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GENERAL GYNECOLOGY

Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice

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Abstract

Purpose Endometriosis is a debilitating disease with high recurrence rates requiring long-term management. Progestins such as dienogest are used empirically when first symptoms occur and post-surgery to reduce recurrence. This retrospective, practice-based study assessed the efficacy and safety of dienogest in women with endometriosis treated for at least 60 months.

Methods 37 women (age 39 ± 8 years) with laparoscopically diagnosed endometriosis received dienogest 2 mg orally once daily. Endometriosis-associated pelvic pain (EAPP) was measured on a 0–100 mm visual analog scale at baseline and every 12 months. Laboratory measures of lipid and liver metabolism, hemostatic and hormonal parameters were investigated in a subgroup of 15 women. Adverse events including bleeding disturbances and depressive symptoms were recorded.

Results In 22 women, dienogest was begun after laparoscopy; median EAPP score was 70 mm pre-surgery and 10, 10, 20, 20, and 20 mm, respectively, after 12, 24, 36, 48, and 60 months of dienogest treatment. Another 15 women began dienogest without prior surgery; median EAPP score was 80 mm pretreatment and 20, 20, 30, 30, and 30 mm, respectively, after 12, 24, 36, 48, and 60 months. All laboratory parameters remained within the normal range. Mean serum estradiol was 28 ± 12 pg/ml after 60 months. Seven women experienced spotting episodes and four women presented with phases of depressed mood, which could all be clinically managed.

Conclusions Long-term (60-month) treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced EAPP and avoided pain recurrence post-surgery. Dienogest was well tolerated and adverse effects were clinically managed.

Keywords Dienogest · Endometriosis · Long-term management

Introduction

Endometriosis is a chronic, recurrent disease associated with debilitating pain and severely reduced quality of life in many affected women [1–3]. In the absence of a definitive cure, the main management options in endometriosis comprise surgery, hormone therapy, or a combination of these two approaches. Excision of endometrial lesions by laparotomy provides a rapid alleviation of symptoms, but lesion recurrence rates are high, estimated at 40–50% at 5 years [4]. For these women, hormone therapy postoperatively can reduce lesion recurrence and extend the pain-free period [5, 6]. Hormone therapy is also widely used as a first-line empirical therapy in symptomatic women and in those cases where surgery is considered impossible or is rejected by the patient [5, 7–10].

Commonly used hormone therapies include gonadotropin-releasing hormone agonists (GnRHas), estrogen/progestin combinations, and progestins. Each hormone therapy utilizes the characteristic estrogen-responsiveness of endometrial lesions to reduce lesion size and associated symptoms. GnRHas induce a profound hypoestrogenism that effectively reduces endometriotic lesions and symptoms, but may require concomitant "add-back" estrogen therapy to prevent the development of hypoestrogenic symptoms and bone loss in the long term [5]. Estrogen/progestin combinations, while widely used in practice to

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treat the symptoms of endometriosis, have demonstrated only inconsistent efficacy in clinical studies, while there is a concern that the estrogen component may actually promote the growth of endometriotic lesions [10].

Progestins represent an alternative option for inhibiting estrogen-induced lesion proliferation and reducing endometriosis-associated pain [5, 8, 11, 12]. A number of progestins approved for the treatment of endometriosis were introduced several years ago and there remains little study evidence to support their efficacy or safety at clinically relevant doses [12]. Among the oral progestins, dienogest is unique in being systematically investigated for the treatment of endometriosis in comprehensive preclinical and clinical study programs.

Dienogest in pharmacological studies demonstrates potent progestogenic efficacy, moderate estrogen-suppressive effects, and anti-inflammatory, antiproliferative, and antiangiogenic properties that effectively reduce the growth of endometrial-like tissue [13–18]. The clinical study programs performed in Europe and Asia showed that dienogest at a 2 mg daily dose provided pain relief in endometriosis significantly superior to placebo and equivalent to the GnRHas, with safety advantages over GnRHas related to its milder hypoestrogenic effects [19–23]. Further comparative studies have reported that dienogest provides greater efficacy than norethindrone acetate, another widely used oral progestin, with a lower risk of adverse events [24, 25].

Longer term clinical studies of up to 15 months' duration demonstrated that dienogest 2 mg provides continued effective lesion reduction and pain relief, associated with improvements in quality of life [26–28]. Sustained reductions in symptoms were also described for dienogest in 6–12-month, single-center cohort studies [29–32], while long-term cohort studies reported significant reductions in lesion recurrence and symptoms post-laparotomy for dienogest 2 mg compared with no medical treatment [33–35].

Dienogest 2 mg possesses a favorable safety profile, characterized by mild hypoestrogenic effects, minimal effect on bone mineral density in adult women, and low rates of treatment discontinuation [19, 21, 22, 26, 27]. A pooled analysis of four randomized European studies with treatment periods up to 65 weeks concluded that the adverse effects associated with dienogest 2 mg—most commonly headache, breast discomfort, depressed mood, and acne—were well tolerated in light of the symptom benefits, while laboratory and vital sign assessments provided no safety concerns [36].

Published assessments of the efficacy and safety of dienogest for treatment periods greater than 15 months are currently limited. This study describes the single-center experience of dienogest 2 mg in women with endometriosis over a treatment period of at least 60 months.

Materials and methods

The study was performed at the Obstetrics and Gynecology Department, Academic Hospital Weyertal, in Cologne, Germany. Women with laparoscopically diagnosed endometriosis were selected to receive dienogest (Visanne®) based on the need for a long-term treatment to manage severe and/or recurrent endometriosis [37], either to prevent lesion recurrence post-laparotomy or to provide a hormone therapy for women unsuitable or unwilling to undergo surgery. The majority of participants ($n = 30$) had received previous treatments with different combined oral contraceptives. All women provided written, informed consent to collect their study data during dienogest treatment.

Dienogest was prescribed as a single 2 mg tablet to be taken orally once daily at the same time each day. Women were instructed to cease dienogest treatment in case of pregnancy, any contraindication described in the product information [38], or the development of adverse events. In such cases, women were requested to inform their treating physician.

The efficacy of dienogest was assessed by measuring endometriosis-associated pelvic pain (EAPP) on a 100 mm visual analog scale (VAS; 0 mm, no pain; 100 mm, unbearable pain), as previously utilized in the European dienogest clinical study program. The VAS score was recorded at baseline (before surgery or the initiation of hormone treatment, whichever was earlier) and after 12, 24, 36, 48, and 60 months. The VAS recall period was for the previous 3 months. Patient satisfaction with treatment was elicited every year using a standard questionnaire at the author's endometriosis center.

Additional scheduled assessments performed annually included ultrasound assessment of the endometrium and the profile of adverse effects, including bleeding disturbances and depressive symptoms. A patient subgroup that required extensive surgery and/or recurrent laparoscopy was assessed for hormone, hemostasis, liver, and lipid parameters at 60 months.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No external ethical approval was required in the study, as the data were collected as part of the routine investigation of all patients during the long-term treatment of endometriosis performed at our center of excellence.

Results

Patients

Thirty-seven women of mean (SD) age 39 ± 8 years at study entry were treated with dienogest 2 mg for at

least 60 months. All women confirmed good compliance at the study visits. Of these, 22 women underwent surgery 1–8 weeks before starting dienogest (group 1) and 15 women received no surgery in the 12 months before initiating dienogest therapy (group 2). The indications for long-term dienogest use in the study population are summarized in Table 1. No women permanently discontinued dienogest during the study. There was no interruption of dienogest except for the treatment of bleeding in seven women for 5–7 days (reported below).

Assessment of endometriosis-associated pelvic pain

In the 22 women treated with surgery prior to dienogest (group 1), the baseline (pre-surgery) median VAS score for EAPP was 70 mm. During dienogest treatment, the median VAS score was 10 mm (range 0–30 mm [min–max]) at 12 and 24 months, and 20 mm (range 0–40) at 36, 48, and 60 months (Fig. 1). In the 15 women treated with dienogest with no prior surgery (group 2), the median baseline VAS score for EAPP was 80 mm. During dienogest treatment, the median VAS score was 20 mm at 12 and 24 months, and 30 mm at 36, 48, and 60 months (range 0–40 mm at all time points) (Fig. 1).

Patient satisfaction

Patient satisfaction with the pain relief provided during dienogest treatment was very high, with 21 women very satisfied and 16 additional women satisfied.

Laboratory parameters

In the subgroup of 15 women assessed by laboratory investigation, mean serum estradiol was 36 ± 13 pg/mL after 36 months and 28 ± 12 pg/mL after 60 months of dienogest treatment. Serum estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and progesterone levels after 60 months were all consistent with local laboratory reference values for the early follicular phase (Table 2).

Hemostasis, liver, and lipid parameters showed no relevant divergences from reference ranges (Tables 3, 4, and 5).

Adverse events

Four women presented with occasional self-reported phases of depressed mood. Two of these women received short-term estradiol gel combined with interruption of dienogest treatment, and two other women were switched to a combination of estradiol 1 mg and dienogest for 3 and 5 months, respectively. Estrogen treatment reduced the symptoms of

Table 1 Indications for long-term therapy (> 60 months) with dienogest 2 mg in 37 women with endometriosis

Indication for long-term dienogest therapy	Surgery before dienogest 2 mg treatment ($n = 22$) Group 1	No surgery in the 12 months before start of dienogest 2 mg treatment ($n = 15$) Group 2
Post-surgery for rectovaginal endometriosis with bowel resection	8	0
Post-surgery for bladder endometriosis with partial resection	5	0
Endometriosis of diaphragm (surgery partial or rejected)	0	2
Bowel and bladder endometriosis (surgery rejected)	0	5
Recurrent endometriosis (≥ 2 laparoscopies)	9	8

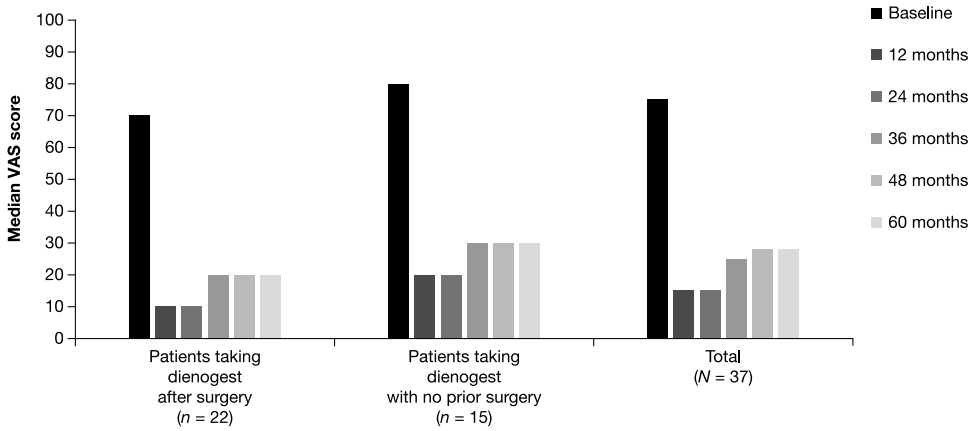

Fig. 1 Endometriosis-associated pain assessed by median VAS score (mm) in women at baseline and after 12, 24, 36, 48, and 60 months of dienogest 2 mg treatment. Baseline was before surgery or initiation of medical treatment

Table 2 Hormone serum parameters after 36 and 60 months of dienogest 2 mg treatment

Parameter	Mean (SD) serum concentration		Reference range (early follicular phase)
	36 months	60 months	
Estradiol	36 ± 13 pg/mL	28 ± 12 pg/mL	20–144 pg/mL
Luteinizing hormone	4.1 ± 3.9 mIU/mL	2.0 ± 1.5 mIU/mL	1.1–18.8 mIU/mL
Follicle-stimulating hormone	10 ± 3.9 mIU/mL	10 ± 4.5 mIU/mL	2.5–10.2 mIU/mL
Progesterone	29 ± 10 ng/dL	26 ± 15 ng/dL	20–81 ng/dL

Table 3 Hemostasis parameters after 36 and 60 months of dienogest 2 mg treatment

Parameter	Mean (SD) value		Reference range
	36 months	60 months	
Platelets	193 ± 49/nL	164 ± 24/nL	140–400/nL
Partial thromboplastin time	26 ± 7 s	24 ± 6 s	22–32 s
Thrombin time	16 ± 3 s	14 ± 5 s	14–22 s
Protein C	102 ± 13%	100 ± 14%	70–140%
Protein S	106 ± 8.7%	105 ± 20%	55–124%
Antithrombin III	102 ± 16%	113 ± 18%	79–110%
Activated protein C resistance	3.4 ± 0.8	3.1 ± 0.8	> 2.3 ratio
Homocysteine	9.9 ± 2.5 µmol/L	11 ± 4.0 µmol/L	< 12.5 µmol/L

Table 4 Lipid metabolism parameters after 36 and 60 months of dienogest 2 mg treatment

Parameter	Mean (SD) value		Reference range
	36 months	60 months	
Lipoprotein(a)	12.5 ± 5.3 mg/dL	15.1 ± 6.2 mg/dL	< 30 mg/dL
Cholesterol	174 ± 18 mg/dL	180 ± 28 mg/dL	< 200 mg/dL
HDL-cholesterol	45 ± 10 mg/dL	55 ± 13 mg/dL	> 40 mg/dL
LDL-cholesterol	114 ± 24 mg/dL	116 ± 27 mg/dL	< 160 mg/dL
LDL/HDL ratio	3.0 ± 0.8	2.5 ± 0.8	< 4.0
Triglyceride	133 ± 17 mg/dL	140 ± 25 mg/dL	< 150 mg/dL

LDL low-density lipoprotein, *HDL* high-density lipoprotein

depressed mood, and dienogest was reintroduced in the two women who interrupted therapy. None of these women required a psychiatric consultation.

Seven women had an onset of spotting episodes after 18–60 months of treatment. There were no more than two bleeding episodes per year in any women. Endometrial thickness was less than 5 mm in all cases. On interruption of dienogest for 5–7 days, spotting ceased in six of the seven women, after which dienogest treatment was restarted. One woman with adenomyosis uteri in addition to endometriosis complained of recurrent non-cyclic bleeding episodes. She rejected further surgery and, due to the satisfactory pain reduction with dienogest, tolerated the adverse effect without additional treatment measures.

Four women reported headache at the initiation of dienogest treatment, which was of short duration and required no treatment. There were no reports of other adverse events. No cases of pregnancy occurred during the study.

Table 5 Liver parameters after 36 and 60 months of dienogest 2 mg treatment

Parameter	Mean (SD) value		Reference range U/L
	36 months U/L	60 months U/L	
GPT (ALT)	22 ± 7.4	14 ± 8	< 35
GOT (AST)	26 ± 6.5	18 ± 10	< 35
Gamma-glutamyl transpeptidase	29 ± 7.7	27 ± 12	< 40
Alkaline phosphatase	71 ± 16	68 ± 24	< 105

GPT (ALT) glutamic-pyruvic transaminase (alanine aminotransferase), *GOT (AST)* glutamate–oxaloacetate transaminase (aspartate aminotransferase)

Discussion

This study describes the single-center experience of dienogest 2 mg once daily in 37 women with endometriosis over a treatment period of at least 60 months. To the author's knowledge, this is the longest duration of dienogest treatment in endometriosis reported to date, which complements and extends on the 52-week data from the ViBriC extension study [39]. Two patient groups are described—women who received prior excisional surgery and those who rejected or were unsuitable for surgery—reflecting common management approaches in practice.

The efficacy of dienogest treatment was assessed by the VAS score system for EAPP that was utilized in the European study program. In women treated with prior laparotomy, dienogest maintained the low EAPP achieved by surgery, while, for women treated with dienogest alone, there was a continued reduction in EAPP versus baseline. The extent of the reduction in EAPP achieved in both groups represents clinically significant improvement [40]. There was limited evidence of a slight increase in VAS score in both groups over time, which will require further investigation in women treated for more than 60 months. Consistent with the sustained improvement in painful symptoms, patient satisfaction with dienogest treatment was very high, related particularly to the opportunity to avoid further surgery.

Adverse events associated with dienogest occurred at low rates. Dienogest, similar to other progestins, is associated with bleeding disturbances in some women at the initiation of treatment. The European study experience was that the number of bleeding/spotting days, the number of bleeding/spotting episodes, and the duration of bleeding/spotting episodes all decreased progressively during continued dienogest treatment [23]. In the current trial, seven women experienced spotting episodes, which were managed successfully by a short interruption in dienogest in each case, with the exception of one woman with both adenomyosis uteri and endometriosis.

The potential role of progestins in influencing mood disturbances and, in particular, exacerbating depressive symptoms represents an existing concern [36, 38, 41]. It is well known that women who suffer from endometriosis are at high risk of developing depressive symptoms. For example, one study reported depressive symptoms in 87% of women with a surgical diagnosis of endometriosis, including 33% who met the criteria for a severe depressive disorder [42]. The degree of chronic pelvic pain associated with endometriosis correlates with depressive symptoms, as shown in a study describing depression in 86% of women with chronic pelvic pain compared to only 38% of women without pelvic pain [43]. The complexities and potential interaction between depression, endometriosis, and progestins make it difficult to identify a causal relationship between depression and progestin use or the disease process [44, 45]. In this study, four women reported depressed moods, which were managed successfully by short-term estradiol or by combining estradiol with dienogest.

The bleeding episodes and the phases of depressed mood were considered by women to be outweighed by the beneficial reductions in pain and they all continued long-term dienogest treatment.

Mean estradiol values were moderately suppressed but remained within the normal reference range and within the therapeutic window for treatment of endometriosis (i.e., 20–50 pg/mL) [46]. These observations are consistent with the results of long-term dienogest treatment in the ViBriC extension study and are in contrast to the profound hypoestrogenism induced by GnRHas in the absence of add-back estrogen therapy ([39, 46, 47]. Other hormone serum parameters, as well as parameters of lipid and liver metabolism and hemostasis, also remained within the normal range during long-term dienogest treatment.

In conclusion, this single-center study in women with endometriosis provides additional information on the efficacy and safety of continued long-term dienogest treatment under conditions of daily practice. Women in the study were willing to tolerate the moderate adverse effects in light of the substantial pain relief provided by dienogest. It is recommended that women receiving long-term dienogest should be checked at least yearly—as in this study—to exclude the development of individual risk factors and to permit the early diagnosis and treatment of potential adverse effects.

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Author contributions TR participated in the project development, data collection and management, data analysis, and manuscript editing.

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Compliance with ethical standards

Conflict of interest Prof. Römer has received honoraria for lectures and advisory boards from: Bayer, MSD, Gedeon Richter, Dr. KADE, and Aristo Pharma.

Informed consent Informed consent was obtained from all individual participants included in the study.

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