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Original Research Article

Dienogest treatment improves quality of life in women with endometriosis: A prospective cohort study

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ABSTRACT

Background: One of the chronic disabling illness affecting approximately 10% of women in midst of their reproductive period is Endometriosis. The treatment goal of endometriosis is to activate decidualization within the hormonally dependent ectopic endometrium and is regularly given to alleviate pain symptoms and reduce its recurrence among women.

Objectives: The aim of the study was to evaluate the effectiveness of dienogest in reducing pain and its influence on (QOL) quality of life among women affected with endometriosis.

Materials and Methods: A prospective observational cohort study was conducted at Karpaga Vinayaga Institute of Medical Sciences and Research Centre including fifty patients with endometriosis treated with dienogest two mg per day for three months. We assessed the pelvic pain symptoms by visual analogue scale and (QOL)quality of life was determined by physical and mental index before and after 3 months of use of dienogest.

Study Design: To perform statistical analysis, we used paired t test.

Results: Women were on average 33.18 ± 4.43 years. The mean ±SD of VAS of 7.72 (0.73) in women with endometriosis was progressively decreased to 4.34(0.66) after 3 months of treatment with dienogest. The physical index score values increased significantly from 31.94 to 42.77 ($p<0.001$). The mental index increased from 35.07 to 45.86 ($p<0.001$). Adverse effects include breast discomfort, headache, depression, acne, hot flushes and weight gain.

Conclusion: The results suggest that among women with endometriosis, dienogest has a relatively favorable safety profile and is well accepted in bettering the quality of life (QOL).

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1. Introduction

Approximately 5-15% of women in reproductive age experience endometriosis which is a long-term estrogen dependent disease.[1] The incidence of endometriosis is difficult to quantify as the disease is often asymptomatic. The imaging modalities have low sensitivity for small implants.[2] Laparoscopy is the primary method of diagnosis with or without biopsy for histological diagnosis.[3]

Combined oral contraceptives, GnRh analogues and synthetic progestins have proven their values in endometriosis over a period of time especially in women not desiring fertility.[4] Prolonged use of GnRh is associated with hypo estrogenic side effects: Decreased libido, hot flushes, irregular menses, and decreased bone mineral density.[5]

Dienogest is a 19-nor testosterone synthetic progestin suitable for effective endometrial lesion reduction, combined with moderate suppression of estrogen and reduction of inflammatory mechanism and angiogenesis.[6] Women with deep infiltrating endometriosis struggle with pain and reduced quality of life which induces high levels of anxiety, stress, and depression.[7]

Currently worldwide, laparoscopic diagnosis is the treatment of choice for endometriosis, however empirical dienogest treatment at a dosage of 2mg daily without

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laparoscopic conformation represents a suitable adjuvant therapy before undergoing surgery.[8] A high progesterone receptor ratio is created by Dienogest and therefore boosts up the responsiveness to progestin.[9] Dienogest is recommended as empirical treatment without laparoscopic conformation and also as a suitable adjuvant treatment following surgery among women with endometriosis by World Endometriosis Society.[10]

The present study aimed to evaluate the effect of dienogest on quality of life in women with endometriosis.

2. Materials and Methods

This prospective study was approved by the research ethics committee of the institution (REC-KIMS/F/2018/6) involved 50 patients diagnosed with endometriosis at KIMS and RC between June 2018 to June 2019. Inclusion criteria were women between 20 and 45 years, diagnosis of endometriosis with chronic pelvic pain, dysmenorrhea and dyspareunia, previous surgery done for endometriosis or in patients who are waiting for surgery. Presence of endometrial polyp, fibroid uterus, malignant uterine and ovarian pathologies liver, heart and kidney diseases, pregnant women were excluded from the study. Total fifty patients were enrolled with average age of 33.18±4.43 years. Subjects were instructed to take dienogest two mg once daily for up to ninety days. All of the women underwent outpatient visits at the beginning (baseline) and after 1 month (V1) and three months (V2) of treatment. At study entry symptoms of the disease such as dysmenorrhea, dyspareunia, chronic pelvic pain, urinary and intestinal pain were evaluated according to Visual Analogue Scale (VAS) of pain on a scale of 0-10, where ten represented maximal pain and zero is the absence of pain. We adapted a SF-12 (short form 12) quality of life (QOL) questionnaire at the inception and after 3 months of treatment. SF-12 is a multipurpose short form (SF) generic measure of health status that assess 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 of life baseline (study entry) to V2 (ninety days) variation in VAS and SF-12 forms scores were computed. At V1 patient was (30 days) interviewed about symptoms of the disease, and wether the subjects meticulously followed the treatment and its adverse effects. The subjects were requested to follow the treatment and report back again after sixty days. At V2 subjects were asked again on the symptoms, daily intake of the drug, and side effects. The subjects were evaluated fot VAS scale pelvic pain integrity and to fill the SF-12 questionnaire. All the participating women signed an informed consent form. The institutional ethical committee of KIMS approved the study.

2.1. Statistical analysis

Study population were described by mean, median and frequency (%). T test is used to evaluate and compute the statistical significance between the baseline to V2 differences in SF-12 questionnaire and VAS scores.

3. Results

Demographic characteristics of the study participants who received 2 mg of dienogest are shown in Table 1. The mean age of patients was 33.18±4.43 years. Of these 22% were nulliparous women. The body mass index was either overweight (34%) and obese (66%). The effects of dienogest were determined by measuring pain using VAS before and after treatment. The mean ±SD score at baseline was 7.72±0.73 in the total series. The VAS scores significantly decreased (p=0.0001) to 4.34±0.66 at the end of the study. Treatment with dienogest for 3 months positively affected several domains of quality of life with a 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).

Table 1: Demographic and clinical profile of study participants

Age	**Frequency**	**Percent**
21-30	13	26
31-40	34	68
41-50	3	6
BMI		
Overweight	17	34
Obese	33	66
Parity		
Nullipara	11	22
P1	22	44
P2	17	34
Duration (YRS)		
2 Yrs	13	26
3 Yrs	18	36
4 Yrs	13	26
5 Yrs	6	12
Total	50	100

4. Discussion

Endometriosis is described as a endometrial like tissue outside the uterus where it causes a chronic inflammatory reaction ending up as a scar tissue. The clinical guidelines provide recommendations on a non-invasive clinical diagnosis based on patient history and symptoms. Four to ten years is the average range of gap between first symptom and precise diagnosis. Combination of laparoscopy with positive histology is the required diagnosis of endometriosis, but this recommendation is not supported by robust evidence.[3,11]

Table 2: Mean comparison of VAS and SF1 index among study participants

	Baseline	After 3 months	T	p
VAS	7.72±0.73	4.34±0.66	27.97	0.0001
SF12PI	31.94±3.6	42.77±3.59	16.32	0.0001
SF12MI	35.07±3.56	45.86±2.79	20.8	0.0001

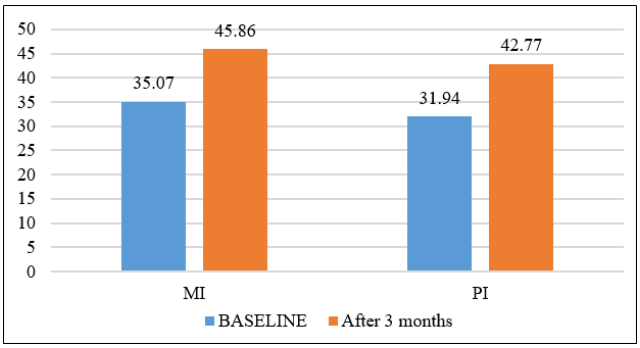

Fig. 1: Mean comparison of SF12 indexes before and after treatment

In Asian countries empirical medical treatment prior to or without surgical managment is widely accepted.[12]

Strowitzki et al,[8] conducted a study worldwide comparing dienogest and GnRH agonists in patients with established diagnosis of endometriosis in one hundred and fifty seven countries, including fifteen Asian countries. They reported in their clinical trials that dienogest demonstrated proportionate efficacy with (GnRH) Gonadotropin Releasing Hormone agonists in decreasing EAPP. This review showed that DNG at 2mg/day demonstrated significant efficacy in reduction of pain intensity and lesion reduction as well as acceptable safety and tolerability data.[3,8]

Recent guidelines has shown that endometriosis should be classified according to cyclical intestinal complaints, pelvic symptoms, and infertility in poor resource setting for begining medical therapy prior to embarking on an invasive treatment like laparoscopy to get histological proof of the disease.[13]

Smorgick et al,[14] reported a forty-seven percent prevalence of endometriosis among adolescent girls with chronic pelvic pain undergoing laparoscopy. Invasiveness, morbidity and complication risk aside, the most recent research have reported that endometriosis recurs at a rate of approximately 40-50% after 5 years following conservative surgery.[15]

Pelvic pain can be alleviated by medical treatment, but recurrence of pain symptoms is unusually observed with discontinuation of hormone suppressive therapy. NSAIDs, combined oral contraceptives, GnRH agonist, and progestins are the most widely used therapies.[16]

Dienogest is a 4th generation steroid with selective progestin which has high selectivity for progesterone receptor. It has the ability to cause decidualization of ectopic endometrium by creating hypo estrogenic, hyper progestrogenic and anti-androgenic environment.[17]

A systematic review showed that dienogest 2mg/day was effective in reducing pelvic pain and was superior to placebo with results similar to GnRH agonists in regulating symptoms of endometriosis. Dienogest two mg/day was also effective in decreasing the endometriotic lesions (11.4 ± 1.71 to 3.6 ± 0.95 p<0.001) with tolerable side effects.[1]

In a 6 months double blind multicenter RTC in 255 Chinese women, the safety and efficacy of dienogest (2mg/day) were assessed by patient reported symptoms and laparoscopy. Greater than 30mm on a 0-100mm Visual Analogue Scale (VAS) was the Endometriosis Associated Pelvic Pain (EAPP) score at baseline among the total population. They concluded that in reducing pelvic pain among subjects with endometriosis, DNG was significantly highly efficient than placebo (24.54mm, 95% CI – 29.93 to 19.15; p<0.0001).[18]

In 2015 Caruso et al studied the effect of dienogest 2mg/day on quality of life (QOL) and sexual function in women with endometrial associated pelvic pain. When compared with the control group (p=NS), at 3 (p<0.05) and 6 months (p<0.001) of treatment, dienogest produced acceptable improvement of pain symptoms.[19]

A prospective study including 30 women with DIE, Leonardo-Pinto et al[20] demonstrated that the use of DNG significantly improved the severity of all pain symptoms including dyspareunia (p=0.0093), dysmenorrhea (p<0.0001), pelvic pain (p=0.0007) and intestinal pain (p<0.0001) with pain score at VAS reduced atleast equal to or less than three for all endometriosis related symptoms.

Vercillini et al[21] compared NETA (2.5 mg) per day with DNG (2mg/day) for the treatment of endometriosis among women. Both treatments were equally effecient in managing pain symptoms and improvement of sexual functioning, psychological status of health related QoL of the patients. The absolute risk reduction in the occurrence of adverse effects after DNG implementation was 13.9% compared to NETA.

5. Conclusion

Long-term management plan is required for endometriosis which is an estrogen dependent benign disease. Patient's age, severity of symptoms, disease location, and

reproductive plan are essential for planning the medical management of endometriosis associated pelvic pain. Symptomatic endometriosis is frequently treated with Progestin therapy. Dienogest is a novel drug, over the past decade its use has increased exponentially in various countries in the management of endometriosis.

6. Abbreviations

VAS – Visual Analogue Scale; EAPP – Endometriosis Associated Pelvic Pain; DNG – Dienogest; NSAIDs – Non-Steroidal Anti-Inflammatory Drugs; NETA- Nor Ethisterone Acetate.

7. Conflict of Interest

None declared.

8. Source of Funding

No Funding sources.

9. Ethical Approval

The study was approved by the Institutional Ethics Committee of KIMS (IEC Reg no: (REC-KIMS/F/2018/6).

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