Journal of
Womens Health and Gynecology

Research Article Open Access

The Impact of Dienogest (2mg) on the Quality of Life of Women with Endometriosis

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Received Date: February 07, 2023 **Accepted Date:** March 07, 2023 **Published Date:** March 10, 2023

Citation: Fátima Faustino, José Lourenço Reis, Filipa Osório, Rui Viana, et al. (2023) The Impact of Dienogest (2mg) on the Quality of Life of Women with Endometriosis. J Womens Health Gyn 10: 1-12

Abstract

Background: Endometriosis is a chronic, often progressive and relapsing disease, characterized by the presence of endometrial glands and stroma outside the uterine cavity. Endometriosis affects woman's life globally, therefore the subjective assessment of the patient's quality of life is central to the management of endometriosis. Currently, there is a lack of medical options as well as real word data regarding dienogest treatment.

Objective: To evaluate the impact of dienogest in health-related quality of life in patients with endometriosis.

Study design: Non-interventional, prospective and multicenter study. Women with endometriosis were eligible to enroll, regardless of previous treatment. Women received dienogest 2 mg once daily as part of their routine clinical practice. Quality of life was assessed through the Portuguese validated endometriosis health profile-30 (EHP-30) questionnaire at the baseline (beginning of the treatment) and at 3- and 6-months following treatment.

Results: A total of 88 women were screened for eligibility of which 86 (97.7%) were enrolled. From those, only 47

participants (54.7%) completed the study. EHP-30 scores improved at 3- and 6-months in all the five studied domains. Treatment with dienogest for 6 months elicited a mean change of -25.0 ± 25.0 (mean ± SD) in control and powerlessness domain (95% CI: -33.2; -18.9), followed by pain (–22.6 ± 23.4 ;95% CI: -30.4;-17.0), emotional wellbeing (–18.0 ± 22.7 ;95% CI: -25.5;-12.2), social support (–15.9 ± 26.0 ;95% CI: -20.6;-4.7), and self- image (–11.1 ± 28.5 ;95% CI: -24.3;-9.0), The percentage of patients with improvement in EHP-30 scores was the highest for control and powerlessness scale at both timepoints evaluated.

Conclusion: Treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced EHP-30 score, improving quality of life in a short-period as 3 months, with continued progress at 6 months.

Keywords: Dienogest; Endometriosis; EHP-30; Pain; Quality of Life

Introduction

Endometriosis is a chronic, often progressive and relapsing disease, characterized by the presence of endometrial glands and stroma outside the uterine cavity [1]. Globally, it is estimated that endometriosis affects approximately 10% of women of reproductive age [2]. The multifactorial nature of this disease hinders the diagnosis and often delays early intervention, demanding the collaboration of a multidisciplinary team.

Clinically, endometriosis is manifested by dysmenorrhea, chronic pelvic pain, dyspareunia, dysuria, dyschezia, infertility and abnormal uterine bleeding, among others. However, as the symptomatology is very heterogeneous among patients, it can take 6–10 years to diagnose endometriosis [3]. The symptomatologic pattern often affects physical, emotional and social morbidity which, by consequence, decrease quality of life [4,5]. Health-related quality of life is a multidimensional and dynamic concept that encompasses physical, psychological and social aspects related to a disease or its treatment. Given that endometriosis affects woman's life globally, the subjective assessment of the patient's quality of life is central to the management of endometriosis [6].

The Endometriosis Health Profile Questionnaire-30 (EHP-30) is currently the most widely used and validated questionnaire to assess quality of life in women with endometriosis [4,7]. The EHP-30 contains 30 questions divided into five subcategories, addressing pain, control and powerlessness, emotional wellbeing, social support and self-image domains. It is recommended by the American Society for Reproductive Medicine (ASMR) and the European Society for Human Reproduction and Embryology for research on health-related quality of life in endometriosis [8,9]. Distinct studies have shown that EHP-30 is sensitive to changes in health status in patients with endometriosis over time [10-12]. This questionnaire has already been validated in several languages, such as Spanish [13], Swedish [14], Brazilian [15], Chinese [16] and also in Portuguese [8].

Currently, the medical management of endometriosis aims to improve symptoms and the related pain or to prevent the recurrence of postsurgical disease[6]. Hormonal treatments such as combined oral contraceptives and progestins are the first therapeutic choice in order to mimetize a hyperprogestogenic environment. By doing that, these medicines inhibit ovulation, decidualization, and result in a decrease in the size of the lesions [1]. Dienogest is an oral progestin with a strong progestogenic effect, resulting in pronounced endometrial lesion reduction [17]. This drug lacks significant androgenic, mineralocorticoid, or glucocorticoid activity and presents good tolerability, potentiating its long-term use. Of note, multiple evidence showed that the prolonged dienogest treatment substantially improves endometriosis-related pain symptoms [18,19]. Thus, dienogest might present a promising first-line treatment option for the long-term management of debilitating endometriosis-associated symptoms, and consequently, quality of life [12,20]. In comparison with gonadotropin-releasing hormone (GnRH) agonists, dienogest demonstrated comparable efficacy in reducing endometriosis pain-associated symptoms with less adverse

events [21]. Importantly, identical results are achieved with combined oral contraceptives (COCs) for the relief of endometriosis-associated pelvic pain and improvement in health-realted quality of life [22].

To date, real word data of the impact of dienogest treatment on quality of life are lacking. Thus, the present study aimed to evaluate the effect that endometriosis has on women's quality of life, using the EHP-30 questionnaire, before starting treatment with dienogest (2 mg/daily) and 3 and 6 months after starting the treatment. Understanding this information can help to improve counseling for women. Furthermore, this study will allow us to deepen our knowledge of the Portuguese reality about the quality of life of women with endometriosis, to evaluate the effect that endometriosis has on women's lives, as well as to identify factors that influence their quality of life, taking into account consideration of several dimensions (pain, sense of control and powerlessness, emotional well-being, social support and self-image).

Methods

Study Design

This study was a non-interventional, prospective and multicentric study conducted in routine clinical practice settings. The study recruited 88 women with endometriosis for whom a decision of being treated with dienogest 2 mg/daily (Zafril®, Gedeon Richter Plt., Hungary) was made by the physician according to the local health authority approved label. No additional diagnostic procedure was applied. Patients who fulfilled all the eligibility criteria were invited by their gynecologist to participate in the study and all patients signed a written informed consent form prior to their admission. The study was approved by the competent Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Study Population

Women with at least 18 years of age, with clinical or surgical diagnosis of endometriosis, with endometriosis associated pelvic pain and/or dysmenorrhea and women that were physically and psychologically able to participate in the study were eligible. Women were excluded if they had any known adverse reactions to the active substance or to any of the excipients, if they were participating in an investigational program with interventions outside of routine clinical practice and if women were exposed to other medicine or medical device in investigation in the 6 months prior to recruiting. The study also excluded patients with a current or recent history of drug or alcohol abuse, and participants with a serious illness, mental disorder or any other cause that could impact their participation.

Data Collection

Following the initial explanation of the study and the signature of the informed consent form by the women, the physician filled a clinical questionnaire where clinical information about the woman was collected (time of diagnosis, method of diagnosis, classification of endometriosis, symptoms presented and previous treatment of endometriosis). Women were asked to respond to the Endometriosis Health Profile Questionnaire-30 (EHP-30) validated Portuguese version. The information collected comprised sociodemographic characteristics (age, education, occupation and marital status) and questions to measure the effect that endometriosis has on women's quality of life. Women answered the questionnaire in person at day 0 (before the start of treatment) and by telephone at day 90 (approximately 3 months) and at day 180 (approximately 6 months) after the treatment started. The questionnaires were performed between January 2021 and June 2022.

The Endometriosis Health Profile-30 (EHP-30)

The EHP-30 contains 30 questions divided into five subcategories. These categories address key problem-areas which are transversally reported by women with endometriosis: pain (questions 1 to 11), control and powerlessness (questions 12 to 17), emotional wellbeing (questions 18 to 23), social support (questions 24 to 27) and self-image (questions 28 to 30). When women were answering EHP-30, they were asked to recall their experience in the last 4 weeks using never, rarely, sometimes, often or always (five-point Likert scale (0–4)). Each scale was translated into a score ranging from 0 (best possible health status) to 100 (worst possible health status) by dividing the subscale scores by the maximum possible

raw score within the subscale and multiplying it by 100. Changes in EHP-30 domains scores were categorized in deterioration, no change and improvement. These categories were defined as >0, 0 and < 0 difference in EHP-30 scores, respectively.

Statistical Analysis

Data collected using the questionnaires were cleaned and coded. Data were entered and analyzed using SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corporation). Proportions, arithmetic means, medians, minimum, maximum and standard deviations (SD) were used as summary statistics. In addition, skewness of score distribution and kurtosis were used to describe the distribution of item responses as well as 95% confidence intervals (CI).

Wilcoxon signed rank test was used to test for statistically significant differences between baseline and follow-up timepoints. P-value < 0.05 indicated a statistically significant change.

Results

Participants

A total of 88 women were screened for eligibility of which 86 (97.7%) were enrolled. From those, only 47 participants (54.7%) completed the study (Figure 1). Among the 39 women who did not complete the study, 21 were drop-out at 3 months' follow-up and the remaining 18 at 6 months' follow-up questionnaire. Voluntary withdrawal and loss to follow-up were the main reasons identified.

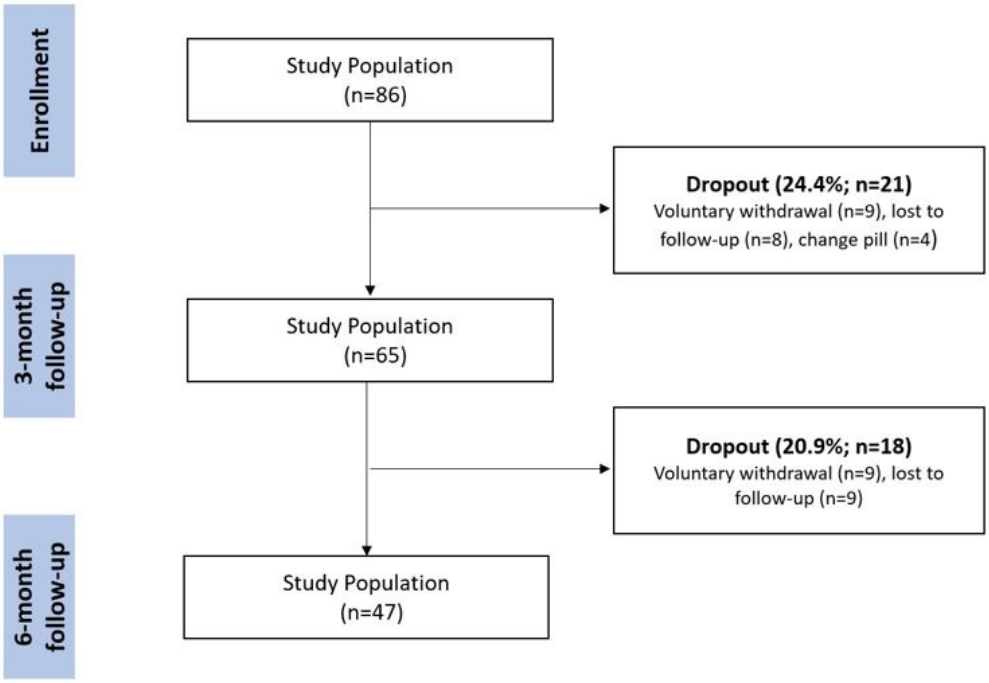

Figure 1: Flow diagram of the study, schematizing the women progress

A summary of the characteristics of the patients is presented in Table 1. The average age of the sample was 35 ± 8 years old, ranging from 18 to 49 years old. In their majority, women had a university degree (bachelor's degree or higher, 60.5%), were married or living in common-law marriage (57.0%) and were working (79.1%).

Table 1: Participant's socio-demographic and clinic characteristics at baseline

Variables	Total Sample (N=86)
Mean age in years ± SD	35 ± 8
Age group	**n (%)**
18-29	21 (24.4)
30-39	37 (43.0)
40-49	28 (32.6)
Highest level of education	**n (%)**
Elementary School	0
Middle School	12 (14.0)
Secondary School	20 (23.3)
Bachelor	6 (7.0)
Master's Degree	37 (43.0)
Doctoral Degree	9 (10.5)
Civil Status	**n (%)**
Single	31 (36.0)
Married or Common-Law Marriage	49 (57.0)
Divorced	6 (7.0)
Widowed	0
Occupation	
Studying	9 (10.5)
Working	68 (79.1)
Inactive	9 (10.5)
Timepoint of first diagnostic	
Less than a year	33 (38.4)
Between 1 to 5 years	27 (31.4)
More than 5 years	26 (30.2)
Method of diagnosis	
Surgical diagnosis	23 (26.7)
Clinical diagnosis only	63 (73.3)
Endometriosis classification+	
Stage I	14 (16.3)
Stage II	11 (12.8)
Stage III	13 (15.1)
Stage IV	29 (33.7)
Not possible to classify	19 (22.1)
Symptoms experienced in the past 4 weeks	
Dysmenorrhea	62 (72.1)
Dysuria	15 (17.4)
Dyschezia	24 (27.9)

Dyspareunia	49 (57.0)
Chronic pelvic pain	57 (66.3)
Asthenia	25 (29.1)
Gastrointestinal alterations	20 (23.3)
Abnormal uterine bleeding	29 (33.7)
Previous treatment	
Surgical	23 (26.7)
Hormonal	36 (41.9)
Analgesic	12 (14.0)

In regard to clinical endometriosis characteristics, 73.3% of the women only had a confirmatory diagnosis based on the clinical framework and 33.7% (n=29) had stage IV endometriosis, according to the ASMR classification. Considering the symptoms experienced in the past four weeks (in relation to the time when baseline questionnaire was completed), most women reported dysmenorrhea (72.1%), chronic pelvic pain (66.3%) and dyspareunia (57.0%) (Table 1). Also, at baseline, most of the recruited women (66.3%) had been subject to a prior treatment. Hormonal therapy (41.9%, n=36) was the most used followed by surgery (26.7%, n=23).

The Effectiveness of Dienogest to Change Health Related Quality of Life

Scores for all EHP-30 core scales improved during the first 3 months of dienogest therapy and continued to improve until month 6 (Table 2). At baseline, the control and powerlessness dimension had the highest average score (64.0) and therefore was the one with the main negative impact on health-related quality of life. In turn, the self-image dimension had the lowest average score (54.6). At 6 months' follow-up, all the five dimensions seemed to weigh the same in the overall health related quality of life (Table 2).

Table 2: EHP-30 modular scores and changes from baseline

		EHP-30 Score							
		mean	std	median	Range		CI 95%		
					min	max	lower limit	upper limit	p-value
Pain	Baseline	60.2	18.4	61.8	20	89.1	51.6	62.9	<0.001
	3M	40.6	20.4	34.5	20	94.5	31.5	42.2	
	6M	33.4	17.7	23.6	20	78.2	28.3	38.8	
	Change from baseline at month 3	-19.1	25.0	-14.5	-74.5	23.6	-26.5	-14.2	
	Change from baseline at month 6	-22.6	23.4	-25.5	-60	25.5	-30.4	-17.0	
Control and powerlessness	Baseline	64.0	23.3	66.7	20.0	100.0	55.6	68.2	<0.001
	3M	43.2	20.7	36.7	20.0	100.0	33.4	46.4	
	6M	35.6	21.4	26.7	20.0	96.7	29.6	42.0	
	Change from baseline at month 3	-20.5	25.0	-18.4	-73.3	33.3	-28.9	-15.0	
	Change from baseline at month 6	-25.0	25.0	-26.7	-66.7	40.0	-33.2	-18.9	
Emotional well-being	Baseline	59.1	18.8	60.0	20.0	96.7	50.0	62.2	<0.001

	3M	43.5	22.0	43.3	20.0	93.3	35.9	48.5	
	6M	36.9	17.6	36.7	20.0	93.3	32.0	42.5	
	Change from baseline at month 3	-14.5	23.5	-13.3	-80.0	46.7	-20.4	-7.4	
	Change from baseline at month 6	-18.0	22.7	-20.0	-63.3	43.3	-25.5	-12.2	
Social Support	Baseline	56.8	21.4	60	15	95.0	48.5	60.9	<0.001
	3M	45.1	24.1	45.0	20.0	100.0	35.6	49.1	
	6M	37.7	21.1	30.0	20.0	100.0	31.7	44.3	
	Change from baseline at month 3	-12.0	26.2	-10.0	-70.0	55.0	-19.9	-4.6	
	Change from baseline at month 6	-15.9	26.0	-15.0	-70.0	50.0	-20.6	-4.7	
Self-image	Baseline	54.6	23.9	30.0	20.0	100.0	43.5	58.2	0.015
	3M	41.9	24.0	33.3	20.0	100.0	32.2	44.9	
	6M	38.7	20.0	33.3	20.0	100.0	32.3	44.2	
	Change from baseline at month 3	-12.3	23.1	-6.7	-66.7	53.3	-19.7	-5.0	
	Change from baseline at month 6	-11.1	28.5	-6.7	-60.0	60.0	-24.3	-9.0	

Treatment with dienogest for 6 months elicited a mean change of -25.0 ± 25.0 (mean ± SD) in control and powerlessness domain (95% CI: -33.2; -18.9), followed by pain (–22.6 ± 23.4 ;95% CI: -30.4;-17.0), emotional wellbeing (–18.0 ± 22.7 ;95% CI: -25.5;-12.2), social support (–15.9 ± 26.0 ;95% CI: -20.6;-4.7), and self- image (–11.1 ± 28.5 ;95% CI: -24.3;-9.0), (Table 2).

At 3- and 6-months follow-up, dienogest treatment had the greatest impact on control and powerlessness and pain domains (Table 3). Percentage of patients with improvement in EHP-30 scores was the highest for control and powerlessness scale (Figure 2).

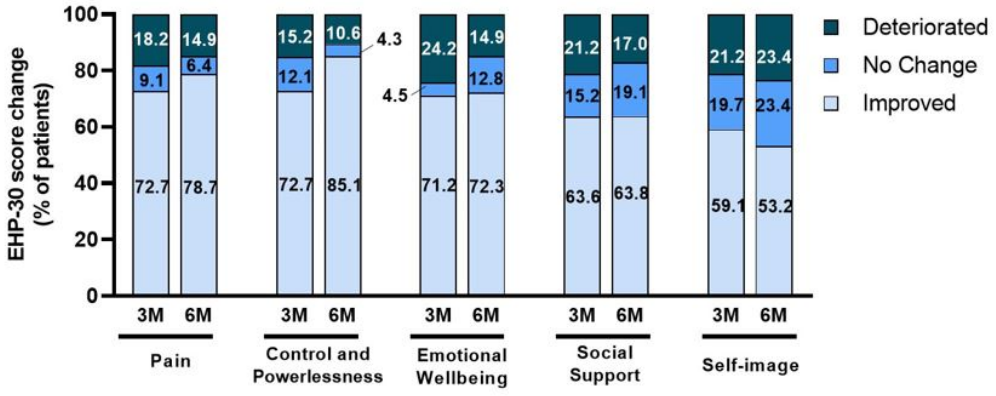

Figure 2: Changes in core EHP-30 scores from baseline to month 3 (3M) and to month 6 (6M) Results demonstrate proportions of patients with deterioration, no change and improvement defined as >0, 0 and < 0 difference in EHP-30 scores between baseline and questionnaires at month 3 and 6. Data were analyzed in 66 and 47 patients after 3- and 6-months follow-up, respectively. EHP-30, Endometriosis Health Profile-30 questionnaire

Table 3: Description of the improved, non-changed and deteriorated group at follow-up [n (%)]

	From baseline to 3 months			From baseline to 6 months		
	Improved	**Non-changed**	**Deteriorated**	**Improved**	**Non-changed**	**Deteriorated**
Pain	48 (72.7)	6 (9.1)	12 (18.2)	37 (78.7)	3 (6.4)	7 (14.9)
Control and powerlessness	48 (72.7)	8 (12.1)	10 (15.2)	40 (85.1)	2 (4.3)	5 (10.6)
Emotional well-being	47 (71.2)	3 (4.5)	16 (24.2))	34 (72.3)	6 (12.8)	7 (14.6)
Social Support	42 (63.9)	10 (15.2)	14 (21.2)	30 (63.8)	9 (19.1)	8 (17.0)
Self-image	39 (59.1)	13 (19.7)	14 (21.2)	25 (53.2)	11 (23.4)	11 (23.4)

In the control and powerlessness domain, the proportion of women with improvement of the EHP-30 score at 6 months was 85.1% (n=40) whereas 4.3% (n=2) reported no change and 10.6% (n=5) showed a deteriorated state. In the pain domain, 78.7% (n=37), 6.4% (n=3) and 14.9% (n=7) reported improvements, no changes and deterioration, respectively. The self-image domain was the dimension in which fewer women reported improvements (53.2%, n=25).

Additional sub-analyses detected no clear correlations between the rate of improvement in EHP-30 scores and clinical characteristics at baseline such as method of diagnosis, endometriosis stage or the presented symptomatology.

Discussion

Although both pharmacological as well as surgical treatment of endometriosis can improve the patients' quality of life, the available therapeutics target the symptomatology rather than the etiology of the disease.

Dienogest reduces endometriotic lesions and it is associated with relatively moderate inhibition of gonadotropin secretion, leading to a modest reduction in the endogenous production of estradiol. When given continuously, dienogest induces a hypoestrogenic, hypergestagenic local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions. Animal studies indicate that dienogest may also reduce plasma estradiol levels directly, through inducing apoptosis of granulosa cells in the ovary [19]. Moreover, the efficacy of dienogest 2 mg daily has been extensively studied in randomized clinical trials for endometriosis related symptoms, demonstrating that long-term use (about 2 and half years) effectively reduced endometriosis-associated pelvic pain and avoided pain recurrence post-surgery [12,19,23]. Nevertheless, real-world studies in different worldwide populations are lacking in order to provide evidence to consolidate the routine clinical practice.

From our study, the therapeutic with dienogest 2 mg once daily significantly improved health-related quality of life in the five studied domains in Portuguese women. Health-related quality of life was evaluated through the validated questionnaire EHP-30. It is noteworthy that, just after 3 months of dienogest therapy, 72.7% of the women reported improved EHP-30 scores in pain and control and powerlessness domain, 71.2% improvements in emotional well-being and 63.9% and 59.1% in social support and self-image domains, respectively. Following the same trend, 6 months of therapy with dienogest 2 mg daily improved the EHP-30 scores in 85.1%, 78.7%, 72.3%, 63.8% and 53.2% of the recruited women in control and powerlessness, pain, emotional well-being, social support and self-image domains, respectively.

The data obtained with this study is in line with previous observations. Over 36-months treatment with dienogest therapy, patients with rectosigmoid endometriosis reported continuous improvement in EHP-30 scores [24]. Similarly, in patients with persistent pain associated with endometriosis, 6-month treatment with dienogest increased health-related quality of life [25]. In similar clinical settings to this study but in Asian women, the ENVISIOeN study also demonstrated significant improvement in health-related quality of life measured by the EHP-30 at 6 and 24 months following dienogest therapy

[12]. Altogether, the available data seems to indicate that dienogest is able to improve health-related quality of life, in all of the associated domains, in a short-time period (3 to 6 months). of note, and besides dienogest did not provide the highest proportion of patients reporting improvement in the pain domain, maximum values for this category were the ones with greatest variation (baseline: 94.2 compared to 6 months follow up 78.2). This data supports the importance of dienogest in controlling endometriosis associated pain, in line with the existent randomized clinical trials results where dienogest therapy significantly reduces pain in endometriosis patients, namely debilitating chronic pelvic pain [19,26,27].

To the best of our knowledge, this is the first study evaluating the impact of dienogest therapy in Portuguese women with endometriosis. Still, this study has some limitations. Firstly, as the women were recruited by medical centers referral, the high intensity/severity of symptoms may be overrepresented. Of note, 33.7% of the participants had stage IV endometriosis. However, this is a common limitation transversal to the majority of clinical studies. Secondly, the participation rate was low while the dropout rate was high. Although a higher participation rate would increase the confidence intervals, it is unlikely that an increased number of participants would drastically change the results. Moreover, the difficulty in recruitment of a representative sample is a widely recognized challenge in endometriosis studies [28].

Conclusion

The results of this study suggest that dienogest 2 mg once daily improves health related quality of life just in the first three months of therapy with continuous improvements throughout time. Therefore, dienogest presents itself as a satisfying option for the long-term management of endometriosis among Portuguese women.

Acknowledgments

The authors would like to thank their colleagues for participating in this study. Data collection, statistical and editorial support were performed by an independent committee, with funding from Gedeon Richter Plc.

Conflict of Interest

The authors have no conflict of interest in relation to this article to disclose.

Patient Consent Statement

All patients signed a written informed consent form prior to their admission. The study was approved by the competent Ethics Committee and conducted in accordance with the Declaration of Helsinki

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