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Effect of Long-term treatment with Dienogest over the quality of life and sexual function of women affected by endometriosis-associated pelvic pain

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Abstract

Introduction: Endometriosis associated pelvic pain is a commonly encountered gynecological problem in reproductive age group women. It may affect at least 5-15% of women once in their life time. It is a significant health problem which may vary in appearance from a minimal lesion to deep infiltrating nodule causing significant distortion of pelvic anatomy and effects woman's physical, social and mental well-being. Thus, it is vital to take a careful note of a woman's complaint in endometriosis.

Aim: To determine the effect of 2 mg dienogest over conventional treatment in terms of reduced pelvic pain, improved quality of life and sexual function in women suffered with endometriosis associated pelvic pain.

Methods: It was a prospective descriptive study conducted in the department of obstetrics and gynecology, jay kay Lon hospital, Kota, Rajasthan from November 2019 to October 2021 over 100 women, recruited women divided into case and controls with 50 patients in each group. Cases were given tab. Dienogest 2 mg continuously over a period of 1 year while controls received symptomatic treatment for pain like ibuprofen or naproxen etc. Follow up done at 3, 6 and 12 months.

Results: Maximum 42% women belonged to the age group of 20-25 years, mean BMI was 20.72, 50 % women were nullipara. All the patients had complaint of chronic pelvic pain followed by dysmenorrhoea and dyspareunia in 76% and 39% patients, when compared with baseline visual analogue scale (VAS) score for chronic pelvic pain, follow up at 12 months showed a reduction of score from 7.8 to 4.02. VAS score for dysmenorrhoea reduced from 8.1 to 2.54 in cases and for dyspareunia it was reduced from 7.0 to 2.4. Quality of life by SF12 score suggested an increase of score from 36.18 to 44.60 at 12 months. Female sexual distress score also showed an improvement from 19.08 at baseline to 12.72 ± 0.75.

Conclusion: Medical management is usually the first line therapy for women with endometriosis associated pelvic pain, Dienogest is a well-tolerated oral drug with convenient once a day dosing.

Treatment with dienogest reduces the severity of chronic pelvic pain, dysmenorrhoea and dyspareunia with an improved quality of life and fall in female sexual distress.

Keywords: endometriosis, pelvic pain, dienogest, dysmenorrhoea, dyspareunia.

Introduction

Pelvic pain is a significant cause of morbidity among women, especially in the reproductive age group.[1]The gynecologist confronts this problem on a regular basis. Endometriosis is one of the common causes for pelvic pain. Although much work remains to be done concerning the epidemiology of this disorder; preliminary survey suggests that it may affect 5% to 15% of women at least once during their life time, predominantly in reproductive year. Endometriosis is a disease with little known about its true prevalence and distribution in the population or its risk factors, despite decades of research dedicated to better understand the complexity of the disease. It is thought to be a relatively common disease.

An estimated prevalence among women of reproductive age is 10%.[2] In women with pelvic pain or infertility it ranges from 20% to 90%.[3] In women with unexplained infertility the prevalence is as high as 50%. While in asymptomatic women undergoing tubal ligation, the prevalence ranges from 3- 43%.[4]

Various risk factors associated with endometriosis are reproductive age group, with a peak between 40 to 44 years, women of all ethnic and racial groups, increased exposure to menstruation, alcohol and caffeine consumption and family history of endometriosis. Endometriosis is a significant public health problem, which also poses an economic burden on the society. Endometriosis is an estrogen dependent enigmatic gynecological pathology, which may be defined as the presence of endometrial-like-tissue (glands or stroma) that is located in places outside the uterine endometrial cavity, commonly in the pelvic cavity, including the ovaries, the uterosacral ligaments, and the pouch of Douglas. Endometriosis varies in appearance from a few minimal lesions on otherwise intact pelvic organs to deep infiltrating nodules and massive ovarian endometrioma with extensive adhesions involving bowel, bladder and ureter resulting in significant distortion of the pelvic anatomy[5]. The associated symptoms may affect woman's mental, physical and social well-being; hence it is important to take careful note of the woman's complaints, her distress and anxieties just like as in other chronic diseases[6].

Women with endometriosis typically have a range of abdominal pain symptoms including dysmenorrhoea, dyspareunia, pain at ovulation, heavy menstrual bleeding, non-menstrual pelvic pain, dyschezia and dysuria, as well as chronic fatigue.[7,8]

Endometriosis is also associated with infertility, with a strong association between severity of disease and impact on fertility[9].Hence it being a physically and emotionally distressing disease, significantly affects the quality of life of the women[10].

Many guidelines agree that this condition needs a long-term medical management. Medical therapy is symptomatic rather than curative. Even if each of these treatments maybe effective and may temporarily improve the quality of life (QoL), pelvic pain usually relapses at suspension of treatment.[11]

Amongst the available options in medical management; dienogest shows promising results in women with endometriosis. Dienogest was synthesized in 1979 in Jena, Germany, and was initially referred to as STS-557. Dienogest is structurally related to 19-nortestosterone derivatives with strong endometrial activity with antiandrogenic profile by oral administration[12].

Since, till date we have little data available over the efficacy of dienogest in endometriosis. This study is an attempt to determine the effect of 2mg dienogest over conventional treatment in terms of improving pelvic pain, quality of life (QOL) and sexual function in women suffered with endometriosis associated pelvic pain.

Methodology

The study was conducted prospectively in the department of obstetrics and gynecology, JK Lon hospital, government medical college, Kota, Rajasthan, over a period of 2 year i.e. November 2019- October 2021. It was a descriptive study.

Sampling size: Considering the prevalence of endometriosis and the number of patients attending our OPD, a sample size of 107 was taken. Patients attending OPD at J K Lon hospital were screened for the following inclusion and exclusion criteria to recruit for the above study.

Inclusion criteria

1. Women of 18-49 years of age.
2. Sexually active women.
3. Women having chronic pelvic pain.
4. Women having dyspareunia.
5. Women having dysmenorrhea.
6. Women willing for follow-up.

Exclusion criteria

1. Women under GnRH analogue treatment during last 6months.
2. Women taking hormonal contraceptive treatment during the last 3 months.
3. Women opted a surgical modality for treatment.
4. Women suffering from any psychological disorder, diabetes, hypertension, cardiovascular disease, respiratory illness or with a history of AUB.
5. Women with a history of or family history of breast cancer or cervical cancer or ovarian cancer.
6. Women with history of non-organic sexual dysfunction (or a partner affected by sexual dysfunction)
7. Women refused for follow-up visit.

All selected women underwent a thorough detailed history taking followed by physical and gynecological examination. Clinical diagnosis of endometriosis was done following the ESHRE (European society of human reproduction and embryology) guidelines (non-cyclical chronic pelvic pain, dysmenorrhea, deep dyspareunia) .

After screening, total 107 patients were enrolled; counseling was done about the objective of present study and written informed consent was taken. Out of the 107 patients, 7 lost to follow up hence the data available with 100 women were analyzed and summarized as below. Among 100 women; 50 were enrolled as study group and 50 as control. Randomization done as per even-odd registration number, to avoid selection biasness. Dienogest -2mg once a day continuously for 1 year was given to cases.

In the control group patients took conventional treatments as tab. Ibuprofen 400mg PO every 4-6 hourly, tab Naproxen 250mg PO every 4-6 hourly. All patients were treated on outpatient basis and called up in OPD for follow up at 3,6 and 12 months. At the first and each follow up visit symptoms of the disease like chronic pelvic pain, dysmenorrhea and dyspareunia were evaluated using the visual analogue scale (VAS). VAS is

a pain scale numbered 0-10 where 10 representing the maximal pain and 0 represent the absence of pain. Then to assess the quality of life (QoL) of women affected by endometriosis, SHORT FORM 12 questionnaire (annexure.1) was used. SF-12 is a multipurpose short form (SF) generic measure of health status that assesses the mental and physical functioning over previous 4 weeks. SF-12 form ranges from zero to hundred for each dimension with hundred indicating optimal quality. The SF-12 health survey was developed from the original SF-36 questionnaire, is a well-known, validated self-administered 12-item instrument. It measures health dimensions covering functional status, well-being, and overall health. Information from the 12 items is used to construct physical (PCS-12) and mental (MCS-12) component summary measures, with higher scores indicating better health perception. For evaluating the sexual dysfunction/distress associated with endometriosis another questionnaire, the female sexual distress scale (FSDS)(annexure.2) was used. The FSDS consists of 12 items, with a maximum score of 48. A score of ≥15 shows a clinically significant distress.

All selected women were followed up at 3,6 and 12 months, after a baseline thorough evaluation at the time of enrollment. At each visit all questionnaires namely VAS, SF12, FSDS were administered to both the study and the control group. Confidentiality of participants and privacy maintained during follow up visits. Data was collected and entered in Microsoft excel sheet to prepare the master chart. Linear variables were summarized as mean and standard deviations. Nominal and categorical data was presented as proportion (%), SOFTWARE SPSS 25 version was used for statistical calculation.

The ethical clearance for the above study was taken from the ethical committee of the institute of government medical college, Kota, prior to the conduct of the study.

Results

Table 1: Complaints at the time of recruitment of participants-

complaints	case (No. of patients)	%	Control (No. of patients)	%
Chronic pelvic pain	50	100	50	100
Dysmenorrhea	36	72	40	80
Dyspareunia	18	36	21	42
others	10	20	10	20

All patients in both the groups had complaint of chronic pelvic pain. 72% patients in the study group had complaint of dysmenorrhea and 36% had dyspareunia. In the control group 80% patients had complaint of dysmenorrhea and 42% had dyspareunia.

Table 2: Visual analogue scale Score for chronic pelvic pain

VAS	CASE	CONTROL	P value
	mean±SD	mean±SD	
Baseline	7.8 ±0.75	7.6±0.69	0.1684
3 months	6.76±0.62	7.4±0.60	0.0001
6 months	4.88±0.62	7.24±0.51	0.0001
12 months	4.02±0.42	7.06±0.42	0.0001

When we take a note on intensity of pelvic pain by VAS score, at 3 months it reduced to 6.76±0.62 in cases from 7.4±0.06 in control with a p value of 0.0001 which is statistically significant. At 6 months the VAS score was 4.8±0.62 and 7.24±0.51 in cases and control giving a p value of 0.0001M and at 12 months the VAS score was 4.02±0.42 in cases and 7.06±0.42 in controls, clearly reflecting the significant reduction in chronic pelvic pain.

When we compared the baseline VAS score with follow up score at 12 months of treatment, in case group, then we find almost a 50% reduction that is from 7.8 to 4.02.

Table 3: VAS Score for Dysmenorrhea

VAS	CASE	CONTROL	P value
	mean±SD	mean±SD	
Baseline	8.1 ±0.86	8.3±0.67	0.1976
3 months	6.26 ± 0.63	8.24±0.71	0.0001
6 months	4.02 ± 0.58	8.14±0.67	0.0001
12 months	2.54±0.86	8.04±0.75	0.0001

The VAS score for dysmenorrhea was 8.1±0.86 and 8.3±0.67 at baseline for case and control respectively. There was a subsequent decrease in this score at 3 months to 6.26±0.63 in cases and in controls it was 8.24±0.71, giving a p value of 0.0001, showing a significant improvement in score in case group. The VAS score at 6 months was 4.02±0.58 in cases and 8.41±0.67 in controls, with a p value of 0.0001. At 12 months the score further dropped in cases to 2.54±0.86 while the controls it was 8.04±0.75. There was around 70% reduction in dysmenorrhea as measured by VAS in the cases, with score of 8.1 at baseline and 2.54 at 12 months of DNG use.

Table 4: Visual analogue scale Score for dyspareunia

VAS	CASE	CONTROL	P value
	mean±SD	mean±SD	
Baseline	7 ±0.94	7.3±0.909	0.1986
3 months	5.72 ±0.70	7.32±0.71	0.0001
6 months	3.6±0.75	6.96±0.85	0.0001
12 months	2.4±0.88	6.8±0.72	0.0001

The score for the severity of dyspareunia as measured by visual analogue scale was 7±0.94 for cases and 7.3±0.909 for controls in first visit. At 3 months the score was 5.72±0.70 in case group and 7.32±0.71 in control group, with a p value of 0.0001, which is statistically significant difference. The score at further follows up at 6 months was 3.6±0.75 and 6.96±0.85 in cases and controls respectively, with a p value of 0.0001. the score at 12 month was 2.4±0.88and 6.80.72 in cases and controls, with again a significant p value of 0.0001

Table 5: Quality of life as per Short form 12 score

VAS	CASE	CONTROL	P value
	mean±SD	mean±SD	
Baseline	36.18±2.44	35.08 ±1.7	0.0103
3 months	37.92±2.30	35.66±1.63	0.001
6 months	41.38±2.11	36.44±1.37	0.001
12months	44.6±1.55	37.88±3.25	0.001

The quality of life was measured by SF12 score, with baseline mean values of 36.18±2.44 in cases and 35.08±1.7 in controls. The mean score at 3 months of follow up was 37.92±2.30 and 35.66±1.63, in cases and controls respectively, giving a p value of 0.0001 which is statistically significant. The score at 6 months for cases was 41.38±2.11, and 36.44±1.37 for controls. At 12 months of follow up the score was 44.6±1.55 and 37.88±3.25 for cases and controls respectively, with a p value of 0.0001 There was a gradual improvement of quality of life observed in cases from baseline score of 36.18 to a score of 44.6 at 12 months.

Table 6: Female sexual distress scale score (FSDS)

FSDS	case	Control	P value
	mean±SD	mean±SD	
Baseline	19.08±0.944	18.82±0.89	0.1596
3 months	17.02±0.755	18.34±1.97	0.001
6 months	14.18±0.66	17.86±0.90	0.001
12 months	12.74±0.75	17.34±0.74	0.001

At baseline, the score was 19.08±0.944 for cases and 18.82±0.89 for controls. The score at 3 months, 6months and 12 months of follow up was 17.02±0.755, 14.08±0.66 and 12.74±0.75 for cases and 18.34±1.97,

17.86±0.90, 17.34±0.74 for controls respectively, this shows a gradual improvement in the score, thus better sexual life in cases at each follow up.

Discussion

This prospective study was done in JK Lon hospital, government medical college, Kota, over a period of 2 years, on OPD basis, to explore the effects of long-term treatment with dienogest in reducing the pain associated with endometriosis and thus improving the quality of life and relieving sexual distress in affected woman. In our study the case and control group were age matched, such that the mean age in study group was 26.88±4.49 and mean age in control group was 26±4.26. The most common complain for which most of our patients visited the outpatient department was pelvic pain, which was present in all the patients. Other complains were dysmenorrhea, which was reported by 76 of the 100 women enrolled in study. Dyspareunia was reported by 39 women along with chronic pelvic pain. Salvatore et al [13] observed similar distribution of complaints in its participants with chronic pelvic pain in 100 % of the participants, dysmenorrhea in 75% and dyspareunia in 67 % of the enrolled subjects. In this study we found out that the VAS score for chronic pelvic pain improved over the treatment period of 12 months from a mean of 7.8 to 4.02 (p=0.0001). Salvatore et al[13] found a similar fall in the trend of VAS score on using dienogest. With the start of improvement at 3rd month (p<0.05), which became even more evident from 6 th to 24 months of follow up (p<0.001). Such intra group improvements were not seen in the control group in both the studies. Aruna devi et al[14] also found a significant decrease of VAS score for pain, from 7.72 at the start of study to 4.34 at the end of study at 3 months of dienogest use (p= 0.0001). Thus results obtained in our study were comparable with previously published similar studies.

When we observed the relief in dysmenorrhea with dienogest over conventional treatment, the VAS score for dysmenorrhea, which was 8.1 at baseline, dropped to 2.54 at 12 months of treatment (p=0.0001). In control group score was 8.3 at baseline and 8.04 at 12 months. Salvatore et al[13] observed a similar trend in their study. With reduction of dysmenorrhea by 50.3% at 3 months to 95.5% at 24 months follow up (p<0.001). There was no significant improvement in the control groups in both the studies.

In this study there was a significant relief in pain due to dyspareunia after using dienogest as shown by the fall in VAS on follow ups. The score was7 at baseline, which dropped to 2.4 at 12 months of dienogest use (p=0.0001). Similar improvements were also observed by Salvatore et al[13], with reduction of 74.4% at 24 months dienogest usage in their study (p=0.001).

The quality of life as assessed by SF12 in this study, is an important parameter in defining the efficacy of dienogest for the treatment of endometriosis. SF12 scores improved gradually over the study period from 36.18 at baseline to 37.92, 41.38, and 44.6 at 3,6,12 months of follow-up. Stefano Luisi et al[15] in their study observed that the baseline score of mental and physical index 39.0±9.8 and 39.6±9.6 respectively improved gradually over the treatment period with dienogest over 90 days. The mental score increased to 46.0±9.1(p<0.001). Likewise, the physical index increased to 47.7±8.5(p<0.001). Aruna devi et al [14] also showed significant improvement in physical index (31.94±3.6 to 42.77, p=0.0001) and mental index (35.07±3.56 to 45.86±2.79, p=0.0001) of SF12 scores in her study. The quality of life in females with endometriosis, as affected by the sexual distress due

to it, assessed using the FSDS score showed improvement in the sexual life of the women after treatment with dienogest. The score started to increase from the 1 st follow up visit at 3 months, from 19.08 to 17.02, it further 60 improved at 12months to 12.74. Salvatore et al[13] [in] their study showed a similar improvement in sexual distress. They used a sexual function scale (FSFI) and a sexual distress scale (FSDS) both of which had statistically significant improvements ($p<0.001$ FSFI; $P<0.001$ FSDS). The mean FSDS score reduced from 18.4 at baseline to 9.8 at 24 months of DNG use. The intra group comparison in the control group did not show any significant change.

The most common adverse event as observed in this study was headache, which was reported in 6% of the total study population. Such findings were also observed by so yun park et al [16] in his study, in Korea, for a period of 12 months. Most commonly observed side effect was frequent or prolonged uterine bedding (3.2%), followed by insomnia (2.7%), acne (2.1%), nausea (2.1%), weight gain (2.1%), lower abdominal discomfort, headache and breast discomfort. All of these were usually mild and were associated with a very low discontinuation rate of DNG. Only 5 women (2.7%) reported uterine bleeding as the reason for discontinuation. Although there are other medications available, but the best option for long term use is still a need of this chronic disease. OCPs widely used for this disease has several side effects and develop resistance to long term therapy, with high recurrence rates. Danazol is not preferred as causes masculinizing side effects along with weight gain, oedema, vaginal dryness, hot flushes, liver toxicity etc.

GnRH agonists also are associated with a loss in bone mineral density, causing osteoporosis, in the absence of add back therapy. It also gives other hypoestrogenic adverse effects. Therefore, a medication with higher compliance and lesser side effects over long term use is needed. Dienogest is a considerable drug with its high tolerability, higher patient compliance and safe for long-term use.

Conclusion

Women in the reproductive age group with endometriosis can present with a range of symptoms. Medical management is usually the first line therapy in these women. Amongst the available options, dienogest is a novel drug with promising results. Dienogest is a well-tolerated drug that offers the combined benefit of 19-nor testosterone derivatives and progesterone derivatives. Dienogest has good pharmacokinetic profile, convenient once a day dosage and oral route of administration with well-tolerated side effect profile.

The long-term treatment with dienogest reveals a reduction in the severity of chronic pelvic pain, dysmenorrhea and dyspareunia. When compared with conventional drugs the long-term treatment with dienogest drug resulted in an improved quality of life with a nadir in female sexual distress. Thus we can conclude that dienogest is an effective medical treatment for endometriosis associated pelvic pain.

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