Original Article

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Continuous Dienogest vs Cyclical Dienogest with Ethinyl Estradiol in the Management of Pelvic Endometriosis- A Prospective Interventional Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Endometriosis is a disease of adolescents and women of reproductive age group characterised by the presence of endometrial tissue outside the uterine cavity. It is a typical gynaecological condition that causes symptoms such as dysmenorrhoea, dyspareunia, dyschezia, chronic pelvic pain, irregular uterine bleeding, and infertility. Being a prevalent disease primarily affecting women of reproductive age, this condition significantly reduces the Quality of Life (QoL) with frequent recurrence of symptoms after discontinuation of conservative therapy.

Aim: The aim of this study was to investigate the alleviation of Endometriosis-associated Pelvic Pain (EAPP), effective cycle control, and to compare the side effects of continuous dienogest and cyclical dienogest with ethinylestradiol, as well as the improvement in QoL in the two study groups.

Materials and Methods: A prospective interventional study was conducted at the Department of Obstetrics and Gynaecology, Medical College Kolkata, West Bengal, India. The study duration was 12 months, from June 2020 to May 2021. Patients attending the Gynaecology Outpatient Department (GOPD) with clinical, sonological, and/or surgical diagnosis of endometriosis were enrolled in the study and divided into two groups of 30 patients each. Group 1 was treated with Dienogest (D) 2 mg, and group 2 received a combination of dienogest 2 mg and Ethinyl Estradiol 30 mcg (D+EE) combination. The Visual Analogue Scale (VAS) was used to define endometriosis-related symptoms. Patient satisfaction in terms of improvement in QoL was measured using a free online calculator based on the 12-item Short Form Health Survey (SF-12), which includes both physical and mental components. Follow-ups were conducted at one, three, and six months. Data were summarised as mean and Standard Deviation (SD) for numerical variables and count and percentages for categorical variables. A p-value <0.05 was considered statistically significant.

Results: A total of 60 patients were enrolled in the study and divided into two groups of 30 patients each. At three and six months, endometriosis-associated pelvic pain significantly decreased in patients receiving Dienogest+Ethinylestradiol (D+EE) compared to patients receiving dienogest alone (p<0.001). The effectiveness in cycle control at three and six months was also higher in the D+EE group (p=0.0098 and 0.0443, respectively). The safety profile was similar in both groups during follow-ups. QoL, as assessed by the Physical Component Score (PCS-12), showed a significant decrease at one, three, and six months with D+EE compared to Dienogest alone (p=0.0135, p=0.0058, and p<0.0001, respectively). The Mental Component Score (MCS-12) at three and six months significantly improved in patients on D+EE (p=0.0101, p<0.0001, respectively).

Conclusion: Cyclical D+EE was found to be more effective in the management of pelvic endometriosis compared to continuous dienogest alone, resulting in reduced EAPP, improved cycle control, and enhanced QoL.

Keywords: Chronic pelvic pain, Dysmenorrhoea, Effective cycle control, Pain relief

INTRODUCTION

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterine cavity. It is a chronic estrogen-dependent and benign inflammatory disease that affects 10-30% of women in the reproductive age group [1]. In India, around 26 million women are reported to have endometriosis, with 20-50% among infertile women [2,3]. Various studies in India have reported the incidence to be about 34-48% as diagnosed by laparoscopy [2,4]. Endometriosis represents one of the most challenging gynaecologic conditions to manage. Endometriotic lesions may be located in various areas, with more frequent findings on the pelvic peritoneum, ovaries, rectovaginal septum, uterosacral ligaments, vesicouterine fold, and more rarely in the bowel, diaphragm, umbilicus, pericardium, and pleura [5].

Dysmenorrhoea, deep dyspareunia, dyschezia, and dysuria are the most frequently reported symptoms [6]. Together, dysmenorrhoea, pelvic pain, and infertility result in a significant reduction in the QoL during reproductive age in patients with endometriosis [7]. Laparoscopy with histologic confirmation is the gold standard technique for diagnosing endometriosis [8]. Medical therapies approved for the treatment of endometriosis include progesterone, danazol, Combined Oral Contraceptives (COCs), and Gonadotropin-Releasing Hormone (GnRH) agonists [9,10]. The use of danazol is limited due to many side effects such as acne, seborrhoea, muscle cramps, fluid retention, hot flashes, liver dysfunction, emotional lability, and androgenic side effects like hirsutism, deepening of the voice, and decreased breast size. Similarly, GnRH agonists, despite their benefits in alleviating endometriosis-related symptoms, are associated with abnormal lipid profiles, hot flashes, urogenital and vaginal atrophy, loss of libido, and loss of bone mineral density [9,10].

Dienogest is a synthetic, fourth-generation progestin that has anti-proliferative, anti-androgenic, anti-inflammatory, and anti-angiogenic properties. It is a derivative of 19-nortestosterone with high selectivity for progesterone receptors [9]. It significantly reduces endometriotic lesions and has effective pain relief with a favourable safety and tolerability profile [11,12]. COCs are widely used to treat the

symptoms of endometriosis. The putative biological effects of COCs include both inhibition of endometrial cell implantation and a protective effect against endometrial lesion necrosis [13]. Dienogest 2 mg+EthinylEstradiol 30 mcg is a novel COC with high contraceptive efficacy and minimal side effects. It reduces EAPP and improves sexual activity and QoL [12]. The primary mechanisms include the inhibition of ovulation, atrophy of the endometrial lining, and changes in cervical secretion. Present study was conducted as a pilot study since no study comparing the safety and efficacy of these two drugs could be found. With this background, the present study was conducted to compare the efficacy of the above two drugs in the management of pelvic endometriosis.

MATERIALS AND METHODS

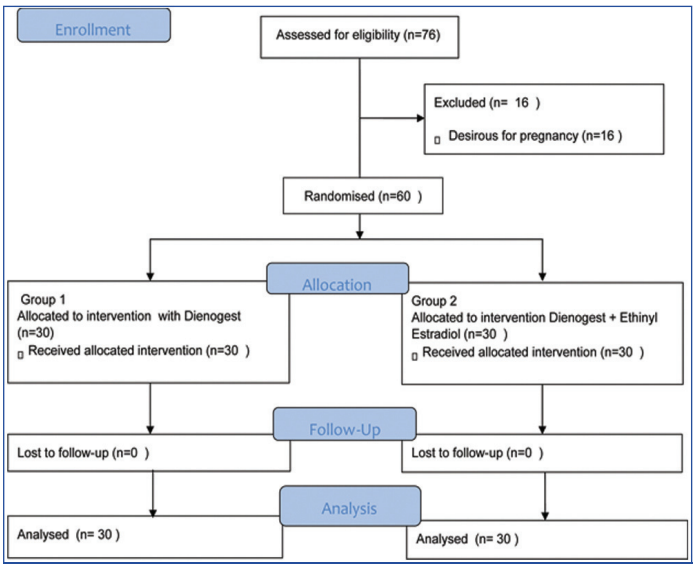
A prospective interventional study was conducted in the Department of Obstetrics and Gynaecology at Medical College Kolkata, West Bengal, India. The study duration was 12 months, from June 2020 to May 2021. The study was conducted after getting approval from the Institutional Ethical Committee (Ref. no. MC/KOL/IEC/NON-SPON/623/02/2020 dated 08/02/20). The sampling frame consisted of patients attending the outpatient department with clinical, sonological, and/or surgical diagnosis of endometriosis. A purposive sampling technique was used.

Inclusion criteria: Women in the age group of 20-40 years who were clinically, sonologically, or surgically diagnosed with endometriosis and had the willingness to participate in the study were included.

Exclusion criteria: Patients with a desire for pregnancy, associated pelvic diseases such as fibroids, pelvic inflammatory disease, suspected malignancy, and liver and circulatory diseases were excluded from the study.

Study Procedure

The sampling frame consisted of patients attending the GOPD with clinical, sonological, and/or surgical diagnosis of endometriosis. A purposive sampling technique was used. A total of 60 patients were included and randomly divided into two study groups of 30 each [Table/Fig-1]. Randomisation was done using a computer-generated randomisation schedule. Group 1 was treated with dienogest 2 mg, and group 2 received a combination of dienogest and ethinylestradiol (D+EE). The drugs were given once a day for a period of six months. Follow-up of patients was conducted at one, three, and six months. The questionnaire for data collection was filled out by one of the authors by interviewing the participants in person during their routine follow-up visits. In each follow-up, patients were assessed for reduction in EAPP using the VAS scoring system [14], intensity and duration of menstrual bleeding, effectiveness in cycle control (cycle length 28±7 days), side effects and tolerability, and patient satisfaction in terms of QoL. Each participant was subjectively inquired at each follow-up visit. QoL in patients was measured using the online calculator based on the 12-item SF-12, which includes both physical and mental components (PCS-12 and MCS-12). The SF-12 is a general health questionnaire that was first published in 1995 as part of the Medical Outcomes Study (MOS) [15]. The SF-12 was constructed using questions drawn from each of the eight dimensions of the MOS 36-item Short Form Survey (SF-36). It is designed to have similar performance to the SF-36 while taking less time to complete. Two summary scores are reported from the SF-12: the MCS-12 and the PCS-12 [16].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram.

STATISTICAL ANALYSIS

For statistical analysis, the data were entered into a Microsoft Excel spreadsheet and then analysed using Statistical Package for Social Sciences (SPSS) version 27.0 and GraphPad Prism version 5. The data were summarised as mean and Standard Deviation (SD) for numerical variables and count and percentages for categorical variables. Unpaired t-test and Chi-square test were performed as applicable. The VAS score and QoL score between the groups were compared using an unpaired t-test. A p-value <0.05 was considered statistically significant.

RESULTS

Both the dienogest group (group 1) and the dienogest+EE group (group 2) were comparable in terms of age distribution and parity [Table/Fig-2,3]. The pretreatment distribution of symptoms like dysmenorrhoea, dyspareunia, and chronic pelvic pain in the two groups was not statistically significant [Table/Fig-4].

Age (in years)	Group 1 n (%)	Group 2 n (%)	Total (N=60)	p-value*
20-30	16 (53.3)	15 (50)	31 (51.7)	0.7958
Row%	51.6	48.4	100	
31-40	14 (46.7)	15 (50)	29 (48.3)	
Row%	48.3	51.7	100	
Total	30 (100)	30 (100)	60 (100)	
Row%	50	50	100	

[Table/Fig-2]: Distribution on age among patients.
*unpaired t-test; {N=60 (30 in each group)}

Parity	Group 1 n (%)	Group 2 n (%)	Total (N=60)
P_{0+0}	11 (36.6)	13 (43.3)	24 (40)
Row%	45.8	54.2	100
P_{0+1}	1 (3.3)	0	1 (1.7)
Row%	100.0	0	100
P_{1+0}	3 (10)	4 (13.3)	7 (11.7)
Row%	42.9	57.1	100
P_{1+1}	4 (13.3)	4 (13.3)	8 (13.3)
Row%	50.0	50	100
P_{1+2}	1 (3.3)	1 (3.3)	2 (3.3)
Row%	50.0	50	100
P_{2+0}	3 (10)	4 (13.3)	7 (11.7)
Row%	42.9	57.1	100
P_{2+1}	5 (16.7)	3 (10)	8 (13.3)
Row%	62.5	37.5	100
P_{2+2}	1 (3.3)	1 (3.3)	2 (3.3)
Row%	50	50	100

P_{3+0}	1 (3.3)	0	1 (1.7)
Row%	100	0	100
Total	30 (100)	30 (100)	60 (100)
Row%	50	50	100

[Table/Fig-3]: Association between parity in both the groups.
Chi-square value: 2.9524; p-value: 0.9373; {N=60 (30 in each group)}

Symptoms	Presence of symptoms	Group 1 (n=30)	Group 2 (n=30)	Chi-square value	p-value
Chronic pelvic pain	No	20	13	3.2997	0.0692
	Yes	10	17		
Dysmenorrhoea	No	2	0	2.0690	0.1503
	Yes	28	30		
Dyspareunia	No	18	23	1.9255	0.1652
	Yes	12	7		

[Table/Fig-4]: Pretreatment association of the presence of symptoms in both groups.

Pain relief, as assessed by the VAS, was significant in the dienogest+EE group (p<0.001) after three and six months of therapy [Table/Fig-5]. There was a statistically significant reduction in the mean duration of menstrual bleeding in the dienogest group at three and six months of therapy. Additionally, 23.33% of patients in this group were found to have amenorrhoea after six months of initiation [Table/Fig-6]. Statistically significant effective cycle control was seen with the dienogest+EE group at three and six months after therapy [Table/Fig-6].

VAS (in months)	Groups	Number	Mean±SD	Mini-mum	Maxi-mum	Median	p-value*
0	1	30	8.4000±0.6215	7.00	9.00	8.00	0.1118
	2	30	8.6333±0.4901	8.00	9.00	9.00	
1	1	30	7.3333±1.0283	5.00	9.00	8.00	0.4052
	2	30	7.1000±1.1250	5.00	9.00	7.00	
3	1	30	6.1333±1.1059	4.00	8.00	6.00	<0.001
	2	30	4.9333±0.9444	3.00	7.00	5.00	
6	1	30	4.7000±0.8367	3.00	6.00	5.00	<0.001
	2	30	2.9333±0.7849	2.00	4.00	3.00	

[Table/Fig-5]: Distribution of mean VAS scoring between both the groups, pre and post treatment.
*Unpaired t-test

Time-line (in months)	Groups (n=30)	Mean duration of menstrual bleeding (in days)		Effective cycle control		
		Mean±SD	p-value*	No	Yes	p-value
0 (Baseline)	1	5.0333±1.4735	0.927	N/A	N/A	-----
	2	5.0000±1.4348		N/A	N/A	
One	1	4.9333±1.2576	0.3998	15	15	0.4362
	2	4.6333±1.4735		12	18	
Three	1	3.3000±0.9523	0.002	10	20	0.0098
	2	4.3667±1.0981		2	28	
Six	1	1.3333±0.9589	<0.001	6	24	0.0443
	2	3.4667±1.0080		1	29	

[Table/Fig-6]: Mean duration of menstrual bleeding and effectiveness of cycle control in two groups.
*Unpaired t-test

The most common side effects reported were headache, breast pain, nausea/vomiting, and weight gain. There was no statistically significant difference between the two groups in terms of side effects [Table/Fig-7]. The mean PCS-12 score of patients significantly improved in the dienogest+EE group during all follow-up visits. The mean MCS-12 score was higher for the same group during the assessment at three and six months, and it was statistically significant [Table/Fig-8].

Adverse reaction	Time-line (at months)	Groups	No. of patients n (%)	Chi-square value	p-value
Headache	One	1	1 (1.67)	0.497	0.4809
		2	0		
	Three	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
	Six	1	2 (3.33)	0.167	0.6830
		2	1 (1.67)		
Breast pain	One	1	1 (1.67)	0.497	0.4809
		2	0		
	Three	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
	Six	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
Nausea/ vomiting	One	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
	Three	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
	Six	1	2 (3.33)	0.167	0.6830
		2	1 (1.67)		
Weight gain	One	1	0	-	-
		2	0		
	Three	1	1 (1.67)	0	1.0000
		2	1 (1.67)		
	Six	1	1 (1.67)	0.497	0.4809
		2	0		

[Table/Fig-7]: Most common adverse events during treatment.

DISCUSSION

In the present study, the EAPP as assessed by the VAS at baseline (mean±SD) in the dienogest group was 8.4000±0.6215. After three months of treatment, the score improved to 6.1333±1.1059, and further improvement to 4.7000±0.8367 was seen after six months of therapy with dienogest. In the dienogest+EE group, the mean VAS score at baseline was 8.6333±0.4901. After three months of treatment, the mean VAS score reduced to 4.9333±0.9444, and further reduction to 2.9333±0.7849 was observed after six months of treatment. The reduction in mean VAS score in the dienogest+EE group was statistically significant (p<0.001) after three and six months of therapy.

The findings of the present study were compared to a study by Strowitzki T et al., (2010), which showed statistically significant mean reductions in VAS score from baseline to week 12, with a reduction of 27.4 mm in the dienogest group and 15.1 mm in the placebo group (p<0.001). Dienogest at a dose of 2 mg daily for 12 weeks was significantly more effective than placebo in reducing EAPP [17].

In terms of the duration of menstrual bleeding, the present study showed that in the dienogest group, the mean duration after six months of therapy further reduced to 1.3333±0.9589, and in the dienogest+EE group, it was 3.4667±1.0080, which was statistically significant (p<0.001). Dmitrovic R et al., (2012) found that the continuous regimen was superior to the cyclic regimen after one month (mean difference: -27.3; 95% Confidence Interval (CI): (-40.5,-14.2); p<0.001) and three months (mean difference: -17.8; 95% CI: (-33.4,-2.1); p=0.03). Continuous Oral Contraceptive Pill (OCP) outperforms cyclic OCP in the short term, but this difference is lost after six months. The primary outcome in their study was the difference in the subjective perception of pain as measured by the VAS over a period of six months [18]. Swailum MB et al., (2017) found that continuous use of low-dose OCPs is an effective

Score	Timeline (at months)	Groups (n=30)	Mean±SD	Minimum	Maximum	Median	p-value*
PCS-12	Zero	1	33.8893±2.5457	28.9900	38.5400	34.2100	0.7711
		2	34.0920±2.8178	26.8300	38.7600	346700	
	One	1	36.6910±3.8276	30.1700	45.4600	36.8500	0.0135
		2	39.0220±3.2312	32.1000	44.8400	39.4450	
	Three	1	41.7010±4.5997	34.3400	55.2400	41.8100	0.0058
		2	45.2047±4.8774	34.8900	54.3200	47.0300	
	Six	1	47.3343±9.1173	4.8700	59.5700	49.2950	<0.0001
		2	55.4760±4.0764	49.8900	62.8600	54.8050	
MCS-12	Zero	1	45.9513±4.7342	36.3200	52.2500	48.1500	0.7478
		2	45.5843±4.0385	35.9900	52.3100	46.6400	
	One	1	48.5280±5.3145	35.3200	54.7800	50.5550	0.8918
		2	48.6953±4.0987	38.7600	56.1000	48.9150	
	Three	1	51.5050±4.1936	41.4500	56.7200	52.5350	0.0101
		2	54.0320±3.0842	48.5600	61.6900	54.3150	
	Six	1	52.1220±5.2067	37.3000	58.1200	53.6500	<0.0001
		2	61.2813±1.7668	57.5700	64.9500	61.1100	

[Table/Fig-8]: Distribution of Physical Component Score (PCS-12) and Mental Component Score (MCS-12) between two groups.
*Unpaired t-test

treatment for pain associated with endometriosis with few adverse effects in women who do not wish to get pregnant in the near future [19]. Moore C et al., showed that the dienogest+EE combination led to a reduction in the incidence of dysmenorrhoea from 28.8% before treatment to 12.9% in the 1st treatment cycle and near zero in the 6th cycle in over 2000 women [20].

There were no reported adverse effects that led to discontinuation of therapy in the present study. Only minor side effects were observed, and the drugs were well tolerated. This is comparable to the study by Strowitzki T et al., who found that dienogest had good tolerability and a favorable safety profile for up to 65 weeks when administered daily at a dose of 2 mg in women with endometriosis. Headache, breast discomfort, depressed mood, and acne were some of the most common adverse side effects, each occurring in <10% of women in their pooled analysis of 332 women with endometriosis [21]. Vercellini P et al., (2016) showed a degree of satisfaction with treatment after six months of progestin therapy. The overall proportion of satisfied and very satisfied women was 71% and 72% in the "before" period (norethindrone acetate) and the "after" period (dienogest), respectively, after six months of treatment. Tolerability was significantly higher in dienogest users (80%) compared to norethindrone acetate users (58%) [22]. No exactly similar study was found in the existing literature, so it was not possible to corroborate the findings of the present study in the same way as the existing literature.

Limitation(s)

The study group was small. Further studies with a larger number of study participants will provide better information regarding the two treatment options.

CONCLUSION(S)

Cyclical dienogest with ethinylestradiol was found to be better in the management of pelvic endometriosis compared to continuous dienogest alone in terms of reducing the EAPP, improving cycle control effectiveness, providing better tolerability, and enhancing QoL. Future trials are needed to establish the use of cyclical dienogest and ethinylestradiol for managing EAPP.

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