statistical package program was used for statistical analysis. While considering the study data, the Kolmogorov-Smirnov distribution test was used to examine the normal distribution and descriptive statistical methods (Frequency, percentage, mean, standard deviation, and median). The Student's T-test was used for statistical significance between two independent groups and The One-Way Analysis of Variance (ANOVA) between three independent groups for variables with normal distribution. The Kruskal-Wallis test was used for the intergroup comparisons of the parameters that did not show normal distribution. Pearson Chi-Square test was used to compare qualitative data. Sociodemographic information and biochemical parameters on various data were also recorded. Data were analyzed at a 95% confidence level and $p<0.05$ was considered significant.

Results

Patient distribution for our study is shown in Figure 1. Eighty-four patients were included, and 18 patients were excluded. In the patient group using dienelle, three patients were excluded from the study because they did not come for their control in the sixth month. Five patients were excluded because they did not use their medication per the treatment protocol. In the patient group using Visanne, one patient was ex-

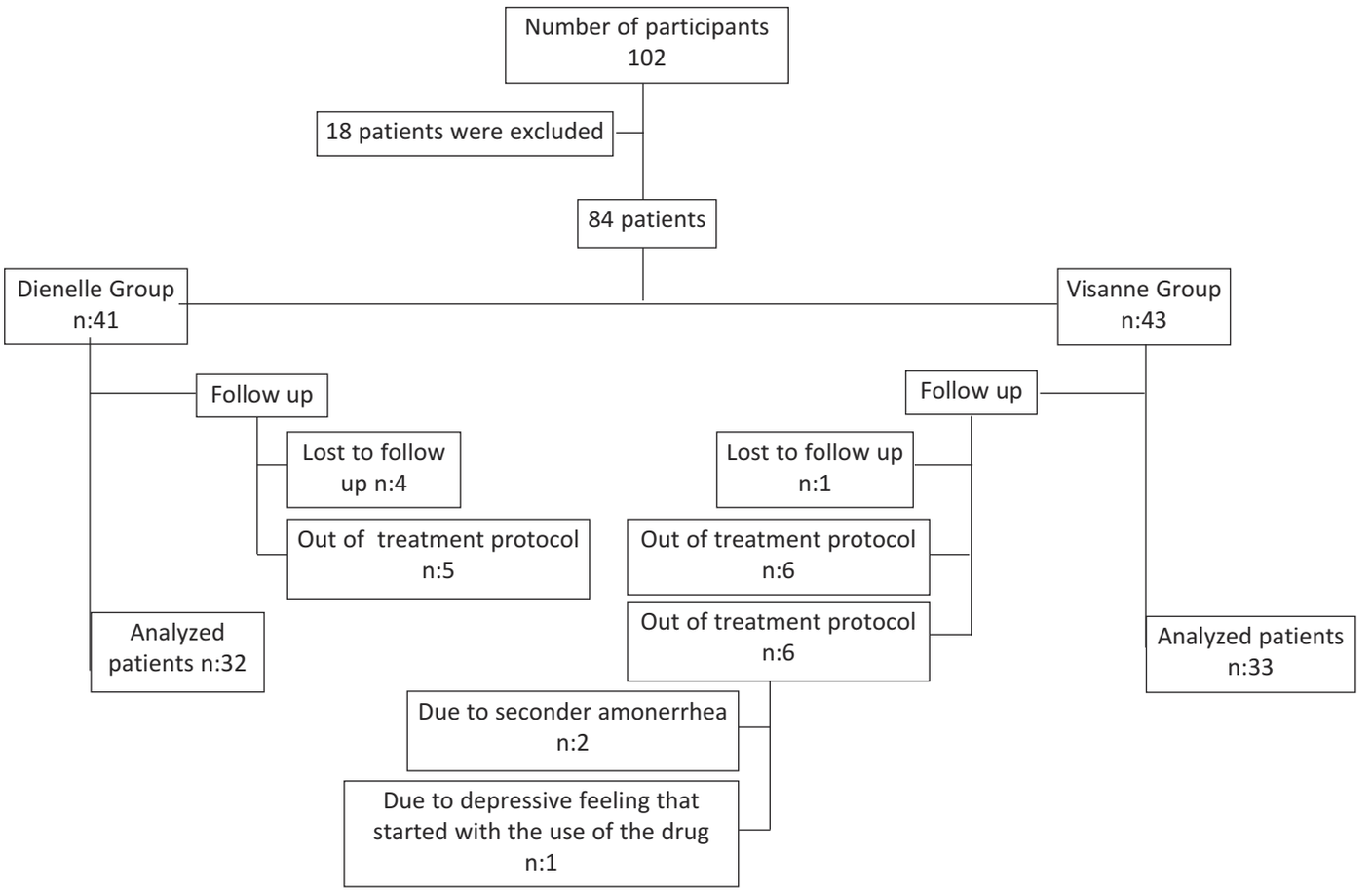

Figure 1: *Patient distribution*

cluded from the study because she did not come to her control at the sixth month, and six patients were excluded because they did not comply with the treatment protocol; at the same time, two patients due to secondary amenorrhea and one patient due to depressive mood left the treatment voluntarily, and they were excluded from the study.

Referring to table I, there was no significant difference between drug groups in terms of Education Status, BMI, Family History, Smoking, Alcohol consumption, and age (p>0.05). The coffee consumption rate (81.2%) of the patients in the Dienelle group was significantly higher than the coffee consumption rate (42.4%) of the patients in the Visanne group (p=0.001). The mean age of the Visanne group was 30.61±7.78, and the mean age of the Dienelle group was 30.66±8.34 (p=0.732).

In the context of table II, there was no significant difference between the drug groups regarding age at menarche, menstruation pattern, duration of menstruation, infertility, gestational status, job loss due to pain complaints, operation, and MRI findings (p>0.05). Mean menarche age of Visanne group; 13.00±1.41, Mean menarche age of Dienelle group; 12.68±1.55 (p=0.399). The mean menstrual period duration of the Visanne group was 5.72±2.58, and the Mean menstrual period duration of the Dienelle group was 5.81± 2.86 (p=0.900).

Figure 2 indicates that the two groups had no significant difference regarding the above complaints (p>0.05).

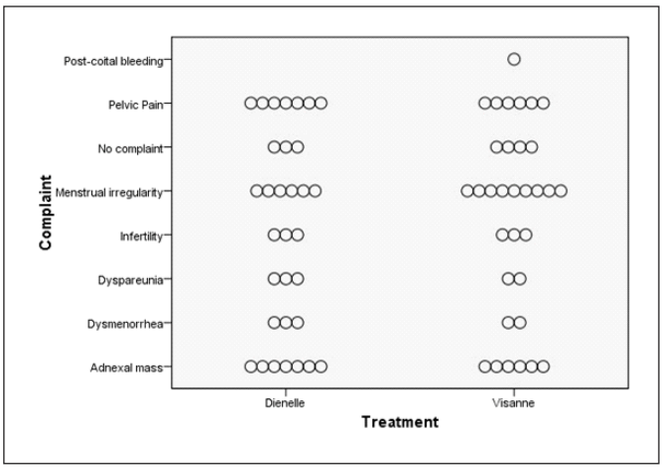

Figure 2: *Complaint Distribution by Drug Groups*

Within table III, there was no significant difference between the drug groups regarding the quality of life before and after treatment (p>0.05).

As depicted in table IV, there was no significant difference between drug groups regarding TVUSG, CA125, and AMH findings (p>0.05).

Table I: *Demographic Characteristics by Drug Groups19*

		2mg Dienogest		Dienogest 2mg + Ethinylestradiol 0.03 mg		p
		n	%	n	%	
Education Status	Literate	3	9.1	4	12.5	0.075
	Primary School	4	12.1	2	6.3	
	Middle School	5	15.2	10	31.3	
	High School	10	30.3	13	40.6	
	University	11	33.3	3	9.4	
Body Mass Index (BMI)	Underweight (BMI: Below 18.5)	13	9.4	11	34.4	0.558
	Healthy (BMI: 18.5-24.9)	10	30.3	14	43.8	
	Overweight (BMI:25-29.9)	9	27.3	7	21.9	
	Obese (BMI:30 and above)	22	66.7	26	81.2	
Family History of Endometriosis	Yes	11	33.3	6	18.8	0.146
	No	11	33.3	18	56.2	
Smoking	Yes	12	37.5	14	42.4	0.440
	No	20	62.5	19	57.6	
Alcohol Consumption	Yes	0	0	1	3	0.508
	No	32	100	32	97	
Coffee Consumption	Yes	6	18.8	18	54.5	0.003
	No	26	81.3	15	45.5	

Table II. *Health Findings by Drug Groups*

		2mg Dienogest	2mg Dienogest + 0.03 Ethinylestradiol mg	p
Menarche age, median (min-max)		12 (11-16)	13(11-16)	0.685
Menstrual cycle, n (%)	Regular	16 (48.5)	17(53.1)	0.450
	Irregular	17 (51.5)	15(46.9)	
Infertility, n (%)	No	28 (84.8)	22 (68.8)	0.106
	Yes	5 (15.2)	10 (31.2)	
Primary infertility Seconder infertility	Primary, n (%)	5 (100)	5 (50)	0.084
	Seconder, n (%)	0 (0)	5 (50)	
Gestational status, n (%)	Nulliparity (non-pregnant)	13 (39.4)	13 (40.6)	0.892
	Multiparity (1 or more pregnancies)	16 (48.5)	14 (43.8)	
	Virgo	4 (12.1)	51 (5.6)	
Loss of job due to pain complaint, n (%)	Yes	22 (66.7)	16 (50)	0.133
	No	11 (33.3)	16 (50)	
Endometriosis Surgery, n (%)	Yes	20 (60.6)	22 (68.8)	0.335
	No	13 (39.4)	10 (31.2)	
MRI results, n (%)	Yes	23 (69.7)	26 (81.2)	0.711
	No	10 (30.3)	6 (18.8)	

Table III: *Change of SF-36 Quality of Life Findings by Drug Groups*

	2mg Dienogest		2 mg Dienogest + 0.03 Ethinylestradiol mg		p
	Mean	SD	Mean	SD	
Pre-Treatment Physical Function	71.360	21.370	64.060	24.044	0.200
Post- Treatment Physical Function	78.480	16.512	73.910	17.215	0.278
Pre-Treatment Limitations Associated with Physical Health	56.520	37.007	42.190	36.166	0.120
Post-Treatment Limitations Associated with Physical Health	77.270	26.044	65.620	24.388	0.068
Pre-Treatment Limitations Associated with Emotional Problems	36.820	25.088	42.090	26.968	0.417
Post-Treatment Limitations Associated with Emotional Problems	61.880	13.910	59.090	15.516	0.449
Pre-Treatment Energy Fatigue	42.420	20.392	42.190	20.750	0.963
Post-Treatment Energy Fatigue	66.360	14.592	66.560	13.880	0.955
Pre-Treatment Emotional Well-Being	51.330	19.803	49.310	22.338	0.701
Post-Treatment Emotional Well-Being	69.330	15.674	68.750	16.459	0.884
Pre-Treatment Social Function	57.420	23.296	51.120	22.236	0.269
Post-Treatment Social Function	74.450	19.571	70.440	20.029	0.417
Pre-Treatment Pain	42.030	20.437	36.280	23.841	0.300
Post-Treatment Pain	69.850	16.031	68.560	17.894	0.761
Pre-Treatment General Health	51.670	20.181	47.660	24.789	0.476
Post-Treatment General Health	69.550	16.026	67.190	16.211	0.558
Pre-Treatment Change in Health	43.940	25.792	40.620	21.767	0.578
Post-Treatment Change in Health	71.970	20.499	68.750	22.895	0.552

Table IV: *Change in TVUSG, CA125, and AMH findings by Drug Groups*

		2 mg Dienogest		2mg Dienogest + 0.03 Ethinylestradiol mg		p
		n	%	n	%	
Change in TVUSG findings	The cyst disappeared	7	21.9	1	3.2	0.051
	The cyst has shrunk	21	65.6	22	71.0	
	The cyst remained the same	1	3.1	0	0.0	
	The cyst size increased	3	9.4	8	25.8	
Ca-125	No change	1	3.0	1	3.0	0.667
	Decrease	30	90.9	27	84.4	
	Increase	2	6.1	4	12.5	
AMH	Decrease	17	51.5	19	59.4	0.349
	Increase	16	48.5	13	40.6	

Discussion

The etiology, development, and recurrences of endometriosis, the mechanisms that cause pain, and the relationship between pain and the stage of the disease are not completely clear. Pain is the most prominent symptom of endometriosis in the clinic, and since it is the cardinal sign of endometriosis, the primary goal of treatment protocols is pain relief. From this point of view, the fact that in addition to pain, the quality of life, physiological status, sexual functions, social life, marriage life, school, and work-life of women with endometriosis are adversely affected should be considered as the burden of the disease (25). Studies have shown that the most negative symptom in the quality of life measure, as expected, is pain (26-32). As with endometriosis, a chronic inflammatory disease, medical studies conducted to elucidate conditions with a high disease burden have found a link between inflammatory diseases and mood disorders (33); considering endometriosis, serious links have been found between immunopathogenic factors resulting in an imbalance between proinflammatory and anti-inflammatory cytokines and the severity of the patient's mood changes, anxiety, and mental health (34). Peripheral immunological changes may affect the central nervous system and induce a disease response, inducing depression-like behaviors, fatigue, hypophagia, irregularities in appetite, sleep and sexual habits, anhedonia, and behavioral changes such as sadness; this negatively affects the patient's social interactions and close relationships (10,35). The psychoneuroimmune nature of the disease increases women's perception of depressive symptoms and stress (25); acute and chronic stress, depression, and anxiety negatively affect the immune system, which creates a vicious circle between inflammation, disease behaviors, and depression (10).

The researchers observed a dramatic decrease in the quality of life and work efficiency in their study of endometriosis patients with chronic pelvic pain and other symptoms, with the deterioration of their mental health due to anxiety and depression-like symptoms, the uncertain and chronic nature of the disease's natural course and, more importantly, the potential risk of infertility it brings to the woman. They tried to explain it with anxiety and similar factors that such conditions spread on the patient (11,12,16,26,27,29-31,36,37). Three randomized controlled studies are in the literature (38,39). Di Francesco et al. and three comparative observational studies (40-43) evaluated the quality of life assessment studies. In five of these studies, the patient's health, physical function, limitations related to physical health, constraints related to emotional problems, energy-fatigue state, emotional well-being, social function, pain, general health, and health changes were evaluated using SF-36 criteria. In another study by Di Francesco et al., SF-12, the abbreviated SF-36, was used by (43). A high score in the SF-36 criterion represents a better quality of life scale (range 0-100). When randomized controlled studies were considered together, it was found that cyclic OCP treatment, continuous OCP treatment, and oral progestin improved the evaluation of quality-of-life measures (38,43). Although the comparison between the groups did not show consistent differences, add-back treatment combined with GnRH agonists was preferred over the administration of OCP and GnRH agonists alone (39). In contrast, oral progestin was preferred over OCP treatment (38).

In the observational comparative study data, improvements were detected in evaluating the quality of life measurements compared to baseline in cyclic OCP use (40,41) and continuous OCP uses (40). In comparing the groups, steady OCP was significantly preferred to cyclic use (40). Within the current literature evaluated, Vercellini et al. used SF-12 while assessing the use of another progestin, NETA, in the group that did not respond to OCP treatment. While they detected an improvement in the physical components in the quality of life

scale, they could not detect it in the mental components (44). Grandi et al. (41), the potential use of DNG and estradiol valerate preparations for 24 weeks was compared with a measure of pelvic pain and quality of life. Grandi et al. obtained a similar result to their study (45); they reported that with both treatment protocols, they improved quality of life scales by reducing mainly intermenstrual pain and, to a lesser extent, dysmenorrhea pain. Their study emphasized that besides the knowledge that DNG treatment improves the quality of life scale, no prospective research enhances the quality of life scale in the OCP treatment option. Caruso et al. compared DNG/Ethinyl estradiol in a continuous regimen to a 21/7 regimen for pelvic pain based on the quality-of-life measurements (40). There were third and sixth-month controls in the study, and while there was an improvement in the first control in the quality of life measurements for both treatment groups, this improvement was also detected in the sixth-month control. In the intragroup evaluation, a more effective improvement was found in each component of the quality of life measurements in the continuous use of DNG/EE compared to the 21/7 regimen.

Strowitzki et al. found significant improvements in the pain and emotional assessment categories in the DNG-administered group in the evaluation with SF-6 compared to the placebo group (46). Maoirana et al., in their study comparing DNG and EE/DNG and evaluating SF-36, suggested that both regimens were beneficial for improving quality of life during treatment. However, they posited that using DNG had a more pronounced effect on dyspareunia complaints (47). Considering this result, especially in the context of deep pelvic endometriosis where dyspareunia is more prominent, it supports the idea that this regimen may be more rational for use in the treatment-resistant group or cases of deep pelvic endometriosis.

Our study statistically proved that pelvic pain, the cardinal sign of the disease, decreased with both treatment regimens. A significant improvement was observed in the SF-36 evaluations of the quality of life measurements. In evaluating the size of the adnexal masses detected in the patients, although both drugs provided a statistically significant reduction in cyst sizes, the reduction achieved in the Dienelle option was slightly higher (p=0.020). While an improvement was observed in CA-125 values due to both treatment options, this improvement was slightly higher in the Visanne group (p=0.028). When the AMH values, another secondary variable, were evaluated in our study, the results were not statistically significant in the Visanne group, while p=0.004 was found to be 0.05 in Dienelle. However, when the results were generally evaluated, no statistically significant superiority of 2 mg DNG treatment was seen over OCP treatments containing the same amount of DNG combined with estrogen. OCP and DNG treatment improved the results of quality of life measurements. Considering the QLS, it was suggested that they do not have an advantage.

Evaluating our data, the efficacy and success of the two treatment protocols were the same. It seems more logical to prefer cost-effective OCP treatments with a low side-effect profile to high-cost DNG. Following the guidelines accepted step therapy in treating mild or moderate endometriosis, cyclic OCP may be recommended as first-line therapy. Due to side effects, continuous OCP may be recommended in treatment failure or non-compliance. In contraindications or complete unresponsiveness to treatment, low-cost progestogen therapy may be preferred first. If the drug is discontinued due to side effects, DNG-like progestogens or GnRH agonists or antagonists may be selected in the future. Improved quality of life and symptoms are increasingly recognized goals in treating endometriosis. In this sense, treating endometriosis should not be limited to medical or surgical treatment. Still, the options should be determined. The effects of the disease on quality of life, mental health, and social life are considered, and the treatment should be multidisciplinary. It is a fundamental goal for women with endometriosis to lead an everyday life as much as possible. However, it must be emphasized that despite there being no consensus in the literature about the primary preference for OCP and DNG treatments., many accepted international guidelines and communities recommend OCP as the first-line treatment for endometriosis. In particular, as stated in the 37th recommendation of NICE's current guide (November 217) NG73 recommendations, there is an expression 'Recommend OCP or progestogen-like hormonal therapy' in the suspicion of endometriosis, definitive diagnosis, and treatment of recurrent endometriosis. The guideline states that treatment goals can be achieved in 2/3 of patients with low-dose OCP and low-cost progestin. Planning long-term OCP or progestogen therapy will reduce the burden of treatment and the burden of the disease and prevent the known consequences of the disease by improving the anxiety and depression level of the woman.

The limitations of our study can be attributed to the small size of our study group and the constraints on our follow-up periods. Other limitations in our study should be reviewed in future studies. Although our study was designed as a prospective cohort study, a six-month follow-up of the patients was evaluated, and the fact that the patients were separated into the treatment groups with social-demographic matching constitutes the weak side of our study in terms of not providing complete randomization. Although the deep pelvic endometriosis group was excluded from our study, stage 3-4, endometriosis was primarily considered in literature studies on the quality of life. In addition, when the literature on endometriosis treatment options is evaluated, the data on combined oral contraceptives appears to be of low quality. The reasons for this are the nonrandomized distribution of treatments, lack of treatment confidentiality, and placebo arm in many studies.

On the contrary, studies on GnRH agonist-antagonists and dienogest appear to be high quality. This situation can be ex-

plained by the pharmaceutical industry conducting such high-cost double-blind, placebo-controlled, multicenter, randomized controlled trials (RCT) not for non-contraception indications of inexpensive combined oral contraceptives but for new high-cost drugs to be brought into the industry. Therefore, studies on OCP still need stronger evidence, as working groups not supported by the pharmaceutical industries and independent researchers contribute to the literature with observational studies rather than expensive RCTs. It is, therefore, no surprise that a drug of which the industry has received so little attention is unlicensed for the treatment of endometriosis.

Finally, in our study, considering the quality of life criteria, instead of high-cost DNG-like treatments, we obtained findings in favor of preferring OCP treatment with positive results by covering the symptomatic patient group with a low side-effect profile, cost-effective, and suitable for a step-by-step treatment approach.

Conclusion

Low-dose POPs and low-cost progestin control endometriotic lesions and symptoms in treating approximately 2/3 of endometriosis patients, including deeply infiltrated forms. The remaining 1/3 of patients require second-line medical treatments or surgery, and future genetic and pharmacological studies should be focused on improving outcomes in the smaller subset of patients with worse prognoses (40).

Demonstrating the efficacy of DNG, GnRH agonists, or antagonists in RCT studies should not be considered a systematic prescription for the routine treatment of all women with symptomatic endometriosis. With the stepped treatment protocol, unnecessary prescription of these drugs to 2/3 of patients who do not need this group of drugs can be prevented.

Endometriosis imposes a significant economic burden on families and society. Frequent gynecological examination visits, imaging, blood tests, delays in diagnosis, high hospitalization rates, surgical interventions, comorbid conditions, costs of medical treatments and side effects, and many hidden costs have made endometriosis a public health issue problem. Treatments planned with long-term OCP or progestin reduce the treatment burden with low cost and ease of use. The impact of endometriosis on a woman's quality of life is significant and wide-ranging. The reasons for the low price of OCP, their prominence with their contraception properties, and not being approved for the treatment of endometriosis cannot be the subject of RCT studies. Further studies with RCT designs are needed to draw attention to step-by-step treatment protocols to provide less cost, more minor side effects, and birth control effectiveness in treating endometriosis.

We hope that the results of our study will contribute to the current literature created to determine treatment protocols that will increase patients' quality of life with affordable cost, less side-effect profile, and good tolerability. In addition, the data we obtained as a result of six-month follow-up periods will emphasize the deficiency in the first step treatment approach since the treatment protocols with low cost and less side-effect profile have not been given sufficient prominence in the literature, instead of the empirically initiated high-cost treatments, which we observed have become a common approach.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Taksim Education and Research Hospital, Ethics Committee of Clinical Trials (Ethics approval reference number: 88 Date 19.09.2018). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The datasets and code used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: No funding

Authors' contributions: MC: raised the presented idea, designed the study, and collected the data. SS: participated in data analysis interpretation results and revised the manuscript. All authors contributed to the writing of the paper and have read and approved the final manuscript.

Acknowledgment

This manuscript results from Mujde Canday's specialization thesis on Gynecology and Obstetrics. Our study was presented at the 8th International Hippocrates Congress on Medical and Health Sciences on March 4-5, 2022.

We are grateful to all participants and their families who spent their precious time participating in this research program. We are also thankful for the tireless efforts of the research team members.

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