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Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial

Lina El Taha [a,b,1], Antoine Abu Musa [a,b,*,1], Dalia Khalifeh [a,b], Ali Khalil [a,c], Sehrish Abbasi [a], Joseph Nassif [a,d,e]

[a] Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut, Lebanon
[b] Division of Reproductive Endocrinology and Infertility, American University of Beirut Medical Center, Beirut, Lebanon
[c] Division of Gynecologic Oncology, American University of Beirut Medical Center, Beirut, Lebanon
[d] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA
[e] Division of Minimally Invasive Gynecologic Surgery, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA

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ABSTRACT

Objective: To compare the efficacy of dienogest with the combined oral contraceptive pill (COC) Yasmin for the control of endometriosis-associated pelvic pain.

Study design: Seventy women with endometriosis-associated chronic pelvic pain, dysmenorrhoea or both for >6 months were randomized to either dienogest (Visanne) 2 mg/day or monophasic COC (Yasmin, 0.03 mg ethinyl estradiol and 3 mg drospirenone) for 24 weeks. The primary efficacy variable was change in non-cyclic pelvic pain and dysmenorrhoea from baseline to end of treatment, assessed using a visual analogue scale (VAS). The secondary efficacy variable was change in the Biberoglu and Behrman (B&B) scale scores for chronic pelvic pain, dysmenorrhoea and dyspareunia. Health-related quality of life (HRQoL) was evaluated using the Endometriosis Health Profile-30 (EHP-30) questionnaire at baseline and 24 weeks. Safety variables included incidence of side-effects, bleeding pattern and treatment tolerability.

Results: Both treatments improved the mean VAS score for endometriosis-associated pelvic pain significantly: mean difference 6.0 [95% confidence interval (CI) 4.9–7.1; $p < 0.0001$] in the dienogest group and 4.54 (95% CI 3.1–5.9; $p < 0.0001$) in the COC group; the difference between them was not significant ($p = 0.111$). Similarly, both dienogest and COC improved HRQoL in various core and modular segments of the EHP-30 questionnaire with comparable requirements for supplemental pain medication ($p = 0.782$ and 0.258 at 12 and 24 weeks, respectively), and redistribution of the B&B severity profile for chronic pelvic pain ($p = 0.052$ and 0.526 at 12 and 24 weeks, respectively), dysmenorrhoea ($p = 0.521$ and 1 at 12 and 24 weeks, respectively) and dyspareunia ($p = 0.376$ and 0.835, respectively). Nevertheless, dienogest was associated with fewer side-effects, and hence had a better safety and tolerability profile than COC.

Conclusions: Dienogest (2 mg/day) is comparable to the COC Yasmin for the relief of endometriosis-associated pelvic pain and improvement in HRQoL.

Clinical Trial Registration: Clinicaltrials.gov under number NCT04256200; date of registration 15/1/2020 (registered retrospectively).

Introduction

Endometriosis is a chronic inflammatory disorder characterized by the presence of endometrial tissue outside the uterus. It affects approximately 6–10% of women of reproductive age, with an estimated 176 million women affected worldwide [1–4]. Despite an enigmatic pathogenesis [4–6], endometriosis is notorious for its painful presentation. It is often associated with symptoms such as dysmenorrhoea, dyspareunia and chronic pelvic pain [7–9]. As endometriosis is a chronic and recurrent disease with an adverse effect on patients' physical and psychological well-being, it requires constant symptom control [10,11]. Current medical therapies aim to alleviate the severity of symptoms and prevent/prolong the time to recurrence in order to improve the quality of life

* Corresponding author at: Department of Obstetrics and Gynecology, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh, Beirut 1107 2020, Lebanon.
E-mail address: aa06@aub.edu.lb (A. Abu Musa).
[1] Joint first authors.

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of women with endometriosis. These include gonadotropin-releasing hormone (GnRH) agonists, danazol, progestins and combined oral contraceptive pills (COCs) [12]. The major drawback with some of these remedies is their suboptimal safety and tolerability. GnRH agonist treatment, for instance, although effective, is associated with hypoestrogenic symptoms (hot flushes, decreased bone density, vaginal dryness, headache and decreased libido); and danazol causes adverse changes in lipid profiles, androgenic side-effects, weight gain, acne, hirsutism and oily skin [13].

Many recent guidelines have recommended the use of either COCs or progestins as a first-line medical treatment for pain associated with surgically confirmed endometriosis, or empirically for clinically suspected endometriosis [13–16]. COCs are considered effective, safe, well tolerated, inexpensive and suitable for delaying recurrence after surgical treatment [17,18]. COCs are the most widely used agents for the medical treatment of endometriosis, with evidence supporting their efficacy in pain control and in reducing the risk of endometriosis recurrence following surgical management [18–21]. COCs act via ovulation suppression, and the consequent reduction of hormonal stimulation by hypothalamic and pituitary hormones on eutopic and particularly ectopic endometrium [20].

Recently, the efficacy of dienogest (Visanne) in the management of endometriosis has been demonstrated. Dienogest is a synthetic progestin, 19-nortestosterone derivative, with good oral bioavailability and high selectivity for progesterone receptors. It has anti-ovulatory, antiproliferative and inhibitory effects [20]. Several studies have shown a significant improvement in pain symptoms following 24 weeks of treatment with dienogest [22–26]. Unlike other progestins, dienogest does not have androgenic properties, glucocorticoid activity or mineralocorticoid activity [20]. Dienogest has been shown to inhibit nerve growth factor expression induced by tumour necrosis factor alpha or interleukin beta, a key mediator in generating pain associated with endometriosis [27]. The inhibitory action of dienogest exhibits a progestogenic response on endometrial stromal cells *in vitro* such as decidualization, increased prolactin production and growth retardation [28]. Several studies have compared dienogest with GnRH analogues or placebo, yet, as far as is known, no studies to date have compared dienogest with COC treatment.

This study aimed to compare the efficacy and safety profile of dienogest with a commonly used low-dose COC (Yasmin) for the control of endometriosis-associated pelvic pain.

Materials and methods

Study design

A randomized, double-blinded, parallel clinical trial was conducted at the Department of Obstetrics and Gynecology at the American University of Beirut Medical Center (AUBMC) between February 2017 and October 2020.

Women referred to, or who presented to, the Women's Health Center at AUBMC with a histologically confirmed diagnosis of stage I–IV endometriosis {based on the Revised American Society of Reproductive Medicine Classification of Endometriosis (r-ASRM stage) [29]} based on laparotomy or laparoscopic surgery, or with a diagnosis of deep endometriosis and/or ovarian endometrioma based on ultrasonography and/or magnetic resonance imaging [14,30,31] plus complaints of dysmenorrhoea, non-cyclic chronic pelvic pain or both for >6 months [32] were approached to participate in the study. The finding of ovarian endometrioma on imaging, if applicable, was distinguished from haemorrhagic cysts through serial ultrasonographic examinations at different times in the menstrual cycle. The eligibility of participants was verified based on the inclusion/exclusion criteria summarized in Table 1.

Treatment randomization

Eligible women were randomized in a 1:1 ratio according to a computer-generated permuted block of six randomization sequences to receive either dienogest 2 mg/day [35] or a COC (Yasmin, 0.03 mg ethinyl estradiol and 3 mg drospirenone) continuously for 24 weeks. Pills were placed in numbered white opaque containers that were indistinguishable in appearance. The information regarding assigned treatment was sealed in opaque envelopes, identified only by number, opened by the study coordinator after the participant had signed the informed consent form. The corresponding numbered container was then dispensed, containing treatment pills for the 24-week treatment period. Patients were instructed to use barrier contraception during the treatment period if they were sexually active.

Patient monitoring

Treatment was started on the second to fifth day of the first menstrual cycle after the baseline visit. Participants were followed-up 12 and 24 weeks after treatment initiation for assessment of outcome variables and to monitor compliance (tablet count).

The primary efficacy variable was absolute change in endometriosis-associated pelvic pain from baseline to the end of treatment. This was assessed using a visual analogue scale (VAS), a standardized, well-established tool for the measurement of pelvic pain [32,36,37]. Participants kept a pain score diary of their endometriosis-associated pelvic pain at baseline and on a monthly basis until the end of treatment. Scores were averaged for their 12-week and 24-week VAS score. The use of analgesics was permitted in the form of self-administered ibuprofen tablets (up to 1200 mg/-day), which participants recorded in their diaries.

The secondary efficacy variable was change in the Biberoglu and Behrman (B&B) scale score [38] for pain symptoms – chronic pelvic pain, dysmenorrhoea and dyspareunia – self-reported as absent, mild, moderate or severe during follow-up visits. Dysmenorrhoea encompassed pain or discomfort experienced during irregular uterine bleeding episodes, because many women do not experience regular menstrual bleeding while on continuous COC or progestin treatment [17,39].

Health-related quality of life (HRQoL) was assessed at baseline and following treatment using the validated Endometriosis Health Profile-30 (EHP-30) questionnaire designed to gauge areas of particular concern to patients with endometriosis [40–42]. EHP-30 is composed of two sections: a core instrument applicable to all patients with endometriosis containing five scales for a total of 30 items covering pain, lack of control and powerlessness, emotional well-being, social support and self-image; and a modular instrument of six separate modules, with a total of 23 questions applying to a subset of women with endometriosis, related to impact of endometriosis on work, relationship with children, sexual relationship, feelings about medical profession, treatment and infertility. The score for each scale was calculated by rating items within the scale from 0 (best health status) to 100 (worst health status).

The safety and tolerability of the administered treatment (one of the secondary endpoint variables) was assessed during follow up visits by the incidence of side-effects commonly associated with use of hormonal therapy in patients with endometriosis, reported using the Medical Dictionary for Regulatory Activities terminology.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Histologically confirmed endometriosis or diagnosis of deep endometriosis and/or ovarian endometrioma via imaging studies	Undiagnosed genital bleeding and/or abnormal findings on gynaecological examination other than endometriosis
Complaints of dysmenorrhoea, non-cyclic chronic pelvic pain or both for >6 months	Use of hormonal therapy for endometriosis within 16 weeks before enrolment
20–45 years old	Pregnancy, lactation, desire to conceive during treatment period
Regular menstrual cycles	Previously failed treatment of endometriosis using medications included in the study
Endometriosis-associated pelvic pain scoring $\geq$ 4 on VAS[a] at baseline	History of severe drug reaction or hypersensitivity to steroid hormones
Presence of one or more subjective symptoms during menstruation (lower abdominal pain, lumbago, defaecation pain, nausea and headache)	Contraindications to COC or dienogest use as recognized by the World Health Organization and Centers for Disease Control and Prevention [33,34][b]
Presence of one or more subjective symptoms outside menstruation (abdominal pain, lumbago, defaecation pain, dyspareunia if sexually active, and pain on internal examination)	Prior surgical treatment or examination for endometriosis within a menstrual cycle before the start of medication

COC, combined oral contraceptive.
[a] VAS, visual analogue scale where 0 cm indicates absence of pain and 10 cm indicates unbearable pain.
[b] History or complication of thrombosis/embolism, migraines with aura, depression, diabetes mellitus with vascular involvement, serious liver diseases, or known/suspected sex-hormone-dependent malignancies.

Statistical analysis

The sample size for this study was calculated by hypothesizing non-inferiority of continuous dienogest treatment to COC treatment for the control of endometriosis-associated pain assessed by VAS. A non-inferiority margin of 1.5 cm with a standard deviation of 2 cm was prespecified based on available data for the difference in VAS score for other conditions associated with chronic pain [43], and on the 1-cm non-inferiority margin recommended by Gerlinger et al. in endometriosis-associated pelvic pain studies, while acknowledging the need for more studies [44]. Accordingly, a minimum of 34 women was required per study arm to achieve non-inferiority at a significance level of 0.05 and power of 80%, accounting for a 20% dropout rate. Modified intention-to-treat analysis was performed for efficacy endpoints, including all randomized women with assessment of at least one efficacy variable. Imputation for missing data, when relevant, was performed by using data obtained from the last follow-up encounter. Participants who received at least one dose of the assigned treatment were included in the safety variable analysis. Data management and statistical analysis were performed using SPSS Version 26 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test for normality of continuous variables was applied, including change in VAS and EHP-30 scores between treatment groups. Student's *t*-test was used for continuous variables with a normal distribution expressed as mean, standard deviation and 95% confidence interval (CI). Paired *t*-test compared the change in VAS scores within each treatment group. Chi-squared test and Fisher's exact test were used to analyse nominal variables, including B&B scale scores and safety variables. HRQoL was evaluated using Wilcoxon paired signed rank test to compare the EHP-30 questionnaire scores at the end of treatment from baseline, and Mann–Whitney *U* test to compare change in scores throughout treatment between the two groups.

Results

Of the 115 women screened, 70 women who met the inclusion criteria were randomized to receive either dienogest (n = 35) or COC (n = 35) after agreeing to participate. Fig. 1 shows a flowchart of participants' admission and adherence to allocated treatment. Seventy-one percent of women in the dienogest group and 74% of women in the COC group completed the 24-week study period. Only one woman in the COC group stopped taking the blinded treatment pills and switched to dienogest; however, this was analysed as allocated in accordance with the modified intention-to-treat analysis. Treatment groups had comparable baseline characteristics, prior use of hormonal treatment, disease severity according to the r-ASRM endometriosis classification, and VAS scoring of endometriosis-associated non-cyclic pelvic pain (Table 2).

The VAS score for endometriosis-associated non-cyclic pelvic pain improved significantly for both the dienogest and COC groups over the 24-week study period. The VAS score decreased from 8.40 ± 1.3 to 2.44 ± 2.1 by week 24 among women in the dienogest group (mean difference 6.0, 95% CI 4.9–7.1; $p < 0.0001$). Similarly, the VAS score decreased from 7.92 ± 1.5 to 3.38 ± 3.1 among women in the COC group (mean difference 4.54, 95% CI 3.1–5.9; $p < 0.0001$). This improvement was more pronounced within the first 12 weeks of treatment (−5.5 vs −0.5 for dienogest; −4.0 vs −0.5 for COC; $p < 0.0001$ for both groups) (Fig. 2). Despite marked improvement in VAS score within each treatment group, the difference between the two treatment groups was not significant (mean change 1.42, 95% CI −0.33 to 3.18; $p = 0.111$). This is also reflected in the comparable proportion of women requiring pain medication at 12 ($p = 0.782$) and 24 weeks ($p = 0.258$) of treatment.

The B&B sign and symptom intensity scores for dysmenorrhea, dyspareunia and pelvic pain for each treatment group at baseline, and 12 and 24 weeks after treatment are summarized in Fig. 3. The B&B scale severity profiles were comparable for dienogest and COC at baseline. A shift towards lower severity categories, from 'severe' and 'moderate' towards 'none' and 'mild', was noted for both treatment groups at 12 and 24 weeks. The redistribution in severity proportions and reduction in severity were similar for dienogest and COC for dysmenorrhoea ($p = 0.521$ and 1 at 12 and 24 weeks, respectively), dyspareunia ($p = 0.376$ and 0.835, respectively) and chronic pelvic pain ($p = 0.052$ and 0.526, respectively). A tendency towards greater reduction in the severity of chronic pelvic pain (Fig. 3c) was noted for both treatment groups, compared with improvement in dysmenorrhoea (Fig. 3a) and dyspareunia (Fig. 3b). At the end of treatment, the proportions of women reporting 'none' or 'mild' severity in the dienogest and COC groups were 80% vs 73.1% for dysmenorrhoea, 75% vs 58.3% for dyspareunia, and 80% vs 88.5% for pelvic pain. Within each treatment group seperately there was significant improvement in HRQoL as assessed by EHP-30 at 24 weeks from baseline. However, when comparing this improvement or change in EHP-30 scores (at 24 weeks from baseline) between the two treatments, it was not significant.The p-values are detailed in (Table 3).

Both treatments were generally well tolerated with no unexpected or grave adverse effects. The incidence of withdrawal from either treatment group was comparable (Fig. 1), with one participant excluded from the dienogest group after 1 week of treatment due to the diagnosis of major depression disorder and one patient excluded from the COC group following a positive pregnancy test. Although 90% of enrolled participants reported one or more side-effects to treatment, the majority of reported adverse events in both groups were self-rated as tolerable with mild or moderate intensity. Most commonly encountered adverse effects were abnormal uterine bleeding, mood swings, headache, nausea and breast pain/tenderness; all of these adverse events were signifi-

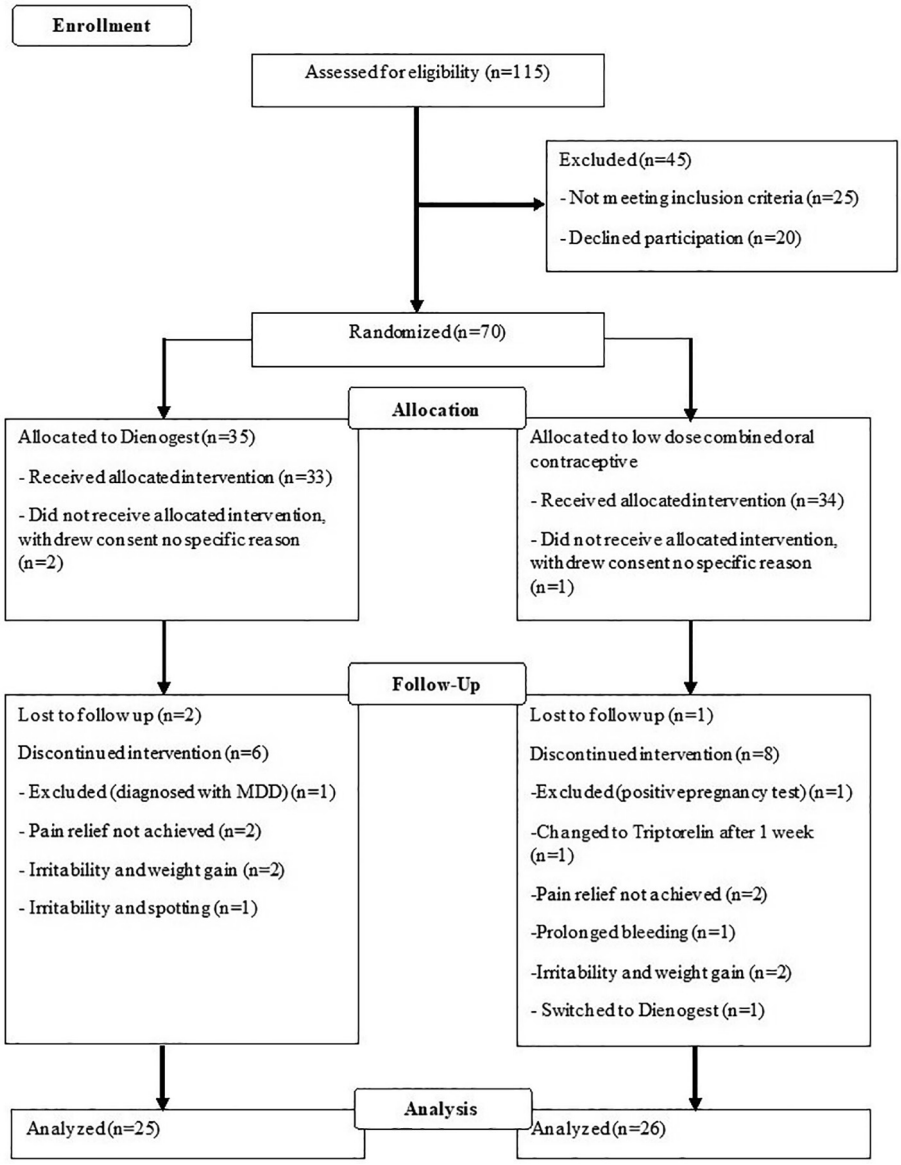

Fig. 1. Study flow chart. MDD, major depression disorder.

Table 2
Baseline characteristics of participants.

Characteristic	Treatment group		
	Dienogest (n = 35)	COC (n = 35)	p-value
Age (years, mean ± SD)	28.3 ± 6.5	29.8 ± 6.5	0.343
Height (cm, mean ± SD)	161.1 ± 5.6	162.9 ± 6.7	0.251
Weight (kg, mean ± SD)	63.2 ± 12.2	61.2 ± 12.0	0.476
BMI (kg/m^2, mean ± SD)	24.3 ± 4.4	23.0 ± 3.9	0.200
Age at diagnosis (years, mean ± SD)	26.5 ± 6.1	27.7 ± 6.9	0.422
VAS score (cm, mean ± SD)	8.3 ± 1.4	7. 8 ± 1.5	0.152
Parous	11 (31.4)	5 (14.3)	0.088
Previous hormonal treatment	15 (42.9)	10 (28.6)	0.212
r-ASRM stage			0.715
Stage I	1 (2.9)	2 (5.7)	
Stage II	12 (34.3)	9 (25.7)	
Stage III	11 (31.4)	8 (22.9)	
Stage IV	5 (14.3)	8 (22.9)	
Deep endometriosis diagnosed via US and/or MRI	6 (17.1)	8 (22.9)	

COC, combined oral contraceptive; SD, standard deviation; BMI, body mass index; VAS, visual analogue scale; r-ASRM, Revised American Society of Reproductive Medicine endometriosis classification stage; MRI, magnetic resonance imaging; US, ultrasonography.
Values reported as frequency (%) unless otherwise indicated.

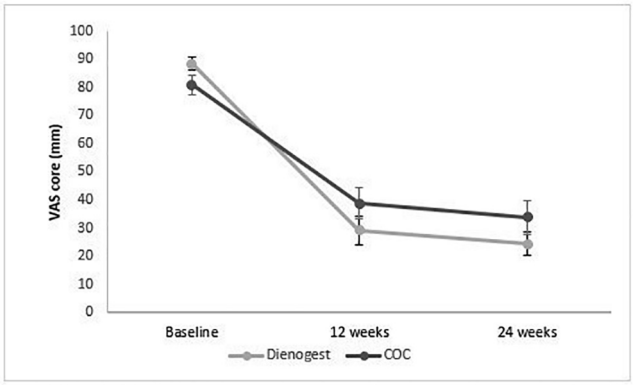

Fig. 2. Mean (±standard error of the mean) of visual analogue scale (VAS) scores at baseline, and after 12 and 24 weeks of treatment with continuous dienogest 2 mg or combined oral contraceptive (COC) (Yasmin; 0.03 mg ethinyl estradiol and 3 mg drospirenone).

cantly more common in the COC group than the dienogest group (Table 4), and were mainly experienced during the first 12 weeks of treatment (77%). Analysis of bleeding patterns according to the World Health Organization 90-day reference period [45] showed that the most common bleeding patterns in the dienogest group were irregular bleeding (34%) and prolonged bleeding (21%) during the first 12 weeks of treatment, and infrequent bleeding/spotting (43%) and amenorrhoea (19%) at 24 weeks. In the COC group, the most common bleeding patterns were prolonged bleeding (40%) and irregular bleeding (34%) during the first 12 weeks of treatment, and infrequent bleeding (30%) and amenorrhoea (14%) at 24 weeks.

Discussion

In this 24-week study, dienogest was found to be as effective as continuous COC treatment in relieving endometriosis-associated non-cyclic pelvic pain, dysmenorrhoea and dyspareunia. This is clinically important given that pain is one of the hallmark debilitating symptoms of endometriosis [9].

The outcomes support findings of previous studies investigating the efficacy of dienogest and COCs in improvement of endometriosis-associated pelvic pain.

A placebo-controlled randomized controlled trial found a significant reduction in endometriosis-associated pelvic pain assessed using a VAS, and in pelvic pain, dysmenorrhoea and dyspareunia assessed using the B&B severity profile following 12 weeks of dienogest 2 mg daily [24]. Although the VAS reduction observed in the present study at 12 weeks is almost double that reported by Strowitzki et al., this is not surprising considering the influence of various ethnic backgrounds on the perceived severity of pain, which is a highly subjective symptom. Similarly, other studies comparing dienogest with GnRH agonists have demonstrated a significant improvement in pain following 24 weeks of treatment [22,25]. The beneficial role of COCs in the management of endometriosis-associated pain has long been established [17,21,46]. The use of continuous low-dose COCs has been demonstrated to outweigh cyclic COC treatment in significantly reducing endometriosis-

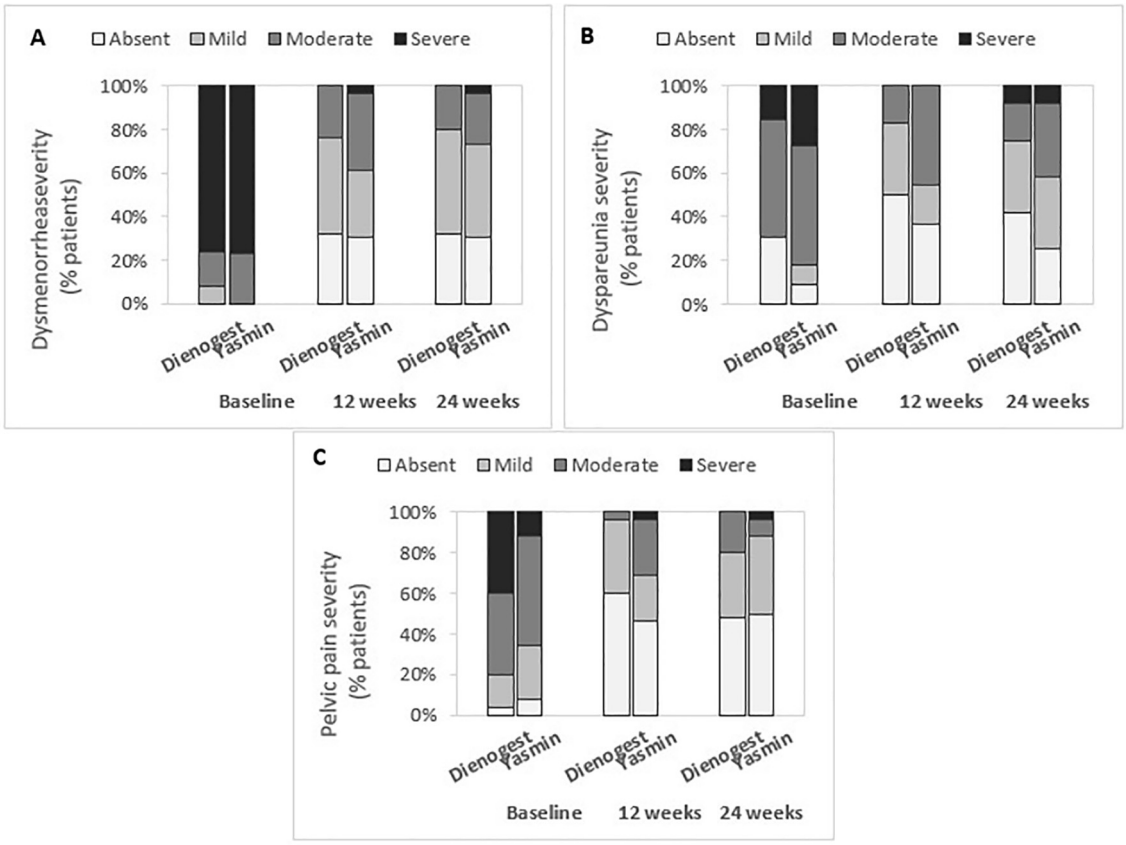

Fig. 3. Biberoglu and Behrman (B&B) severity profile at baseline, after 12 weeks and after 24 weeks of dienogest or combined oral contraceptive (Yasmin) treatment for (A) dysmenorrhea, (B) dyspareunia and (C) pelvic pain.

Table 3
Endometriosis Health Profile-30 questionnaire results at baseline and 24 weeks post treatment.

	Dienogest			COC			Between treatments
Parameter	Baseline	24 weeks	*p*-value	Baseline	24 weeks	*p*-value	*p*-value
Core questionnaire							
Pain	69.7 ± 22.8	19.6 ± 18.0	<0.001	61.6 ± 22.5	29.0 ± 30.0	<0.001	0.078
Lack of control and powerlessness	69.0 ± 27.7	18.5 ± 19.8	<0.001	74.0 ± 29.7	36.2 ± 31.4	<0.001	0.187
Emotional well-being	55.7 ± 27.2	32.1 ± 30.6	0.006	66.3 ± 31.4	52.2 ± 35.1	0.068	0.174
Social support	48.5 ± 31.8	22.7 ± 26.1	0.004	65.6 ± 29.9	48.8 ± 36.2	0.015	0.400
Self-image	40.7 ± 31.0	17.9 ± 18.1	0.003	53.2 ± 31.4	31.7 ± 31.3	0.001	0.947
Modular questionnaire							
Effect of endometriosis on:							
Work	55.4 ± 31.0	15.9 ± 20.0	0.001	61.3 ± 34.9	35.0 ± 33.5	0.009	0.249
Sexual relationship	40.0 ± 31.1	15.5 ± 25.6	0.004	55.5 ± 32.0	39.5 ± 33.7	0.385	0.237
Relationship with child/children	44.6 ± 32.2	17.9 ± 23.8	0.063	65.6 ± 34.4	25.0 ± 28.9	0.125	0.282
Feelings about:							
Medical profession	38.4 ± 35.5	7.0 ± 11.4	<0.001	34.1 ± 37.2	11.1 ± 15.7	0.004	0.315
Treatment	53.0 ± 29.4	22.6 ± 24.8	0.007	59.8 ± 29.3	34.3 ± 25.5	0.004	0.348
Possibility of infertility	50.0 ± 35.4	35.0 ± 31.9	0.297	58.2 ± 30.5	66.1 ± 30.7	0.413	0.217

COC, combined oral contraceptive.

Table 4
Proportion of women with adverse effects that were possibly treatment related in the dienogest and combined oral contraceptive (COC) groups.

	Dienogest (n = 31)	COC (n = 32)	*p*-value
Headache	10 (32.3)	19 (59.4)	0.044
Breast pain/tenderness	6 (19.4)	15 (46.9)	0.021
Sleep disorder	3 (9.7)	9 (28.1)	0.062
Decreased libido	1 (3.2)	3 (9.4)	0.613
Fatigue	3 (9.7)	9 (28.1)	0.062
Nausea/vomiting	5 (16.1)	17 (53.1)	0.002
Mood swings	14 (45.2)	24 (75%)	0.016
Abdominal discomfort/bloating	5 (16.1)	12 (37.5)	0.056
Weight gain	3 (9.7)	11 (34.4)	0.018
Abnormal uterine bleeding	21 (67.7)	29 (90.6)	0.032

associated dysmenorrhoea at both 12- and 24-week follow-up [18].

The physical and psychological dimensions of endometriosis involve an inherent reduction in HRQoL. Pain and infertility are among the symptoms adding to the burden of the disease, adversely impacting economic and personal productivity [47]. Pain cognition and severity have been recognized as contributors to derangement of the HRQoL of patients with endometriosis [48–50]. Consequently, as well as improvement in pain symptoms, an improvement in HRQoL is a crucial aspect in the management of endometriosis [3,51]. The present findings demonstrate a significant improvement in HRQoL, reflected in various aspects of the core and modular domains of the EHP-30 questionnaire, using either dienogest or COC.

A major determinant of treatment choice is the safety profile and tolerability of various medications used in endometriosis, which can also affect HRQoL. Essentially, both dienogest and COCs lack unsolicited side-effects experienced with other medical treatments, including hypoestrogenism and hyperandrogenism. Although the incidence of possible treatment-related adverse effects with both dienogest and COCs was substantially higher than reported in prior studies, they were generally tolerable and rated by participants as mild–moderate in intensity. The majority of these adverse effects (77%) were experienced upon initiation of treatment and gradually decreased/resolved. The trifling severity of reported side-effects is supported by an improvement in HRQoL. Similarly, the bleeding pattern with both treatments showed a tendency towards milder forms over time. A better reflection of the true incidence of side-effects is expected with larger scale studies that are adequately powered for this purpose.

This study serves as an essential contributor to evidence-based prescribing of medical therapy for the management of pain associated with endometriosis. To the best of the authors' knowledge, this is the first head-to-head study comparing continuous dienogest with COC for the control of endometriosis-associated pelvic pain. The strengths of the study include the randomized controlled study design, use of multiple efficacy measures and the generalizability of results to patients with endometriosis at various r-ASRM stages; two-thirds of participants had a diagnosis of severe endometriosis (stage III, IV or deep pelvic endometriosis), and the remaining one-third of participants had a diagnosis of stage I or II. Notably, <5% of recruited women were lost to follow-up. Similarly, the extent of imputation for missing data was negligible, with none involving efficacy variables. Furthermore, the incidence of protocol deviations was low and balanced between the two groups, suggesting robust and consistent conclusions.

One of the principal shortcomings of this study is the relatively short duration of follow-up, limiting the extrapolation of the results to long-term treatments beyond 6 months. Although a third placebo-control group would be ideal, ethical considerations preclude withholding established treatments for endometriosis-associated pelvic pain to allow such comparison. Another concern is that patients with chronic pain often have access to various types of analgesics that are not necessarily limited to the protocol-approved 'over the counter' ibuprofen. The confounding influence from the possible use of any of these analgesics on the improvement experienced by participants during the study period would be difficult to monitor.

Furthermore, the inherent bias introduced by the subjective nature of the efficacy measures used (VAS and B&B scale) is offset

by the standardization of these scales for pain assessment [32,36–38] and the lack of alternative verified objective measures. This is in addition to the idiosyncratic nature of patients with chronic pain as motivated study participants, which contributes to the reliability and accuracy of reported pain perception.

Conclusion

This study demonstrated that dienogest 2 mg daily was not inferior to the COC Yasmin (0.03 mg ethinyl estradiol and 3 mg drospirenone) daily in improving endometriosis-associated pelvic pain, dysmenorrhea and dyspareunia, and enhancing HRQoL. Although dienogest was associated with substantially lower incidence of side-effects, both treatments were clinically robust for pain relief, were feasible medical options with a satisfactory safety profile, and were well tolerated for the management of women with endometriosis-associated pelvic pain and deep endometriosis. Nevertheless, more adequately powered studies are necessary to address differences in the long-term efficacy and safety of both treatments, and to verify the persistence of the observed improvement and possible delay in time to recurrence.

Acknowledgements

Some of the study data were included in an abstract/poster presentation during ESHRE's 35th annual meeting in Vienna: Abu Musa A, El Taha L, Khalife D, Ghunaim S, Khalil A, Nassif J. Efficacy of dienogest versus oral contraceptive pills (OCPs) on pain associated with endometriosis: randomized controlled trial. Hum Reprod 2019;34:305.

Conflict of interest

None declared.

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Ethical approval

The Institutional Review Board ethics committee approved the study protocol, which was conducted in accordance with the amended version of the Declaration of Helsinki and conformed with Good Clinical Practice regulations. All enrolled women provided written informed consent. The trial was registered at Clinicaltrials.gov (NCT04256200).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2021.10.029.

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